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(54) Title: PYRIDINE DERIVATIVES AS PROTEIN KINASE INHIBITORS

(57) Abstract: The present invention relates to a compound suitable for use as a kinase inhibitor.

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PYRIDINE DERIVATIVES AS PROTEIN KINASE INHIBITORS

Field of the invention

The present invention is in the field of medicinal chemistry and pharmaceuticals.

Background of the invention

Protein phosphorylation is the most common form of reversible post-translational modification, with an estimated 50% of all proteins undergoing phosphorylation. The phosphorylation state of any given protein is controlled by the coordinated action of specific kinases and phosphatases that add and remove phosphate, respectively. Particularly, protein kinases are a kind of protein phosphotransferases bringing the phosphate of ATP to the specific amino acid residue. They may conventionally be divided into five classes: tyrosine protein kinases, serine/threonine protein kinases, histidine protein kinases, tryptophan protein kinases and aspartyl/glutamoyl protein kinases.

Signaling networks that employ phosphorylation to modulate target activities have been shown to be critically involved in all aspects of cellular function, the abnormal activation of protein phosphorylation is frequently either a driver or direct consequence of the disease. Kinase signaling pathway dysregulation is associated with cancer, inflammatory disease, cardiovascular disease, neurodegenerative disease, and metabolic disease, through the constitutive activation of many downstream pathways, such as phosphatidyl-inositol 3-kinase/v-akt murine thymoma viral oncogene homolog 1 (PIK3/AKT), mitogen-activated protein kinase/extracellular signal regulated kinase (MAPK/ERK) and signal transducer and activator of transcription 5 (STAT5). Consequently, protein kinases represent important therapeutic targets.

In tumours, the abnormal oncogenic activation of protein kinases derives from multiple types of genetic and epigenetic changes. These alterations result in increased specific activity of the kinase itself, its overexpression, or the loss of negative regulation leading to uncontrolled cellular growth and sustained malignant behaviour. The signalling networks operating in cancer cells can also contribute to innate or acquired resistance

to treatment, since they are able to create the most common or rare oncogenic mutations different from tumour to tumour. Hence, the search for small-molecule inhibitors targeting the altered protein kinase molecules in tumour cells has become a major research focus in the academia and pharmaceutical companies.

Such inhibitors can be products that are derived (isolated) from sources such as plants, animals or microorganisms, or can be small-molecules that are designed (synthetized).

WO 2004/022572 discloses classes of biologically active compounds interacting with kinases, and the preparation of these compounds.

In cancerology, there are currently multiple examples of small molecule kinase inhibitors with both selectivity and suitable pharmaceutical properties that have produced meaningful clinical benefit. For instance, pexidartinib is utilized to inhibit the colony-stimulating factor-1 receptor (CSF1R), the KIT proto-oncogene receptor tyrosine kinase (KIT) and the FMS-like tyrosine kinase 3 (FLT3) in, for example, the treatments of patients with symptomatic tenosynovial giant cell tumors (TGCT); edicotinib to inhibit the CSF1R and currently in phase II for acute myeloid leukemia, cognition disorders or Crohn's desease; or nintedanib to inhibit the endothelial growth factor receptor (VEGFR), fibroplast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and CSF1R in, for example, the treatment of idiopathic pulmonary fibrosis.

There is still a great need to develop potent inhibitors of protein kinase that are useful in treating the various protein kinase-related conditions.

In this sense, WO 2011/090738 A2 discloses compounds that are able to inhibit B-RAF and B-RAF mutations and methods for treating diseases related to B-RAF and B-RAF mutation modulation.

US 2009/0325945 describes active compounds, specifically, certain imidazo[4,5-b]pyridin-2-one and oxazolo[4,5-b]pyridin-2-one compounds and analogs inhibiting RAF (e.g., B-RAF) activity in a cell, in vitro or in vivo, inhibiting receptor tyrosine kinase (RTK) activity, such as FGFR, Tie, VEGFR and/or Eph activity, for example, FGFR-1, FGFR-2, FGFR-3, Tie2, VEGFR-2 and/or EphB2

activity, in a cell, in vitro or in vivo.

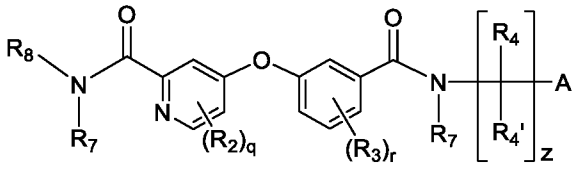
US 2015/0182526: This document describes therapeutic compounds for treating proliferative disorders, cancer, etc., and more specifically certain pyrido[2,3-b]pyrazin-8-substituted compounds, which, inter alia, inhibit RAF (e.g., B-RAF) activity and inhibit receptor tyrosine kinase (RTK) activity.

However, despite the growing effort in developing new protein kinase inhibitors based therapies, there is still a need for protein kinase inhibitors which may overcome the disadvantages of current protein kinase therapies such as side effects, limited efficacy, the emerging of resistance, and compliance failures.

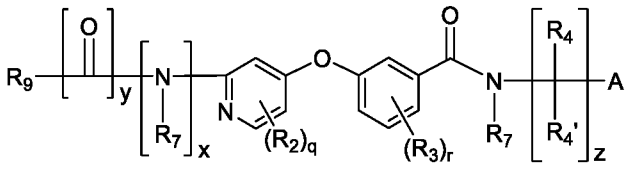
Summary of the invention

The inventors have surprisingly found that the use of protein kinase inhibitors according to the invention allows to provide an improved treatment of dysregulated protein kinase related diseases, by developing a therapy that is more effective, that reduces side effects, that limits the emerging of resistance and that facilitates compliance.

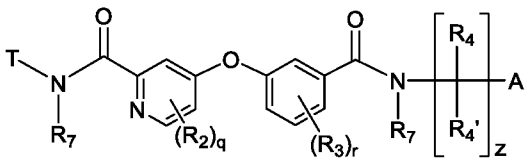
Therefore, the present invention provides a compound suitable for use as a protein kinase inhibitor according to any one of formulae (I) to (VII) [compound (C) hereinafter], or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof,



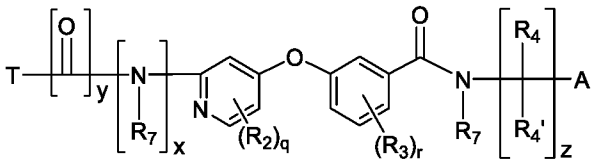
Formula (I)



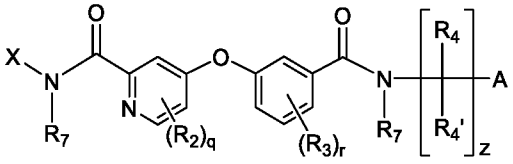
Formula (II)



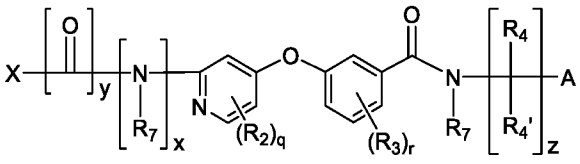
Formula (III)



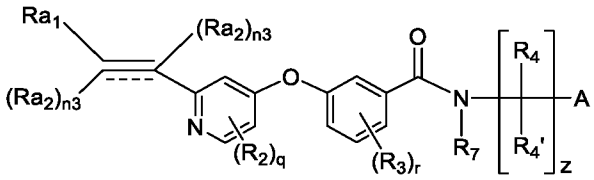
Formula (IV)



Formula (V)



Formula (VI)



Formula (VII)

wherein:

- each of A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $S(O)R_{12}$, SO_2R_{12}, $SO_2N(R_{11})_2$, $S(O)_3R_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl substituents is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, COR_{11}, $CON(R_{11})_2$, $OC(O)R_{11}$, CN, or

OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, C_{1-6} alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl.

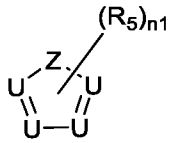
- each of R_4 and R'_4, independently from each other and at each occurrence, are selected from hydrogen or C_{1-6} alkyl, and z is an integer in the range from 0 to 2; with the proviso that when z = 0, then A and R_7 may form together a saturated or unsaturated cyclic moiety;
- each of R_7, independently from each other and at each occurrence is selected from hydrogen, C_{1-6} alkyl, cycloalkyl, wherein said alkyl and cycloalkyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, and CF_3;
- each of R_3, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{21}, SR_{21}, $N(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $OC(R_{21})_2O$, and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31}

or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of r is an integer in the range from 0 to 3; with the proviso that when $R_3 = NR_{21}$, and $R_7 = H$, then R_3 and NR_7 may form together a saturated or unsaturated cyclic moiety;

- each of R_2, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CF_3, CN, NO_2, OR_{21}, SR_{21}, $N(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, $OC(R_{21})_2O$ and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, CF_3, COR_{21}, $CON(R_{21})_2$, $C(O)OR_{21}$, $N(R_{21})_2$, CN, or OR_{21}, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituent is further optionally substituted with heterocyclyl, $N(R_{11})_2$, or OR_{11}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of q is an integer in the range from 0 to 2;
- each of x and y are independently integers equal to 0 or 1;
- R_8 is independently selected from the group consisting of C_{6-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl,

C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl;

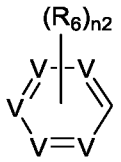
- R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, $N(R_{11})_2$ and CN, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, an heterocyclyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl optionally substituted with a C_{1-4} alkyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl, with the proviso that if x = 1 and y = 0, R_9 is different from heterocyclyl, and from C_{1-6} alkyl wherein said alkyl is optionally substituted with heterocyclyl; and with the proviso that if x=0 and y=0, R_9 is different from hydrogen, and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$; with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.
- each of T is independently the moiety of formula (T-a) herein below:



(T-a)

wherein:

- each of U, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen or C_{1-4} alkyl; with the proviso that at least one U is different from N;
- each of Z, independently from each other and at each occurrence is selected from $C(R)_2$, O, S and NR_7, wherein R, independently from each other and at each occurrence is selected from hydrogen or an C_{1-6} alkyl which is optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein R_7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, cycloalkyl, heterocyclyl, aryl, aralkyl and CF_3;
- each of R_5, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n1 is an integer in the range from 0 to 2;
- each of X is independently the moiety of formula (X-a) herein below:



(X-a)

wherein :

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from hydrogen or C_{1-4} alkyl;
- each of R_6, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n2 is an integer in the range from 0 to 4;
- the dash bond represents an optional triple bond;
- R_{a1} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, , cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, , COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and

aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl.

- each of R_{a2}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl; and wherein n3 is an integer equal to 0 or 1; with the proviso that when the dash bond represents a triple bond, n3 is 0;

wherein said cycloalkyl is a monocyclic, bicyclic or tricyclic ring system of 3-6 ring members per ring; said heterocyclyl is a saturated, partially saturated or completely saturated monocycle, bicycle or tricycle containing 3 to 12 carbon atoms and 1 or 2 heteroatoms independently selected from O or N; said aryl is phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of 5-7 ring members; said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

The present invention further relates to a pharmaceutical composition comprising a carrier, and as active ingredient an effective amount of a compound as defined in any one of the embodiments presented herein.

The present invention relates to a compound as defined in any one of the embodiments presented herein, for use as a medicament.

The present invention relates to a compound as defined in any one of the embodiments presented herein for use in the treatment of a disease selected from cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases.

The present invention relates to a compound as defined in any one of the embodiments presented herein, for use in the treatment of pain sensitization.

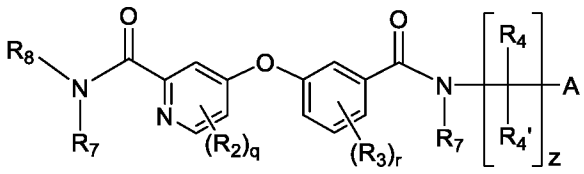
The present invention further relates to a method of inhibiting protein kinase activity in a warm-blooded animal said method comprising the administration to an animal in need thereof, of a kinase-inhibitory effective amount of a compound according to any one of the embodiments presented herein.

The present invention further relates to a method of treating a disease selected from cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral

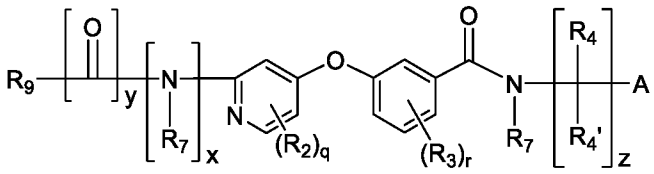
induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases in a warm-blooded animal said method comprising the administration to an animal in need thereof of an effective amount of a compound according to any one of the embodiments presented herein.

Detailed description of the invention

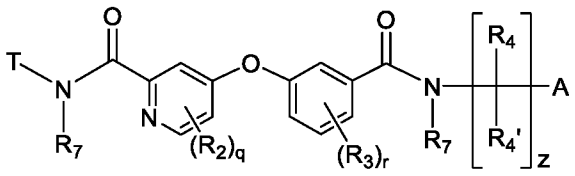
A first aspect of the present invention relates to a compound suitable for use as a protein kinase inhibitor according to any one of formulae (I) to (VII) [compound (C) hereinafter], or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof,



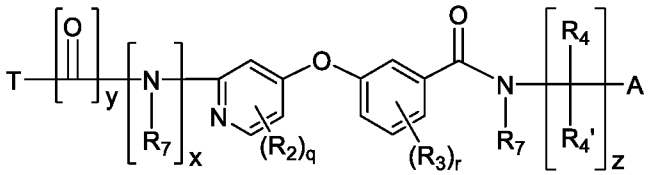
Formula (I)



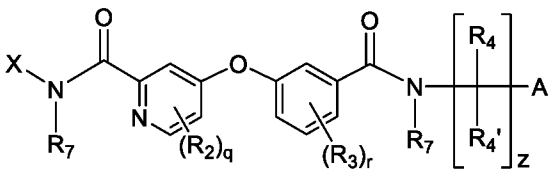
Formula (II)



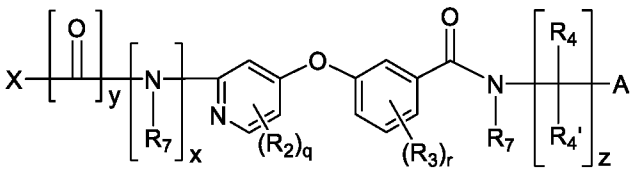
Formula (III)



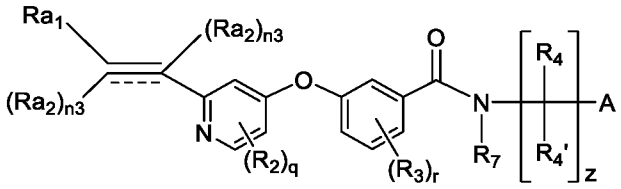
Formula (IV)



Formula (V)



Formula (VI)



Formula (VII)

wherein:

- each of A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $S(O)R_{12}$, SO_2R_{12}, $SO_2N(R_{11})_2$, $S(O)_3R_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl substituents is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, COR_{11}, $CON(R_{11})_2$, $OC(O)R_{11}$, CN, or OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, C_{1-6} alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and

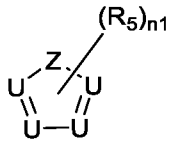
at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl.

- each of R_4 and R'_4, independently from each other and at each occurrence, are selected from hydrogen or C_{1-6} alkyl, and z is an integer in the range from 0 to 2; with the proviso that when z = 0, then A and R_7 may form together a saturated or unsaturated cyclic moiety;
- each of R_7, independently from each other and at each occurrence is selected from hydrogen, C_{1-6} alkyl, cycloalkyl, wherein said alkyl and cycloalkyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, and CF_3;
- each of R_3, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{21}, SR_{21}, $N(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $OC(R_{21})_2O$, and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of r is an integer in the range from 0 to 3; with the proviso that when $R_3 = NR_{21}$, and $R_7 = H$, then R_3 and NR_7 may form together a saturated or unsaturated cyclic moiety;
- each of R_2, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl,

C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CF_3, CN, NO_2, OR_{21}, SR_{21}, $N(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, $OC(R_{21})_2O$ and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, CF_3, COR_{21}, $CON(R_{21})_2$, $C(O)OR_{21}$, $N(R_{21})_2$, CN, or OR_{21}, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituent is further optionally substituted with heterocyclyl, $N(R_{11})_2$, or OR_{11}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of q is an integer in the range from 0 to 2;

- each of x and y are independently integers equal to 0 or 1;
- R_8 is independently selected from the group consisting of C_{6-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl;

- R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, $N(R_{11})_2$ and CN, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, an heterocyclyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl optionally substituted with a C_{1-4} alkyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl, with the proviso that if x = 1 and y = 0, R_9 is different from heterocyclyl, and from C_{1-6} alkyl wherein said alkyl is optionally substituted with heterocyclyl; and with the proviso that if x=0 and y=0, R_9 is different from hydrogen, and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$; with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.
- each of T is independently the moiety of formula (T-a) herein below:



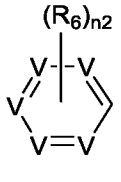
(T-a)

wherein:

- each of U, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are

optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen or C_{1-4} alkyl; with the proviso that at least one U is different from N;

- each of Z, independently from each other and at each occurrence is selected from $C(R)_2$, O, S and NR_7, wherein R, independently from each other and at each occurrence is selected from hydrogen or an C_{1-6} alkyl which is optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein R_7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, cycloalkyl, heterocyclyl, aryl, aralkyl and CF_3;
- each of R_5, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n1 is an integer in the range from 0 to 2;
- each of X is independently the moiety of formula (X-a) herein below:



(X-a)

wherein :

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from hydrogen or C_{1-4} alkyl;

- each of R_6, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n2 is an integer in the range from 0 to 4;
- the dash bond represents an optional triple bond;
- R_{a1} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl.
- each of R_{a2}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally

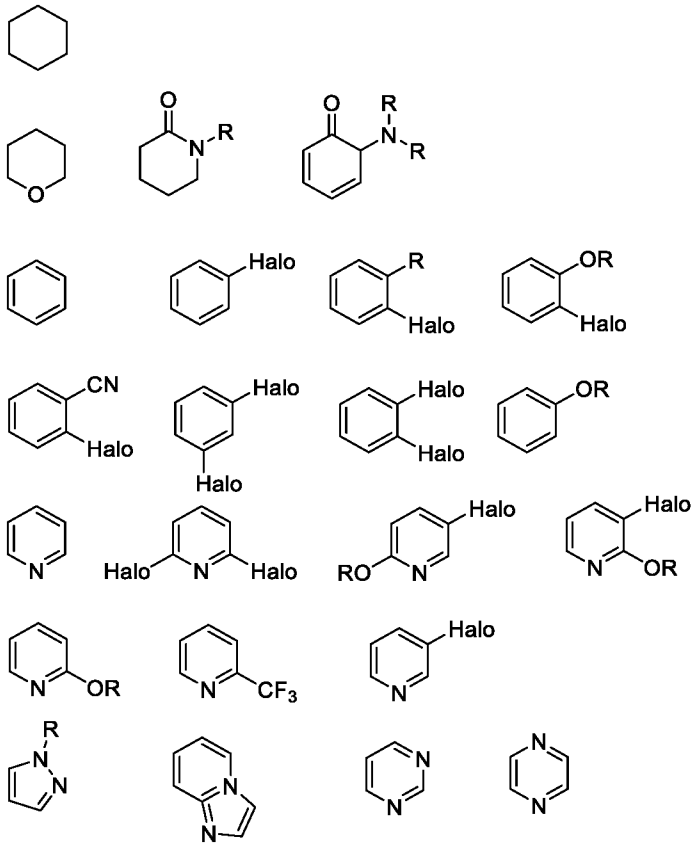
substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl; and wherein n3 is an integer equal to 0 or 1; with the proviso that when the dash bond represents a triple bond, n3 is 0;

wherein said cycloalkyl is a monocyclic, bicyclic or tricyclic ring system of 3-6 ring members per ring; said heterocyclyl is a saturated, partially saturated or completely saturated monocycle, bicycle or tricycle containing 3 to 12 carbon atoms and 1 or 2 heteroatoms independently selected from O or N; said aryl is phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of 5-7 ring members; said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

In a preferred embodiment of the present invention, A in compound (C) of formulae (I) to (VII) is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, or heterocyclyl. More preferably, A is independently selected from the group

consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $P(=O)(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl substituent is further optionally substituted with C_{1-4} alkyl or cycloalkyl; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3. More preferably, A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3, CN, OR_{11}, and $P(=O)(R_{11})_2$; and wherein each of R_{11}, at each occurrence, is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl.

In one embodiment of the present invention, A in compound (C) of formulae (I) to (VII) is independently selected from the following moieties:



wherein each of halo is F, Cl, Br or I, and each of R is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl, preferably R is hydrogen, methyl, ethyl, 2-methylpropyl or tert-butyl.

In a preferred embodiment of the present invention, each of R_4 in compound (C) of formulae (I) to (VII) is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl and the like. Even more preferably, R_4 is hydrogen or methyl.

In a preferred embodiment of to the present invention, each of R_4' in compound (C) of formulae (I) to (VII) is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl and the like. Even more preferably, R_4' is hydrogen.

In a preferred embodiment of to the present invention, z in compound (C) of formulae (I) to (VII) is an integer equal to 0 or 1. Even more preferably, z is 1.

In a preferred embodiment of the present invention, each of R_7 in compound (C) of formulae (I) to (VII), independently from each other and at each occurrence, is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl and the like. More preferably, each of R_7 independently from each other and at each occurrence is hydrogen or methyl. Even more preferably, each of R_7 independently from each other and at each occurrence is hydrogen.

In a preferred embodiment of the present invention, each of R_3 in compound (C) of formulae (I) to (VII), independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, CF_3, CN, OR_{21}, and $N(R_{21})_2$, wherein said alkyl, cycloalkyl and heterocyclyl, are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, or aryl. Preferably, R_3 is independently selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, cycloalkyl, CF_3, CN, OR_{21}, and $N(R_{21})_2$, wherein said alkyl, and cycloalkyl, are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, and C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl. More preferably, R_3 is independently selected from the group consisting of hydrogen, halo, and C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, isobutyl, CF_3, CN, OR_{21}, and $N(R_{21})_2$, and wherein each of R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, and C_{1-4} alkyl. More preferably, R_3 is independently selected from the group consisting of hydrogen, halo, OC_{1-4} alkyl, and C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and

isobutyl. Even more preferably, R_3 is independently chosen from the group consisting of hydrogen, halo, OCH_3 and methyl.

In a preferred embodiment of the present invention, each of r in compound (C) of formulae (I) to (VII) is an integer equal to 0, 1 or 2. More preferably, each of r is an integer equal to 0 or 1. Even more preferably, each of r is an integer equal to 1.

In a preferred embodiment of the present invention, each of R_2 in compound (C) of formulae (I) to (VII) independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CN, OR_{21}, and $N(R_{21})_2$, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, cycloalkyl, $N(R_{21})_2$, CN, or OR_{21}; wherein R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl. More preferably, R_2 is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, cycloalkyl, heterocyclyl, CN, OR_{21}, and $N(R_{21})_2$; wherein R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl and C_{3-6} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Even more preferably, R_2 is independently chosen from the group consisting of hydrogen, halo, C_{1-4} alkyl, and $N(R_{21})_2$ wherein R_{21} is selected from the group consisting of hydrogen and C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl.

In a preferred embodiment of the present invention, q in compound (C) of formulae (I) to (VII) is equal to 0 or 1.

According to certain embodiments of the present invention, x in compound (C) of formulae (II), (IV) or (VI) is an integer equal to 0 and y is an integer equal to 1.

According to certain embodiments of the present invention, x in compound (C) of formulae (II), (IV) or (VI) is an integer equal to 1 and y is an integer equal to 0.

According to certain embodiments of the present invention, x in compound (C) of formulae (II), (IV) or (VI) is an integer equal to 1 and y is an integer equal to 1.

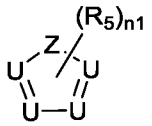
According to certain embodiments of the present invention, x in compound (C) of formulae (II), (IV) or (VI) is an integer equal to 0 and y is an integer equal to 0.

In a preferred embodiment of the present invention, R_8 in compound (C) of formulae (I) is selected from the group consisting of C_{6-12} alkyl, cycloalkyl and heterocyclyl, wherein said alkyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl. More preferably, R_8 is C_{6-12} alkyl, wherein said alkyl, is optionally substituted by a halogen atom. Even more preferably, R_8 is C_{6-12} alkyl.

In a preferred embodiment of the present invention, R_9 in compound (C) of formulae (II) is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, $N(R_{11})_2$, and CN, wherein said alkyl, and cycloalkyl, are optionally substituted by a halogen atom, CF_3, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and CF_3wherein said alkyl, and alkenyl substituents are optionally substituted with an heteroaryl group optionally substituted with a C_{1-4} alkyl with the proviso that if x=0 and y=0, R_9 is different from hydrogen and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$; with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole. More preferably, R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, $N(R_{11})_2$, and CN, wherein said alkyl, and cycloalkyl, are optionally substituted by a halogen atom, CF_3, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence,

is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and CF_3, wherein said alkyl, and alkenyl substituents are optionally substituted with an heteroaryl group optionally substituted with a C_{1-4} alkyl; with the proviso that if x=0 and y=0, R_9 is different from hydrogen and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$ and with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole. Even more preferably, R_9 is selected from the group consisting of hydrogen, C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl, a C_{2-6} alkenyl such as propene or butene, C_{3-6}, cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, $N(R_{11})_2$, and CN, wherein said alkyl, and cycloalkyl, are optionally substituted by a halogen atom, CF_3, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and CF_3, wherein said alkyl, and alkenyl substituents are optionally substituted with an heteroaryl group optionally substituted with a C_{1-4} alkyl; with the proviso that if x=0 and y=0, R_9 is different from hydrogen and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$ and with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.

In a preferred embodiment of the present invention, each of T in compound (C) of formulae (III) or (IV) is independently the moiety of formula (T-a) herein below:



(T-a)

wherein:

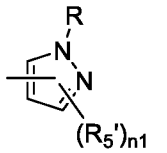
- each of U is preferably selected, independently from each other and at each occurrence, from C, C-halo, C-R, or N; wherein R is hydrogen or C_{1-4} alkyl with the proviso that at least one U is different from N. More preferably, each of U is selected, independently from each other and at each occurrence, from C, C-R or N; wherein R is hydrogen or C_{1-4} alkyl with the proviso that at least one U is different from N.

- each of Z is, independently from each other and at each occurrence, preferably selected from the group consisting of CH_2, and O, S and NR_7, wherein R_7 is an hydrogen, or a C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl. More preferably, each of Z is, independently from each other and at each occurrence, selected from the group consisting of CH_2, O, and NH.

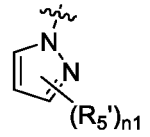
- each of R_5, independently from each other and at each occurrence is preferably selected from the group consisting of C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl. More preferably, each of R_5, independently from each other and at each occurrence, is selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, CF_3, OR_{11}, and each optional alkyl, cycloalkyl, heterocyclyl, substituent is further optionally substituted with halo, C_{1-4} alkyl, cycloalkyl, CN, OC_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl, $P(=O)(OC_{1-4}$ alkyl$)_2$, $P(=O)(C_{1-4}$ alkyl$)_2$

- n1 is preferably an integer equal to 0, 1 or 2. More preferably, n1 is an integer equal to 1 or 2.

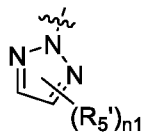
In a preferred embodiment of the present invention, each of T in compound (C) of formulae (III) or (IV), independently from each other and at each occurrence is selected from the moiety of formula (T-a-1) to (T-a-11) herein below:



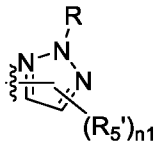
(T-a-1)



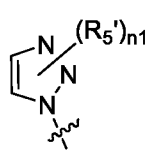
(T-a-2)



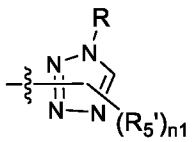
(T-a-3)



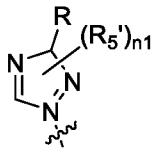
(T-a-4)



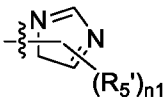
(T-a-5)



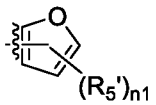
(T-a-6)



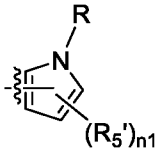
(T-a-7)



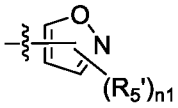
(T-a-8)



(T-a-9)



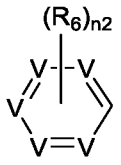
(T-a-10)



(T-a-11)

wherein each R is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, cycloalkyl, heterocyclyl, wherein said C_{1-4} alkyl, cycloalkyl and heterocyclyl is optionally substituted with halo, CN, cycloalkyl, OC_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl, $P(=O)(C_{1-4}\text{alkyl})_2$, $P(=O)(OC_{1-4}\text{alkyl})_2$ preferably R is hydrogen or methyl, and wherein each of R_5' is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, CF_3, and cycloalkyl; and wherein n_1 is an integer equal to 1 or 2.

In a preferred embodiment of the present invention, each of X in compound (C) of formulae (V) or (VI) is independently the moiety of formula (X-a) herein below:



(X-a)

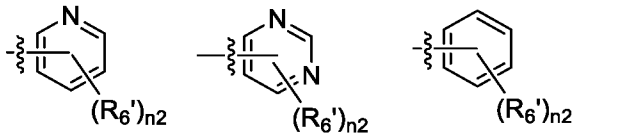
wherein:

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is hydrogen or C_{1-4} alkyl ; More preferably, each of V is selected, independently from each other and at each occurrence, from C, C-R or N; wherein R is hydrogen or C_{1-4} alkyl.
- each of R_6, independently from each other and at each occurrence is preferably selected from the group consisting of C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl. More preferably, each of R_6, independently from each other and at each occurrence, is selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, heteroaryl, halo, CF_3, OR_{11}, $N(R_{11})_2$ and each optional alkyl, cycloalkyl, heterocyclyl and heteroaryl substituent is further optionally substituted with halo, C_{1-4} alkyl, cycloalkyl, heterocyclyl, CN, OC_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl, $P(=O)(OC_{1-4}$ alkyl$)_2$, $P(=O)(C_{1-4}$ alkyl$)_2$, wherein said heterocyclyl is further optionally substituted with C_{1-4} alkyl, and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, and C_{1-4} alkyl. Even more preferably, each of R_6, independently from each other and at each occurrence, is selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, heteroaryl, halo, CF_3, OR_{11}, $N(R_{11})_2$ and each optional alkyl, cycloalkyl, heterocyclyl and heteroaryl substituent is further optionally substituted with C_{1-4} alkyl, or heterocyclyl, wherein said heterocyclyl is further optionally substituted

with C_{1-4} alkyl, and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, and C_{1-4} alkyl.

- n2 is preferably an integer equal to 0, 1 or 2. More preferably, n1 is an integer equal to 0 or 1.

In one embodiment of the present invention, each of X in compound (C) of formulae (V) or (VI) is independently selected from the moiety of formula (X-a-1) to (X-a-3) herein below:



(X-a-1) (X-a-2) (X-a-3)

wherein

- each of R_6' is independently selected from hydrogen, halo, C_{1-4}alkyl, OC_{1-4}alkyl, NH_2, $N(C_{1-4}alkyl)_2$, heterocyclyl, heteroaryl, wherein said C_{1-4} alkyl, heteroaryl and heterocyclyl are optionally substituted with halo, C_{1-4}alkyl, heterocyclyl which is optionally substituted with C_{1-4} alkyl
- n_2 is an integer equal to 1 or 2.

In a preferred embodiment of the present invention, the dash bond in compound (C) of formulae (VII) represents a triple bond.

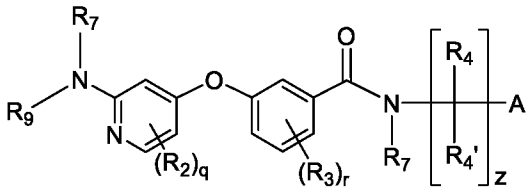
In a preferred embodiment of the present invention, R_{a1} in compound (C) of formulae (VII) is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-4} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, or C_{1-4} alkyl. More preferably, R_{a1} is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, heterocyclyl, aryl, heteroaryl, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen and C_{1-4} alkyl. Even

more preferably, R_{a1} is independently C_{1-4} alkyl, wherein said alkyl, is optionally substituted by aryl, heteroaryl, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, and C_{1-4} alkyl.

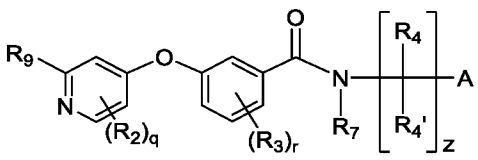
In a preferred embodiment of the present invention, R_{a2} in compound (C) of formulae (VII) is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-4} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, or C_{1-4} alkyl. More preferably, R_{a2} is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, heterocyclyl, phenyl, heteroaryl, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, or C_{1-4} alkyl. Even more preferably, R_{a2} is independently C_{1-4} alkyl, wherein said alkyl, is optionally substituted by aryl, heteroaryl, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, and C_{1-4} alkyl.

In a preferred embodiment of the present invention, n3 in compound (C) of formulae (VII) is an integer equal to 0.

According to one embodiment of the present invention, the compound (C) according to formula (II), or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, preferably is a compound chosen among those of formulae (II-a) or (II-b) [compound (C) of class (II) herein after]:



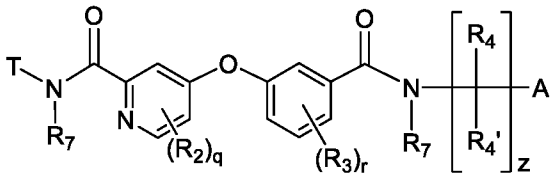
Formula (II-a)



Formula (II-b)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q and R_9 have the same meaning as defined above for formula (II).

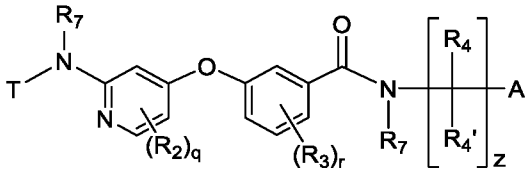
According to one embodiment of the present invention, the compound (C) according to formula (III), or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, preferably is a compound of formulae (III-a) [compound (C) of class (III) herein after]:



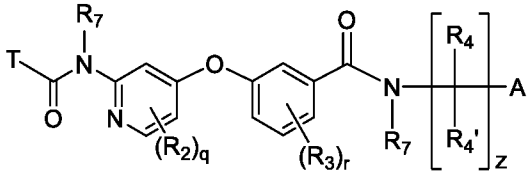
Formula (III-a)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, and T have the same meaning as defined above for formula (III).

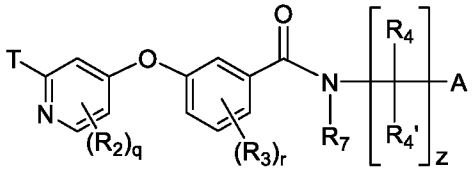
According to one embodiment of the present invention, the compound (C) according to formula (IV), or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, preferably is a compound chosen among those of formulae (IV-a) to (IV-c) [compound (C) of class (IV) herein after]:



Formula (IV-a)



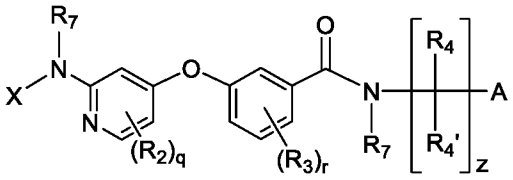
Formula (IV-b)



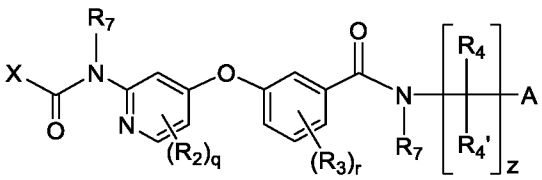
Formula (IV-c)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, and T have the same meaning as defined above for formula (IV).

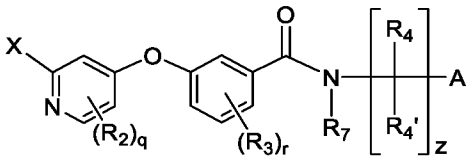
According to one embodiment of the present invention, the compound (C) according to formula (VI), or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, preferably is a compound chosen among those of formulae (VI-a) to (VI-c) [compound (C) of class (VI) herein after]:



Formula (VI-a)



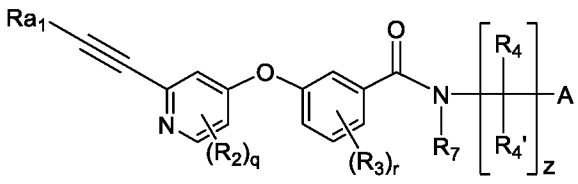
Formula (VI-b)



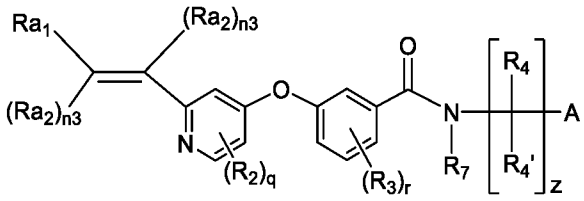
Formula (VI-c)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, and X have the same meaning as defined above for formula (VI).

According to one embodiment of the present invention, the compound (C) according to formula (VII), or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, preferably is a compound chosen among those of formulae (VII-a) or (VII-b) [compound (C) of class (VI) herein after]:



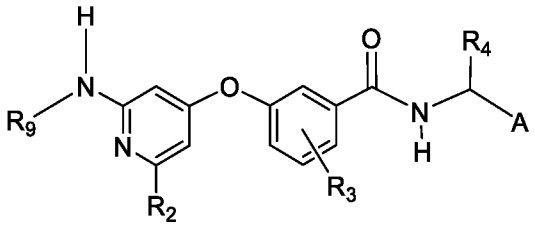
Formula (VII-a)



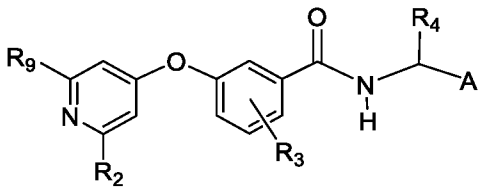
Formula (VII-b)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, R_{a1}, R_{a2} and n3 have the same meaning as defined above for formula (VII).

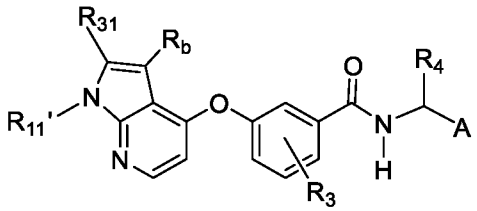
In compounds (C) according to the present invention, preferably R_4' and R_7 are hydrogen and r and q are equal to 1. Preferred compounds (C) of class (II) are thus selected from those of formulae (II-a-1) to (II-c-1) herein below:



Formula (II-a-1)



Formula (II-b-1)



Formula (II-c-1)

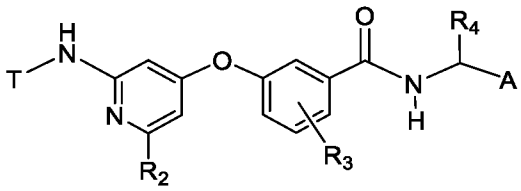
wherein A, R_4, R_3, R_2, and R_9 have the same meaning as defined above for formula (II); wherein R_{31} is a heteroaryl which is optionally substituted with a C_{1-4} alkyl, wherein R_{11}' is hydrogen or C_{1-4} alkyl; and wherein R_b is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-6} cycloalkyl.

wherein said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

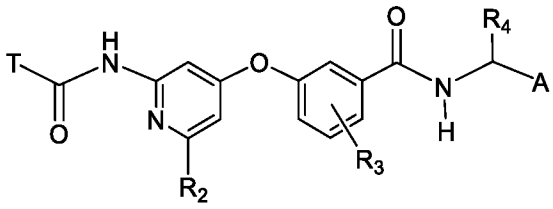
In one embodiment of the present invention, the compounds (C) of class

(II) are selected from those of formulae (II-a-1) to (II-c-1).

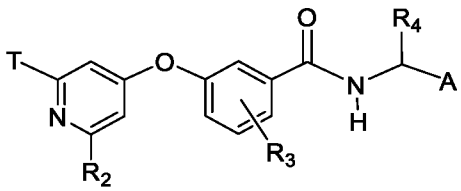
In compounds (C) according to the present invention, preferably R_4' and R_7 are hydrogen and r and q are equal to 1. Preferred compounds (C) of class (IV) are thus selected from those of formula (IV-a-1) to (IV-c-1) herein below:



Formula (IV-a-1)



Formula (IV-b-1)

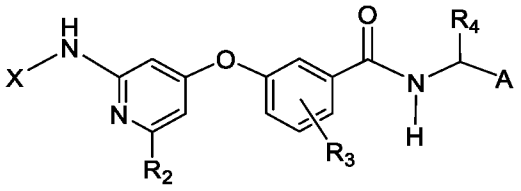


Formula (IV-c-1)

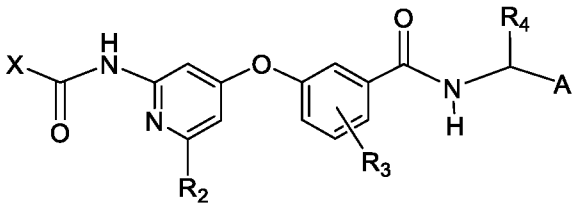
wherein A, R_4, R_3, R_2, and T have the same meaning as defined above for formula (IV).

In one embodiment of the present invention, the compounds (C) of class (IV) are selected from those of formula (IV-a-1) to (IV-c-1).

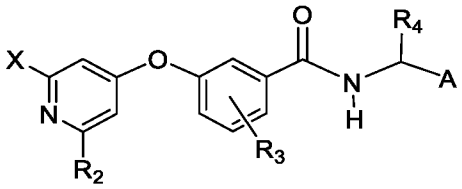
In compounds (C) according to the present invention, preferably R_4' and R_7 are hydrogen and r and q are equal to 1. Preferred compounds (C) of class VI are thus selected from those of formula (VI-a-1) to (VI-c-1) herein below:



Formula (VI-a-1)



Formula (VI-b-1)

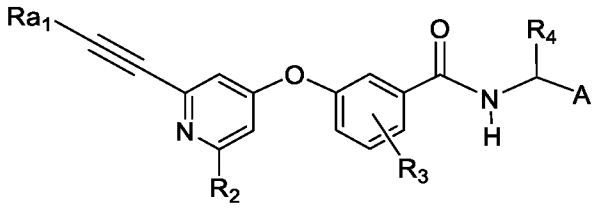


Formula (VI-c-1)

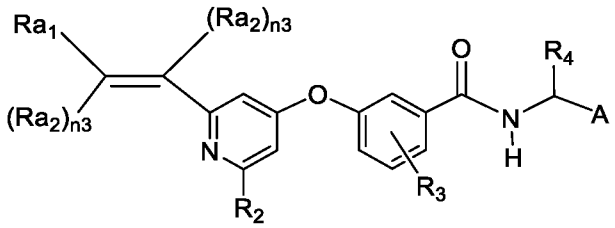
wherein A, R_4, R_3, R_2, and X have the same meaning as defined above for formula (VI).

In one embodiment of the present invention, the compounds (C) of class (VI) are selected from those of formula (VI-a-1) to (VI-c-1).

In compounds (C) according to the present invention, preferably R_4' and R_7 are hydrogen and r and q are equal to 1. Preferred compounds (C) of class (VII) are thus selected from those of formulae (VII-a-1) or (VII-b-1) herein below:



Formula (VII-a-1)



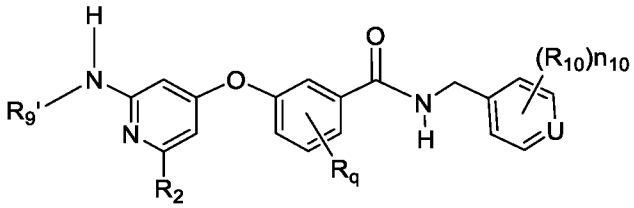
Formula (VII-b-1)

wherein A, R_4, R_3, R_2, R_{a1}, R_{a2}, and n3 have the same meaning as defined above for formula (VII).

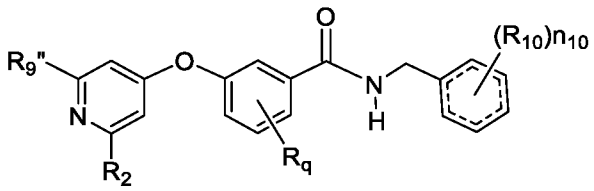
In one embodiment of the present invention, the compounds (C) of class (II) are selected from those of formulae (VII-a-1) or (VII-b-1).

In a preferred embodiment of the present invention, the compound (C) of

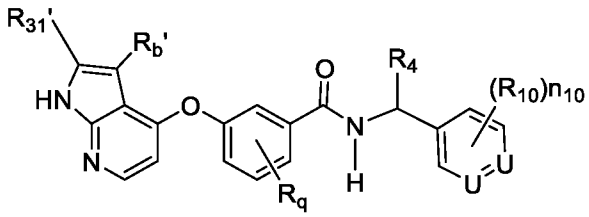
class (II) according to the present invention are selected from those of formula (II-a-2) or (II-b-2) or (II-c-2) herein below:



Formula (II-a-2)



Formula (II-b-2)



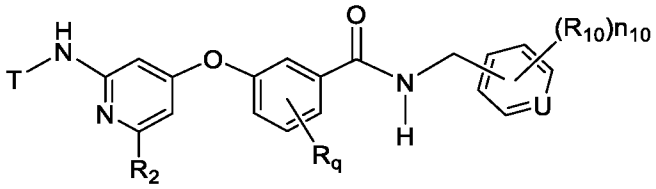
Formula (II-c-2)

wherein:

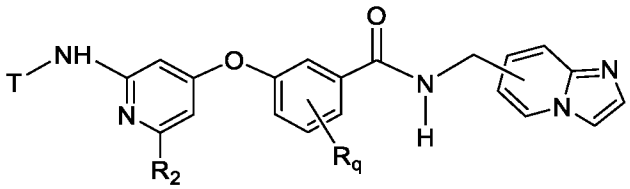
- each of R_9' is selected from the group consisting of hydrogen, CN and C_{3-6} cycloalkyl such as cyclopropyl;
- each of R_9" is selected from the group consisting of hydrogen, C_{1-4} alkyl, CN and C_{3-6} cycloalkyl such as cyclopropyl;
- each of R_2 is independently selected from hydrogen or halo;
- each of R_q is independently selected from the group consisting of hydrogen, CH_3, OCH_3, and halo, such as F or Cl.
- each of R_{10} is independently selected from the group consisting of H, F, Cl, OCH_3, or CF_3;
- each of U is selected from the group consisting of C, C-R_{10} and N;
- n_{10} is an integer equal to 0, 1 or 2; and
- each of R_{31}' is selected from the group consisting of pyrazyl, N-methylpyrazyl, and pyridyl.

- R_b' is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-4} cycloalkyl; preferably R_b' is selected from the group consisting of Cl, CH_3, and cyclopropyl.
- the dash bond represents an optional double bond.

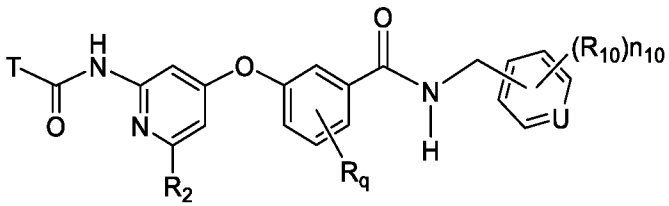
In a preferred embodiment of the present invention, the compound (C) of class (IV) according to the present invention are selected from those of formula (IV-a-2-1), (IV-a-2-2), (IV-b-2-1), (IV-b-2-2), or (IV-c-2) to (IV-c-2-4) herein below:



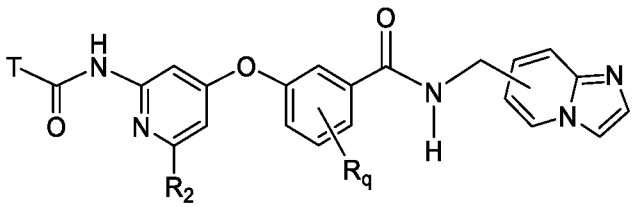
Formula (IV-a-2-1)



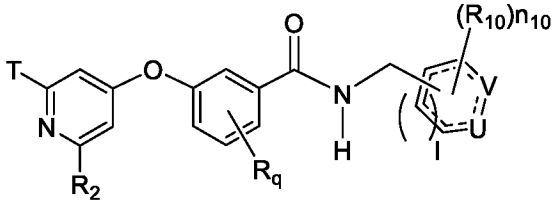
Formula (IV-a-2-2)



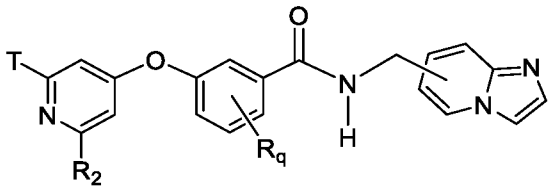
Formula (IV-b-2-1)



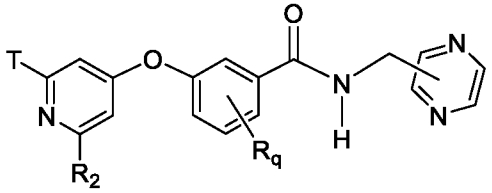
Formula (IV-b-2-2)



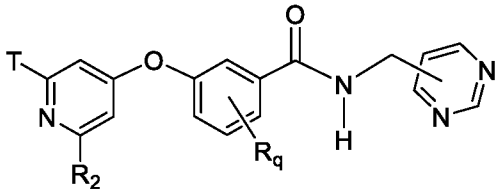
Formula (IV-c-2-1)



Formula (IV-c-2-2)



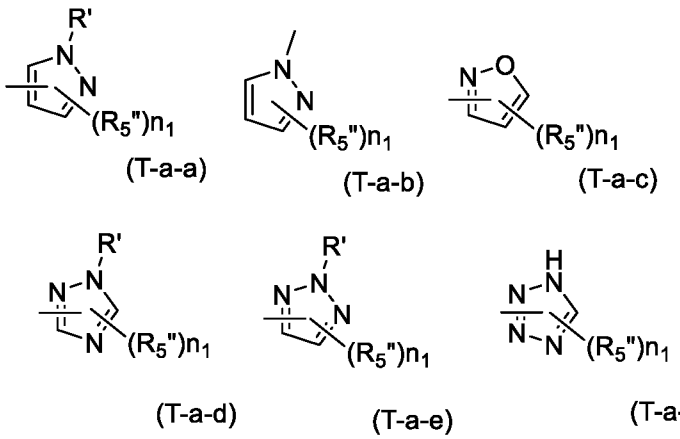
Formula (IV-c-2-3)



Formula (IV-c-2-4)

wherein:

- T is, independently from each other and at each occurrence, selected from the moiety of formula (T-a-a) to (T-a-f) herein below:



(T-a-a) (T-a-b) (T-a-c)

(T-a-d) (T-a-e) (T-a-f)

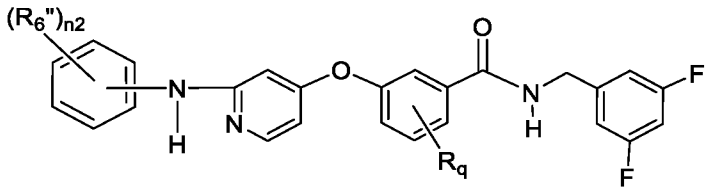
wherein:

- each of R' is independently hydrogen, C_{1-4} alkyl, cycloalkyl selected from the group consisting of cyclopropyl and cyclobutyl; heterocyclyl selected from the group consisting of oxetanyl, tetrahydropyranyl, azetdinyl, and piperidinyl; wherein said alkyl is further optionally substituted with F, OC_{1-4}

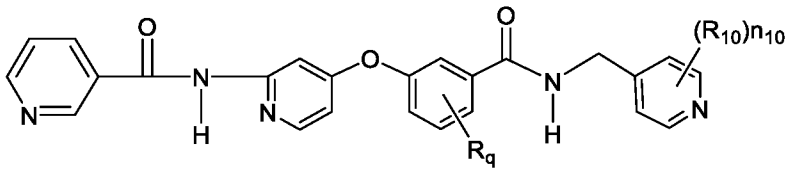
alkyl, $P(=O)(OC_{1-4}alkyl)_2$, $P(=O)(C_{1-4}alkyl)_2$, CN, cyclopropyl, or cyclobutyl; and wherein said heterocyclyl is further optionally substituted with $C(=O)(OC_{1-4}alkyl)$,

- each of $R"_5$ is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, CF_3 and cyclopropyl;
- each of n1, independently from each other and at each occurrence is an integer equal to 0, 1 or 2.
- R_2 is independently hydrogen, halo, or NH_2;
- each of R_q is independently selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl;
- each of R_{10} is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, CF_3, OC_{1-4}alkyl, and CN,
- each of U and V are independently C, C-R_{10} or N;
- n_{10} is an integer equal to 0, 1 or 2.

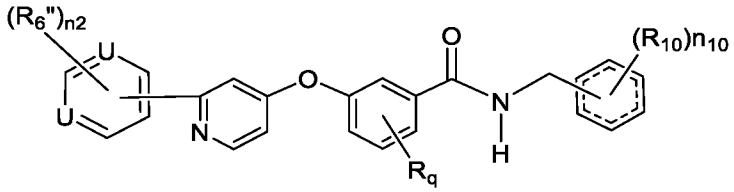
In a preferred embodiment of the present invention, the compound (C) of class (VI) according to the present invention are selected from those of formula (VI-a-2) to (VI-c-2) herein below:



Formula (VI-a-2)



Formula (VI-b-2)

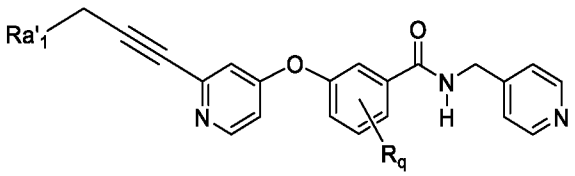


Formula (VI-c-2)

wherein

- each of R"$_6$ is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, $N(R_{21})_2$, OR_{21}; heterocyclyl selected from the group consisting of pyrrolidyl, piperidyl, morpholinyl, piperazyl; a pyrazyl wherein said heterocyclyl and pyrazyl are optionally substituted with C_{1-4} alkyl, and wherein R_{21} is a C_{1-4} alkyl.
- each of R_q is independently selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl;
- each of R_{10} is independently selected from the group consisting of hydrogen, halo, OC_{-4} alkyl, and CN;
- each of U is independently C, C-R_{10} or N;
- n_{10} is an integer equal to 0, 1 or 2
- n_2 is an integer equal to 0, 1 or 2.

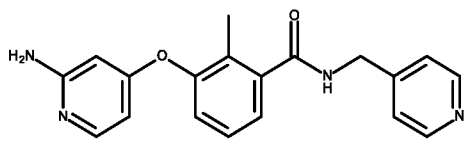
In a preferred embodiment of the present invention, the compound (C) of class (VII) according to the present invention are selected from those of formula (VII-a-2) herein below:



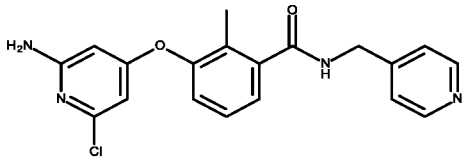
Formula (VII-a-2)

wherein Ra'$_1$ is selected from the group consisting of benzyl, pyrazyl, OH, OC_{1-4} alkyl, NH_2, and NH(C_{1-4} alkyl) and wherein R_q is selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl; preferably R_q is H or CH_3.

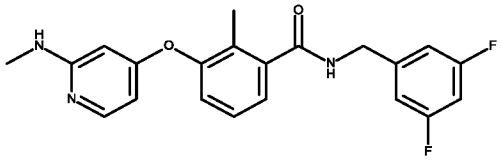
In a preferred embodiment of the present invention, the compound (C) according to general formula (II-a) is a compound chosen among those of formulae (VIII) to (XXXII-3) herein below:



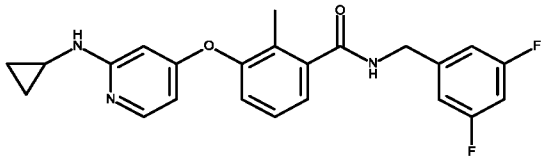
Formula (VIII)



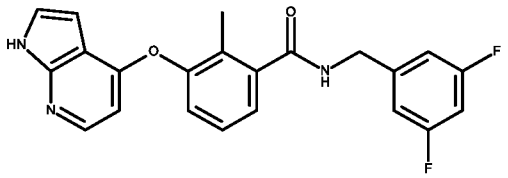
Formula (IX)



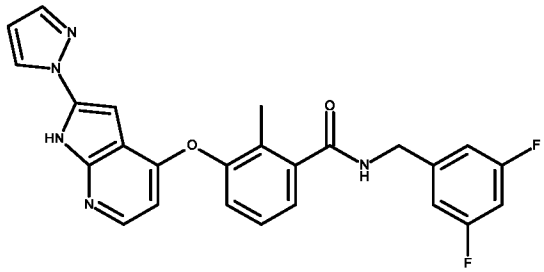
Formula (X)



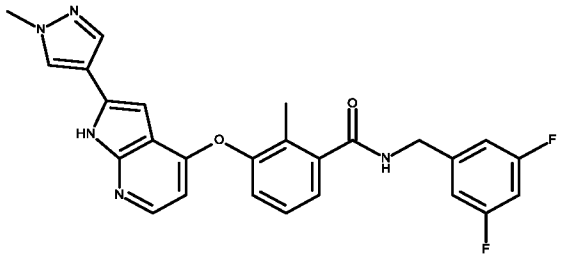
Formula (XI)



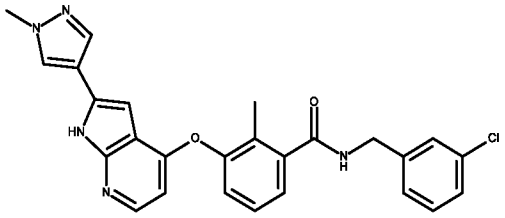
Formula (XII)



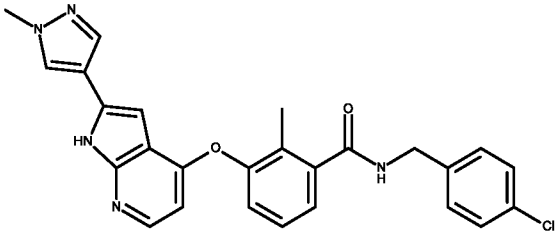
Formula (XIII)



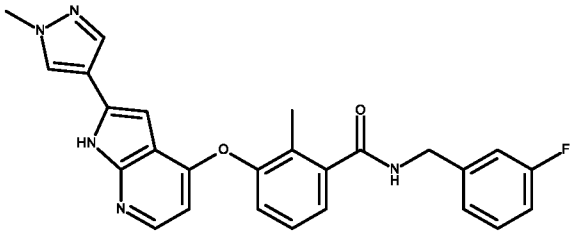
Formula (XIV)



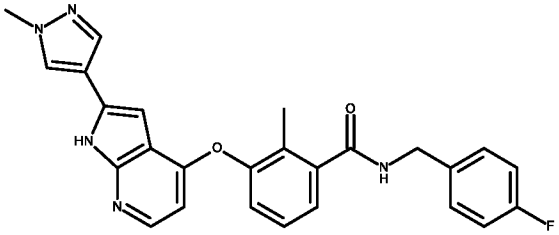
Formula (XV)



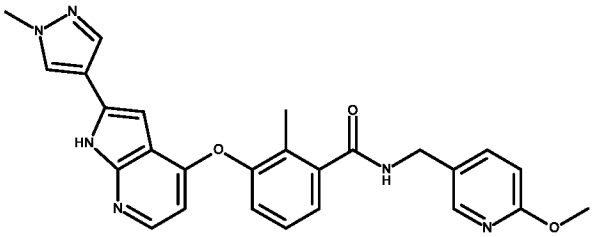
Formula (XVI)



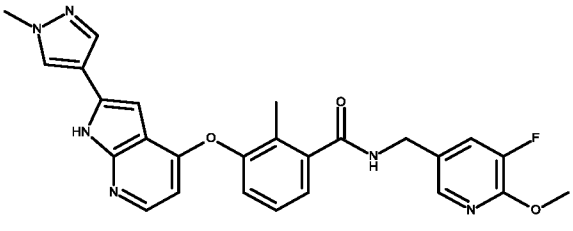
Formula (XVII)



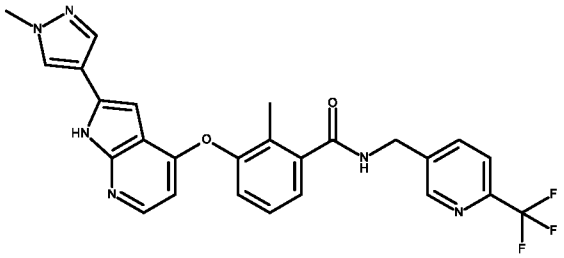
Formula (XVIII)



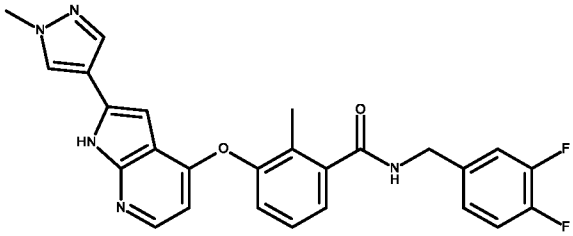
Formula (XIX)



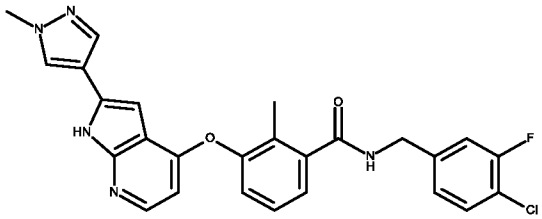
Formula (XX)



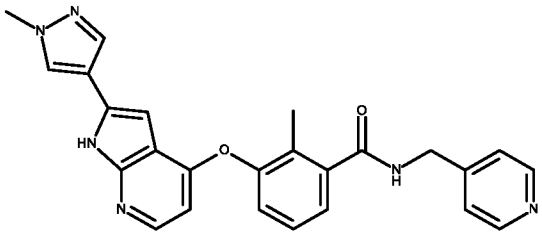
Formula (XXI)



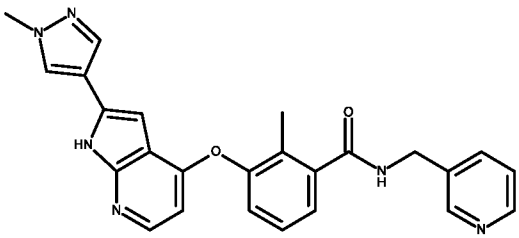
Formula (XXII)



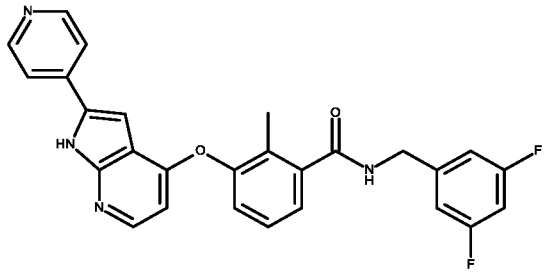
Formula (XXIII)



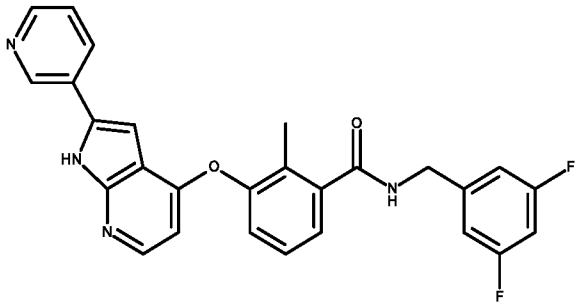
Formula (XXIV)



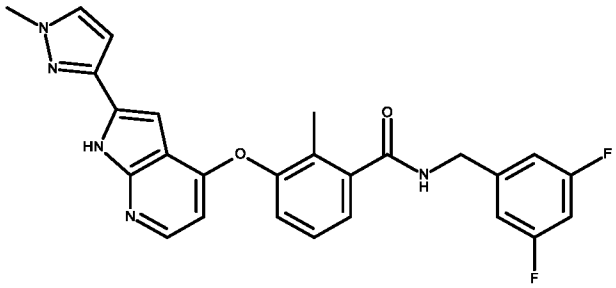
Formula (XXV)



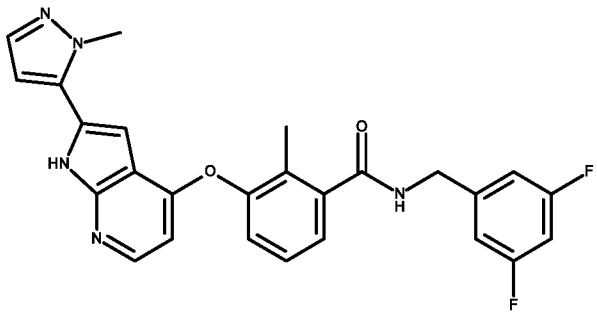
Formula (XXVI)



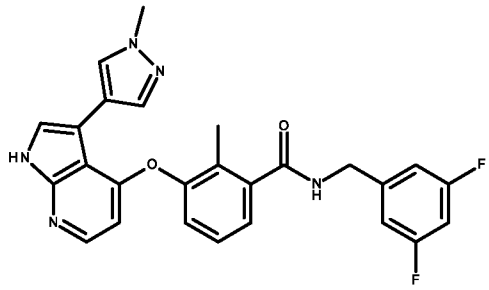
Formula (XXVII)



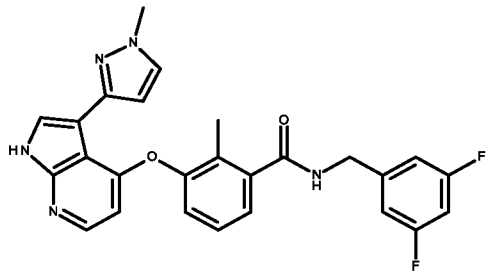
Formula (XXVIII)



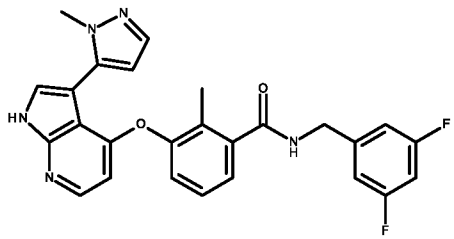
Formula (XXIX)



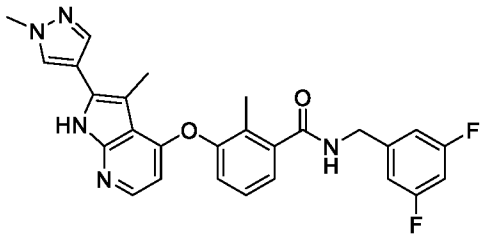
Formula (XXX)



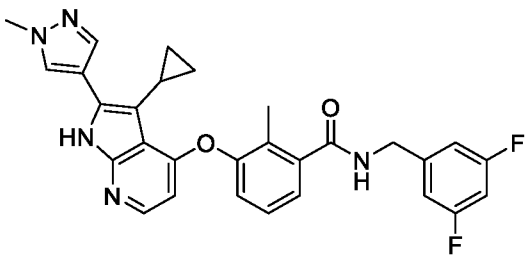
Formula (XXXI)



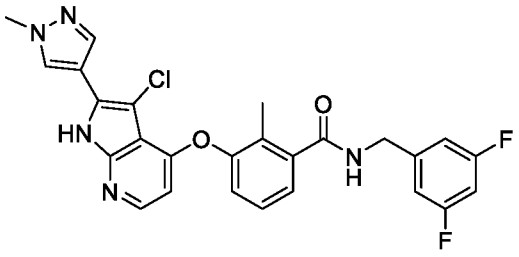
Formula (XXXII)



Formula (XXXII-1)

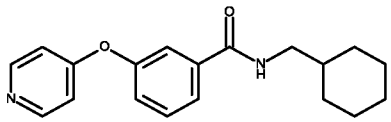


Formula (XXXII-2)

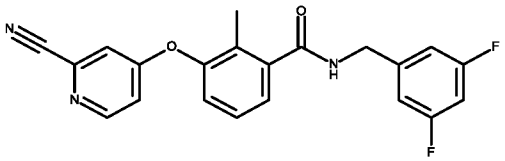


Formula (XXXII-3)

In a preferred embodiment of the present invention, the compound (C) according to general formula (II-b) is a compound chosen among those of formulae (XXXIII) to (XXXIV) herein below:

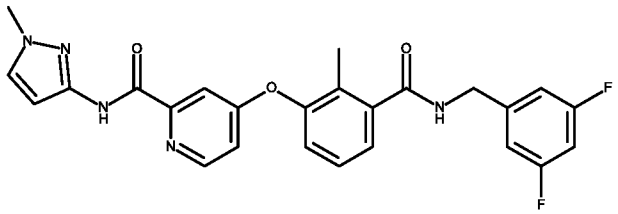


Formula (XXXIII)

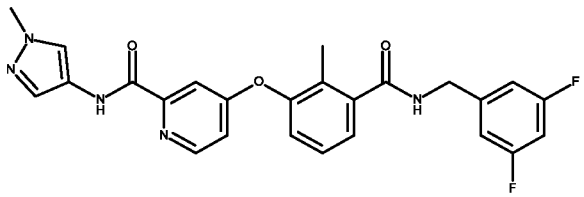


Formula (XXXIV)

In a preferred embodiment of the present invention, the compound (C) according to general formula (III-a) is a compound chosen among those of formulae (XXXV) to (XXXVI) herein below:

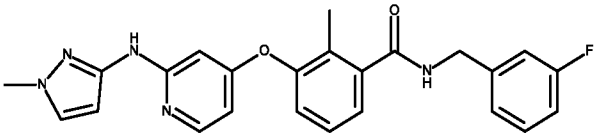


Formula (XXXV)

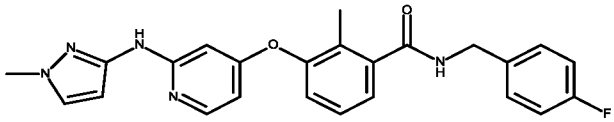


Formula (XXXVI)

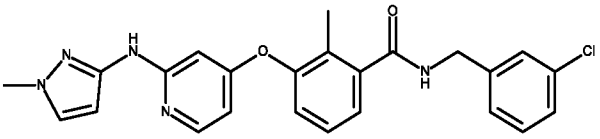
In a preferred embodiment of the present invention, the compound (C) according to general formula (IV-a) is a compound chosen among those of formulae (XXXVII) to (LXXI-2) herein below:



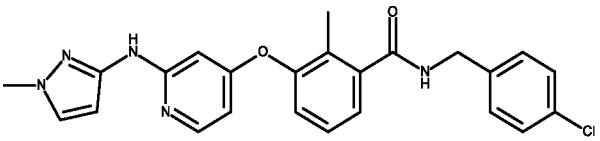
Formula (XXXVII)



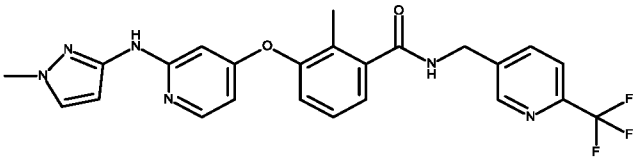
Formula (XXXVIII)



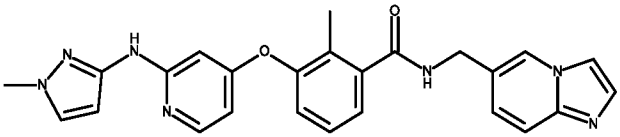
Formula (XXXIX)



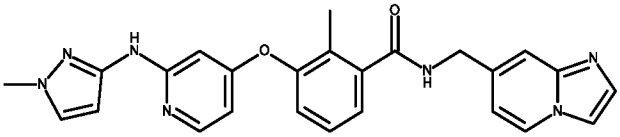
Formula (XL)



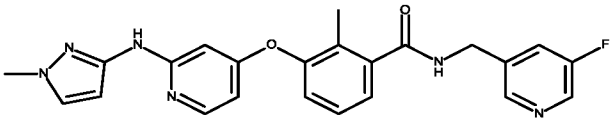
Formula (XLI)



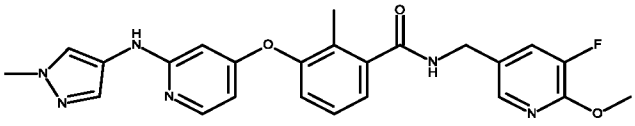
Formula (XLII)



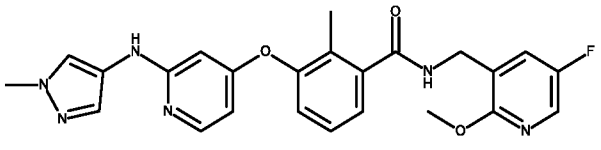
Formula (XLIII)



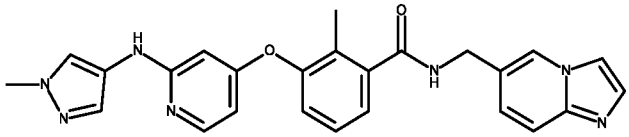
Formula (XLIV)



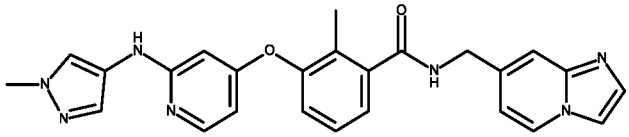
Formula (XLV)



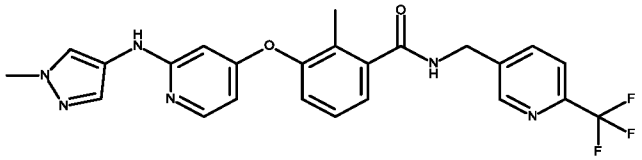
Formula (XLVI)



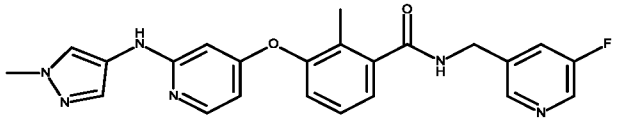
Formula (XLVII)



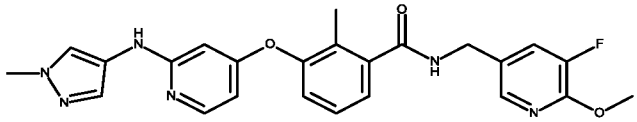
Formula (XLVIII)



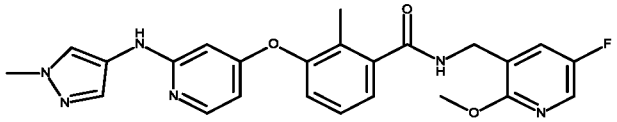
Formula (XLIX)



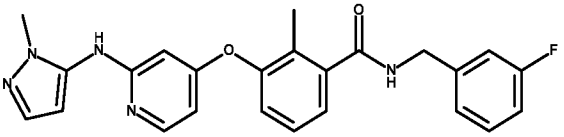
Formula (L)



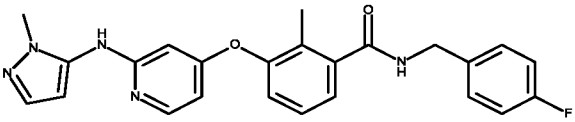
Formula (LI)



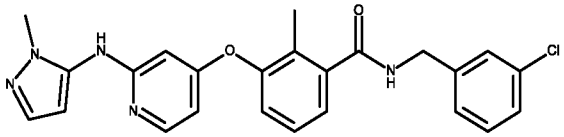
Formula (LII)



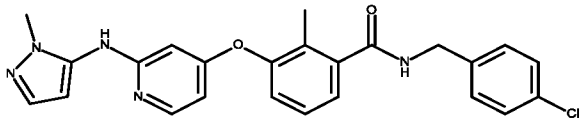
Formula (LIII)



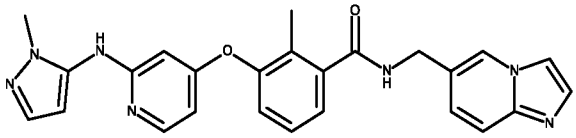
Formula (LIV)



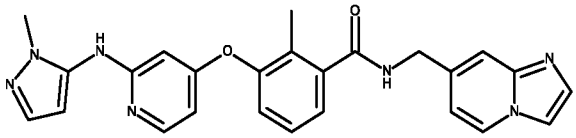
Formula (LV)



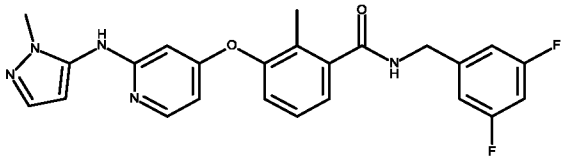
Formula (LVI)



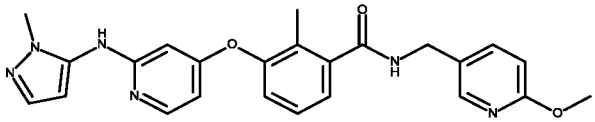
Formula (LVII)



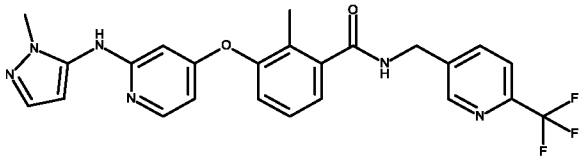
Formula (LVIII)



Formula (LIX)



Formula (LX)



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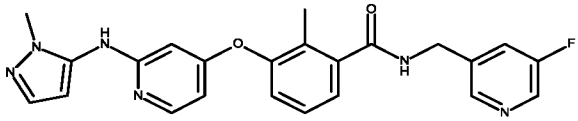
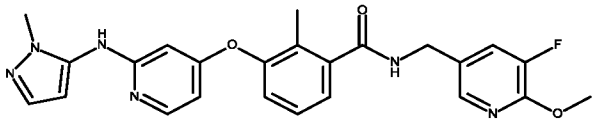


Formula (LXII)



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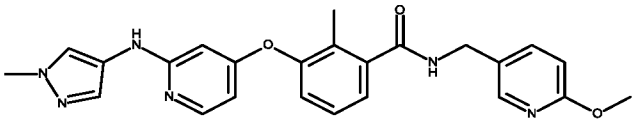
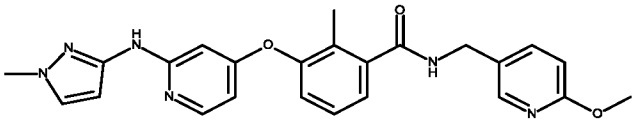
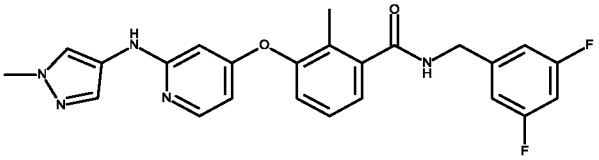


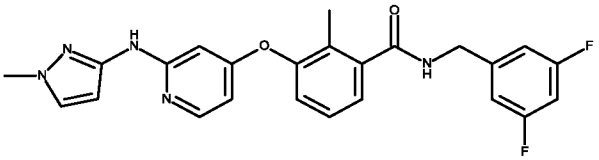
Formula (LXIV)



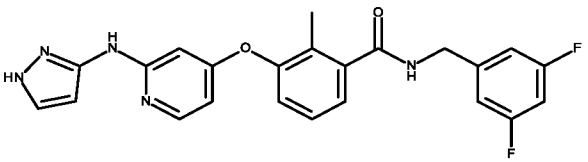
Formula (LXV)



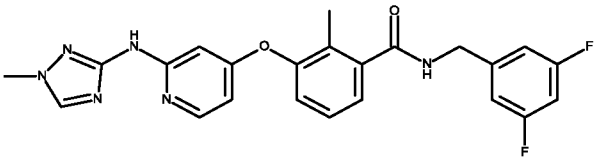
Formula (LXVI)



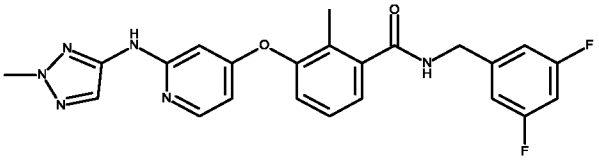
Formula (LXVII)



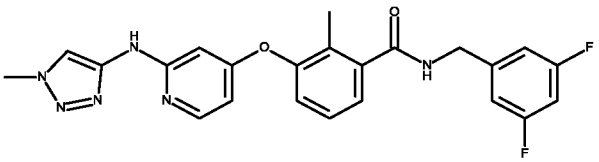
Formula (LXVIII)



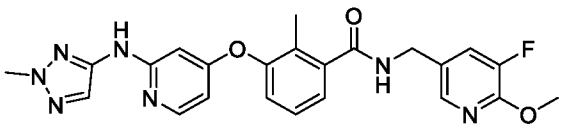
Formula (LXIX)



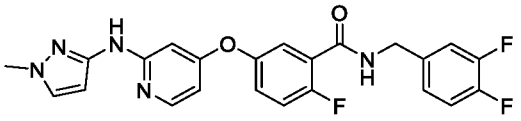
Formula (LXX)



Formula (LXXI)

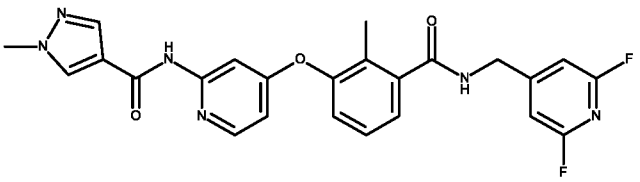


Formula (LXXI-1)

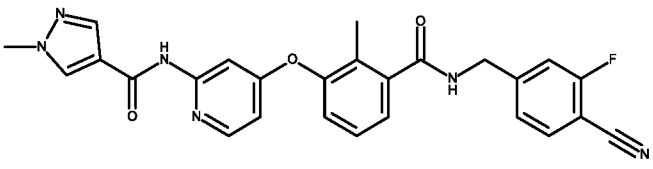


Formula (LXXI-2)

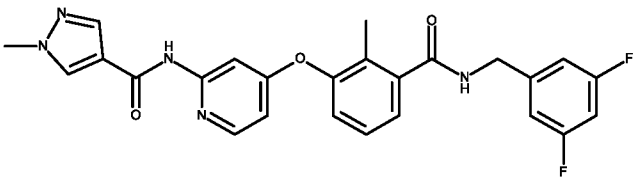
In a preferred embodiment of the present invention, the compound (C) according to general formula (IV-b) is a compound chosen among those of formulae (LXXII) to (CV) herein below:



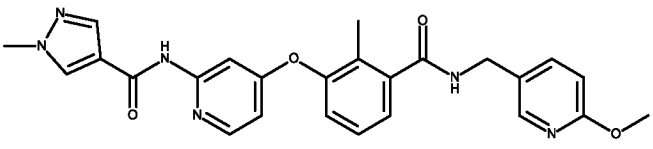
Formula (LXXII)



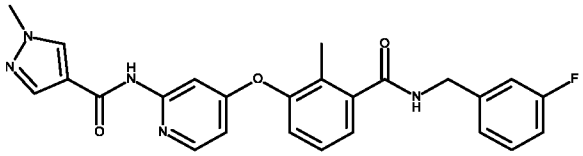
Formula (LXXIII)



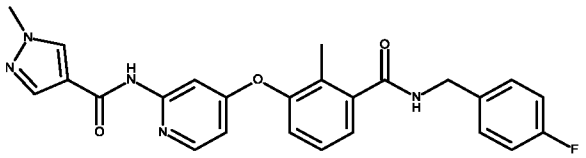
Formula (LXXIV)



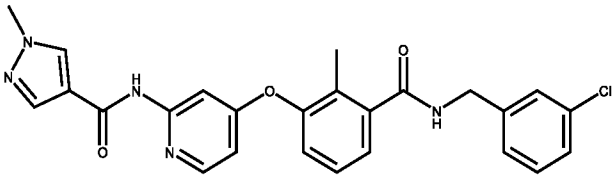
Formula (LXXV)



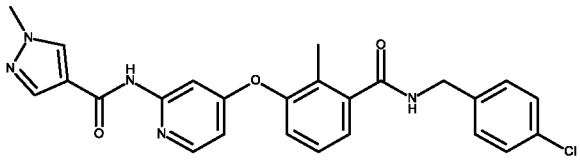
Formula (LXXVI)



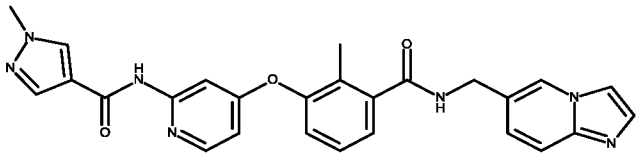
Formula (LXXVII)



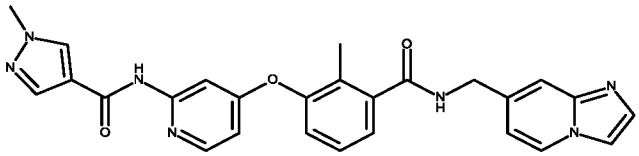
Formula (LXXVIII)



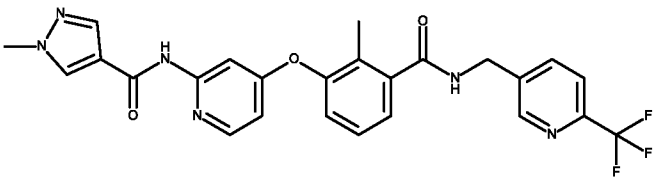
Formula (LXXIX)



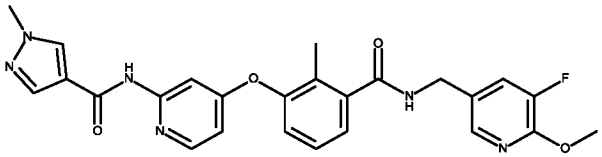
Formula (LXXX)



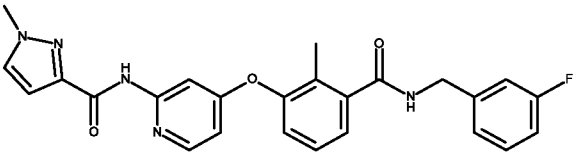
Formula (LXXXI)



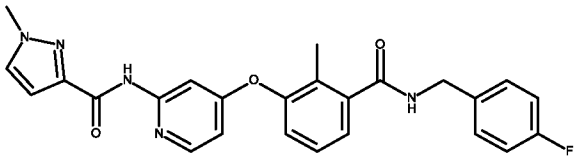
Formula (LXXXII)



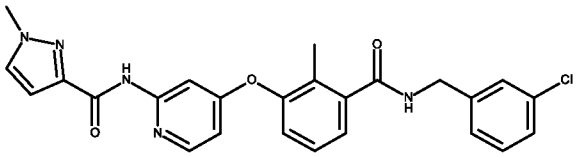
Formula (LXXXIII)



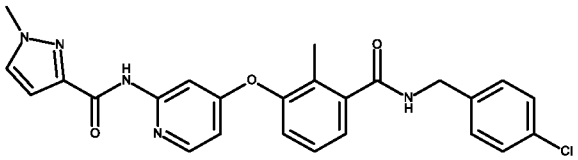
Formula (LXXXIV)



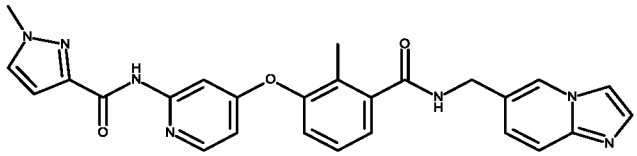
Formula (LXXXV)



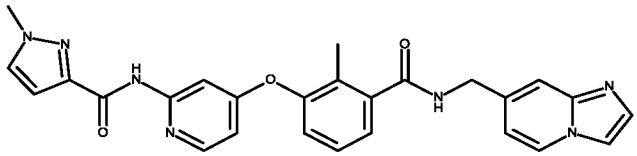
Formula (LXXXVI)



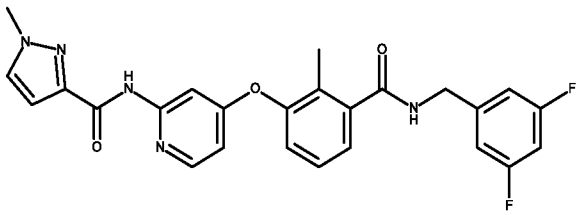
Formula (LXXXVII)



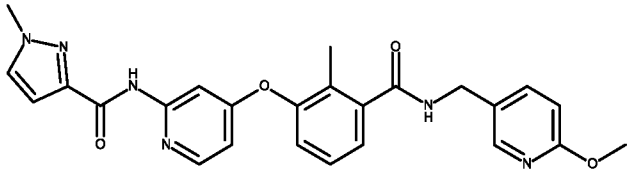
Formula (LXXXVIII)



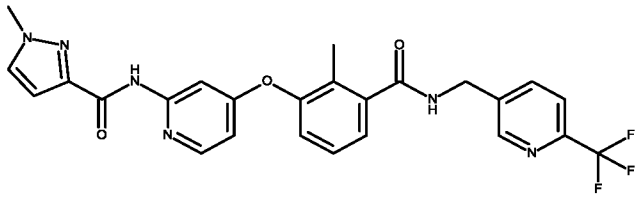
Formula (LXXXIX)



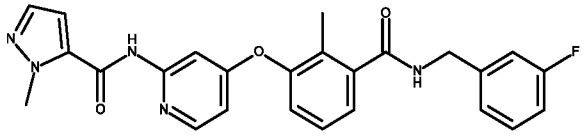
Formula (XC)



Formula (XCI)



Formula (XCII)



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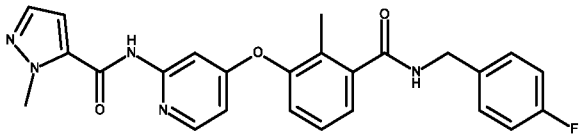
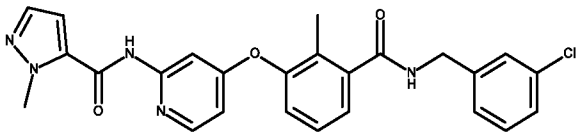
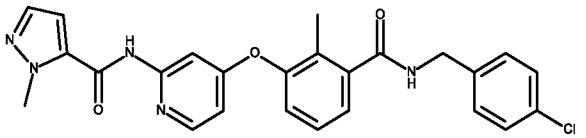


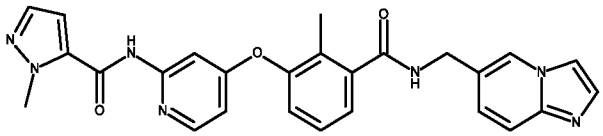
Formula (XCIV)



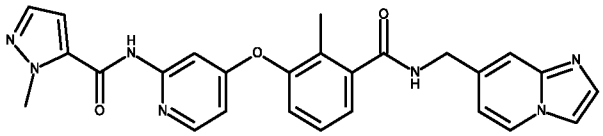
Formula (XCV)



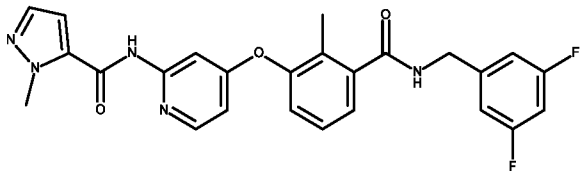
Formula (XCVI)



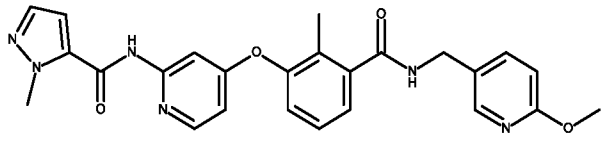
Formula (XCVII)



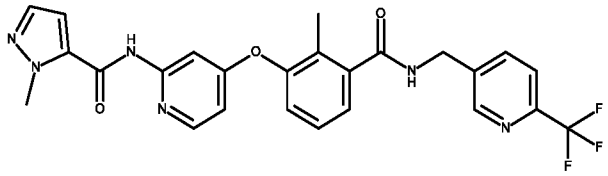
Formula (XCVIII)



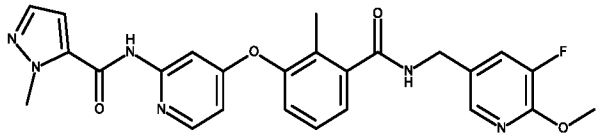
Formula (XCIX)



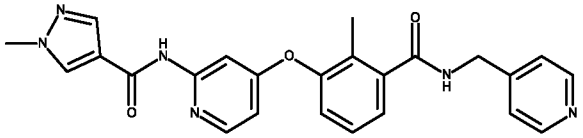
Formula (C)



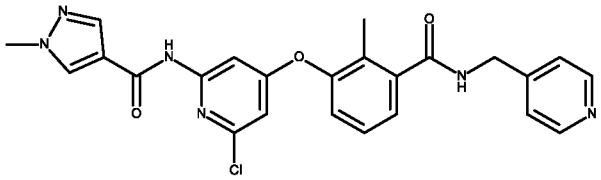
Formula (CI)



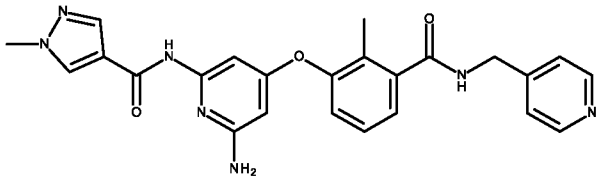
Formula (CII)



Formula (CIII)

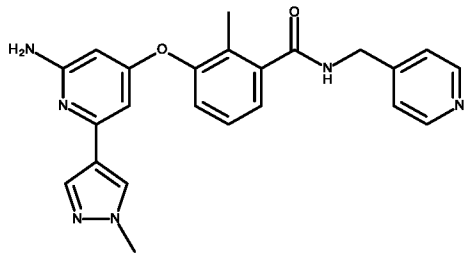


Formula (CIV)

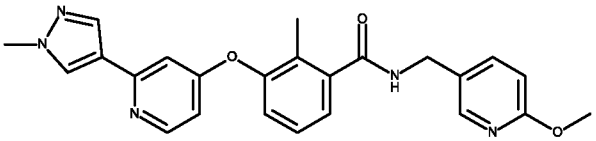


Formula (CV)

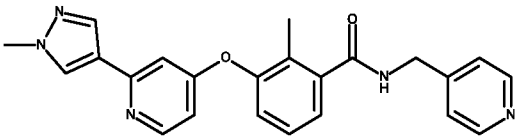
In a preferred embodiment of the present invention, the compound (C) according to general formula (IV-c) is a compound chosen among those of formulae (CVI) to (CXCVIII-5) herein below:



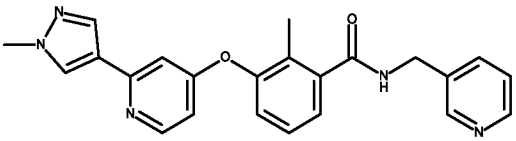
Formula (CVI)



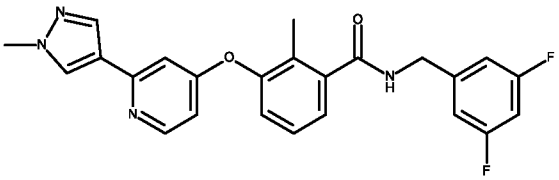
Formula (CVI-1)



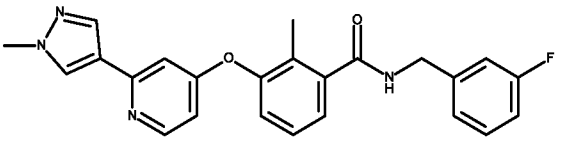
Formula (CVII)



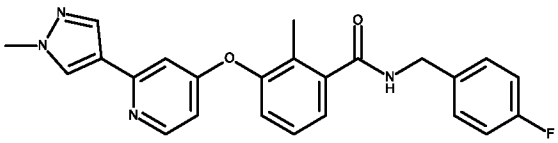
Formula (CVIII)



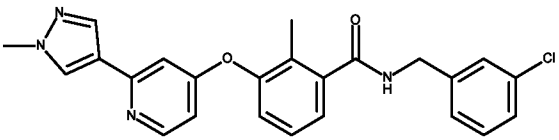
Formula (CIX)



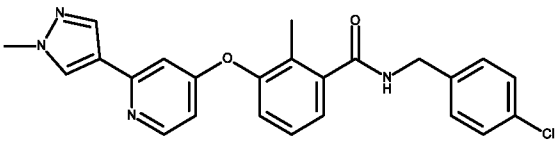
Formula (CX)



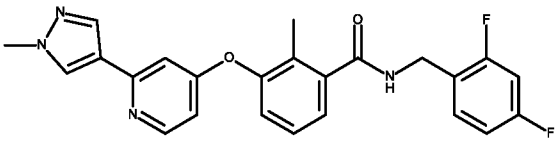
Formula (CXI)



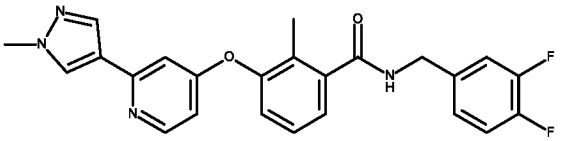
Formula (CXII)



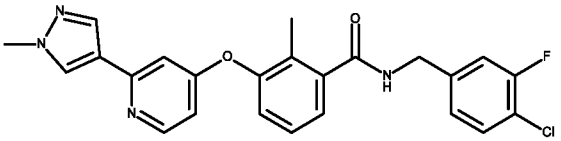
Formula (CXIII)



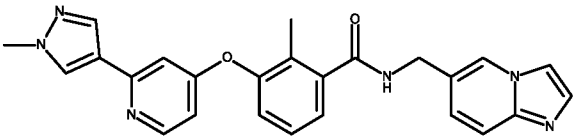
Formula (CXIV)



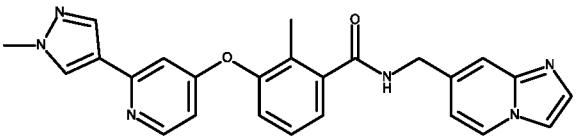
Formula (CXV)



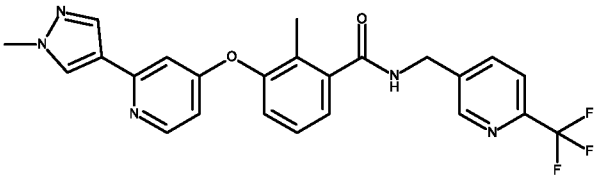
Formula (CXVI)



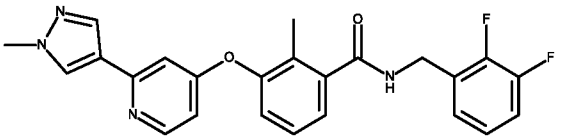
Formula (CXVII)



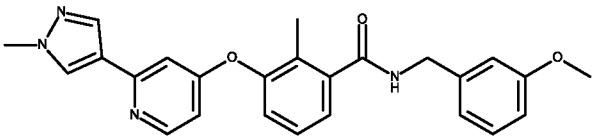
Formula (CXVIII)



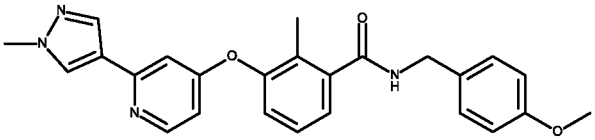
Formula (CXIX)



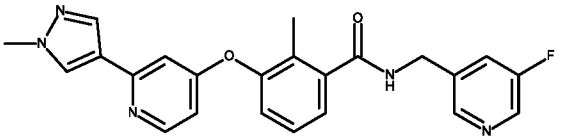
Formula (CXX)



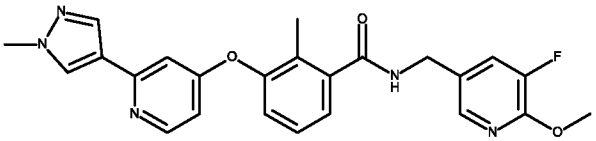
Formula (CXXI)



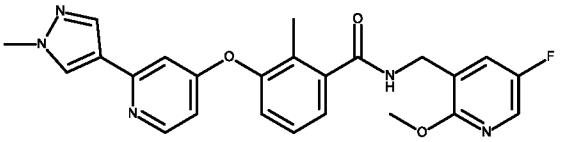
Formula (CXXII)



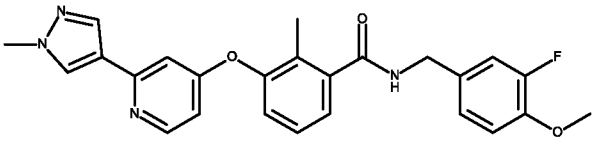
Formula (CXXIII)



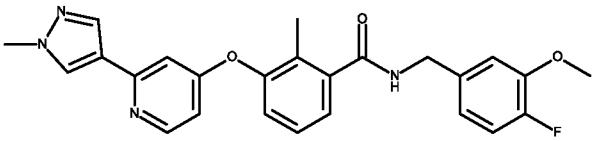
Formula (CXXIV)



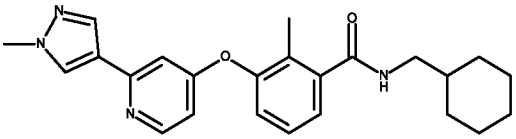
Formula (CXXV)



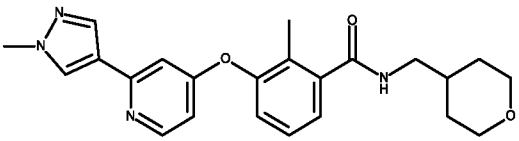
Formula (CXXVI)



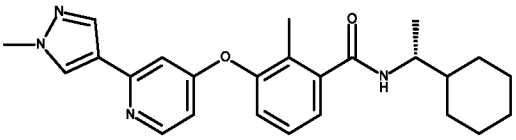
Formula (CXXVII)



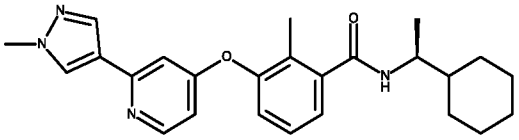
Formula (CXXVIII)



Formula (CXXIX)



Formula (CXXX)



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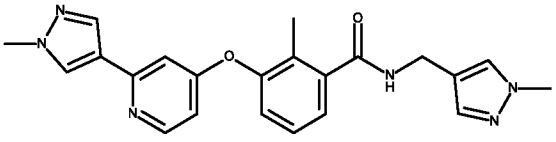
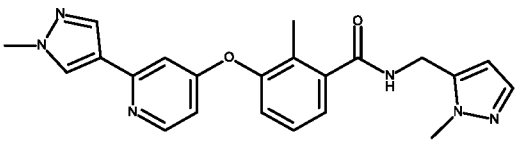


Formula (CXXXII)



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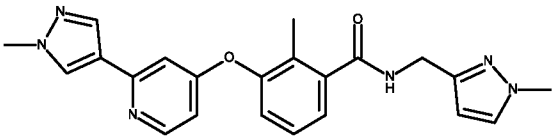

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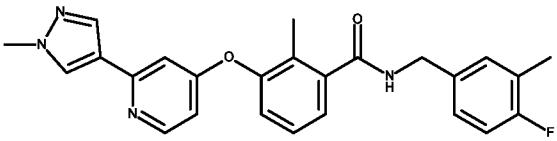

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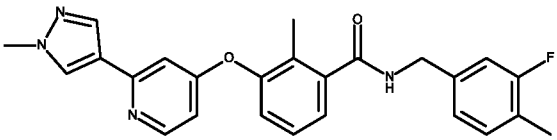

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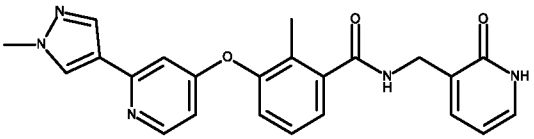

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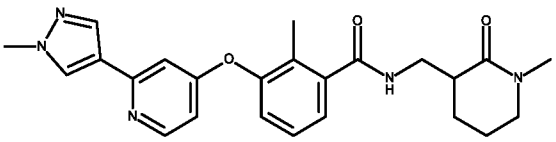

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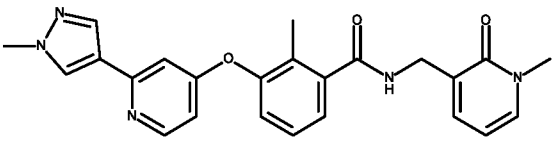

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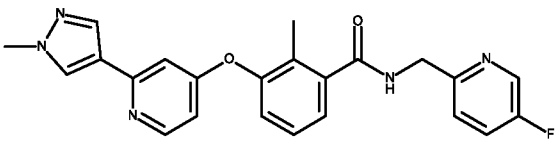

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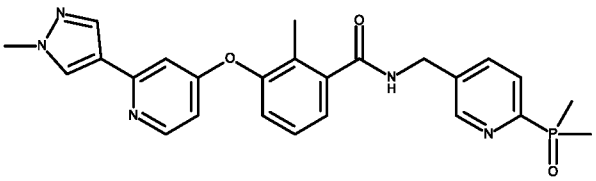

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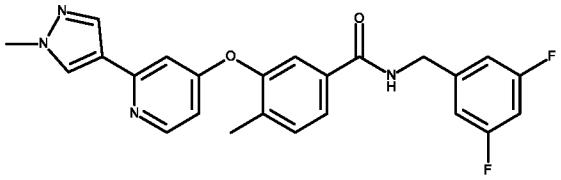

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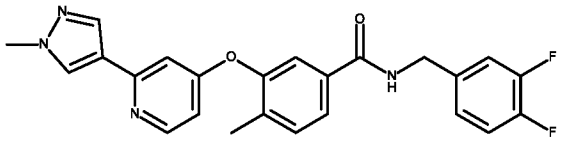

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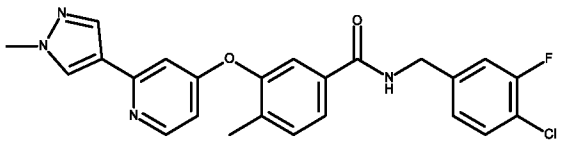

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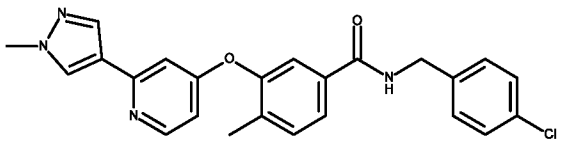

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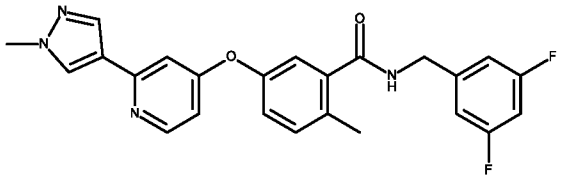

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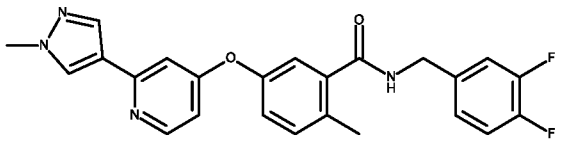

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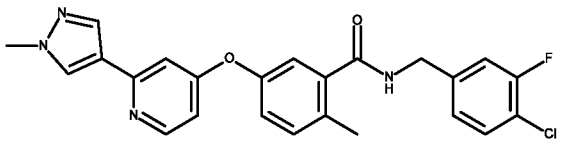

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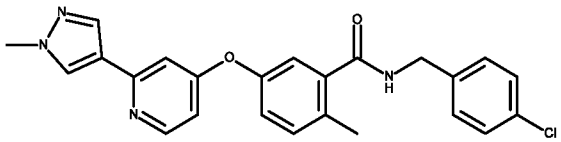

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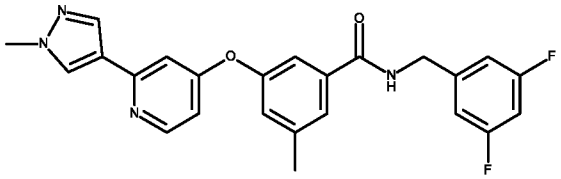

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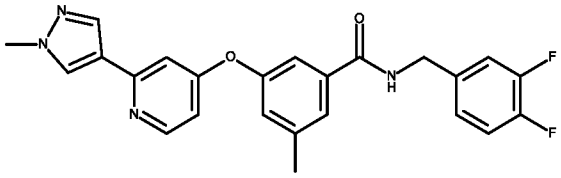

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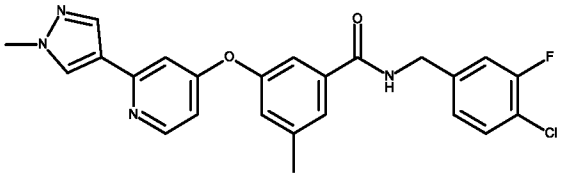

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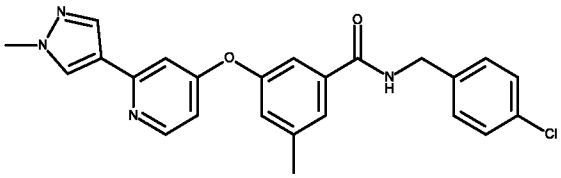

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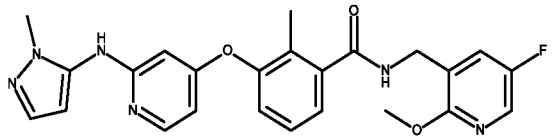

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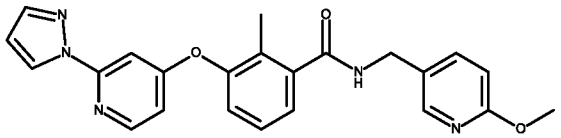

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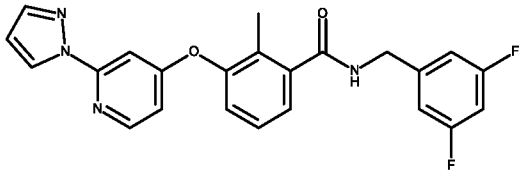

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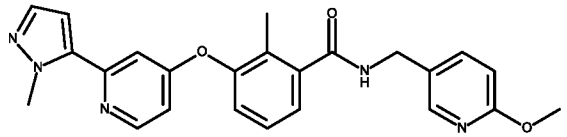

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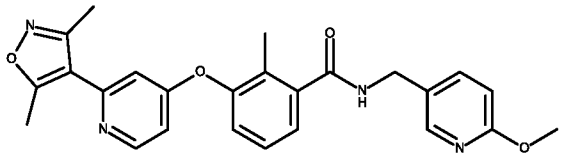

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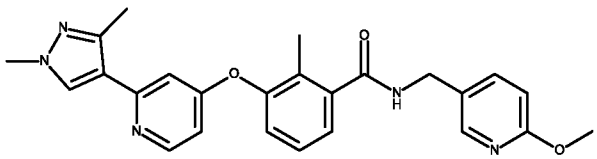

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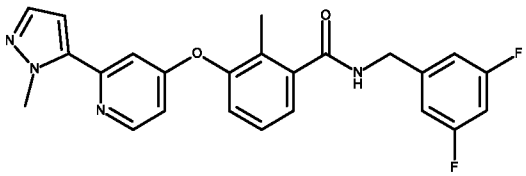

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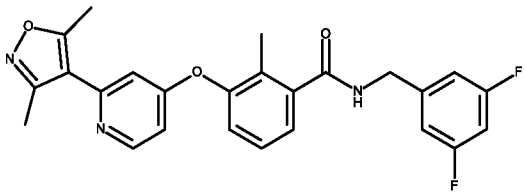

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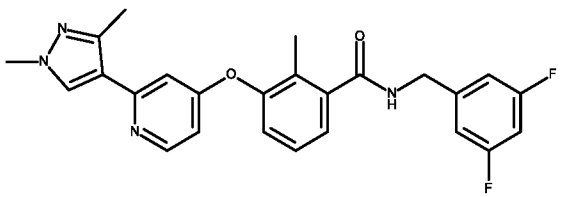

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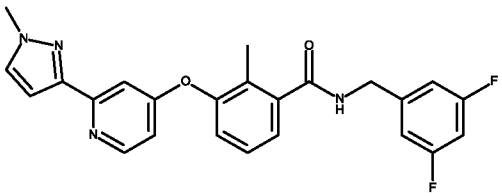

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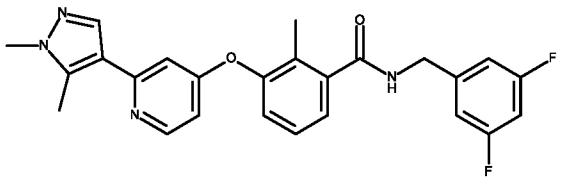

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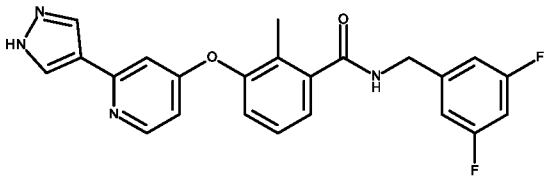

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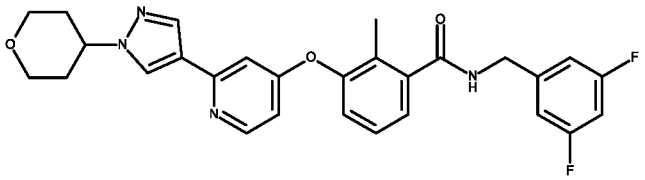

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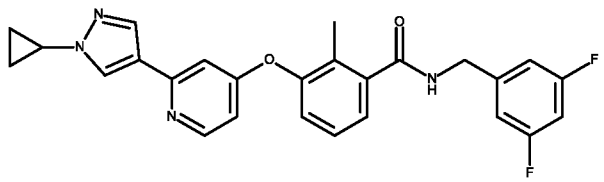

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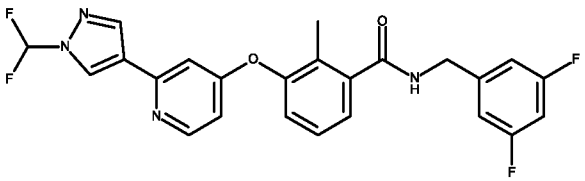

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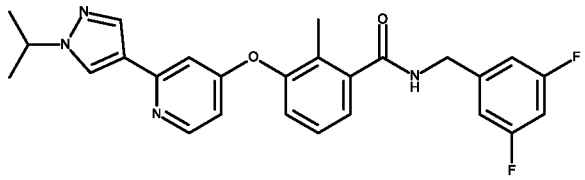

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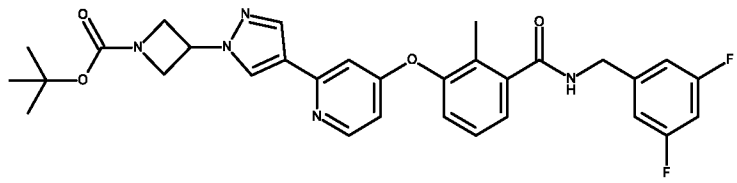

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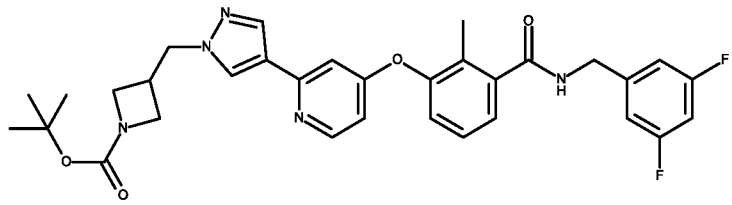

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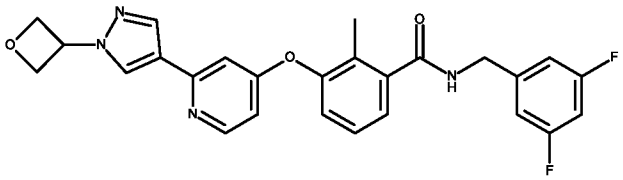

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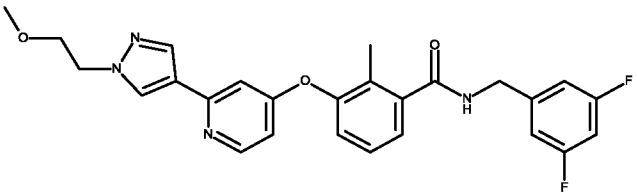

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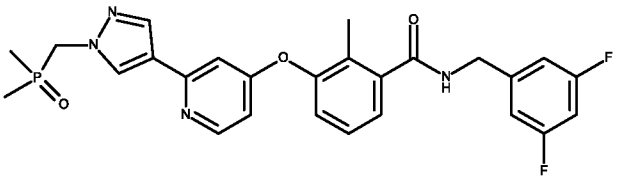

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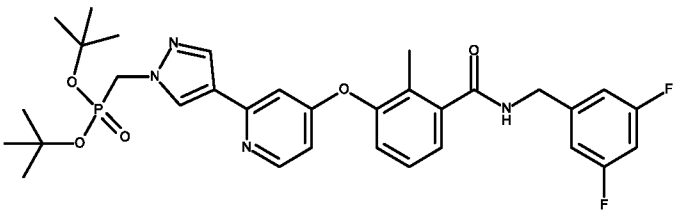

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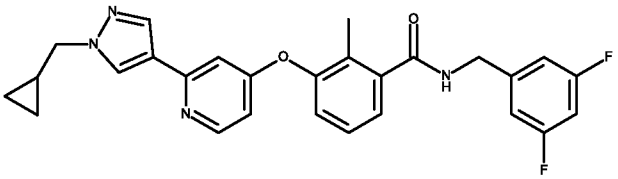

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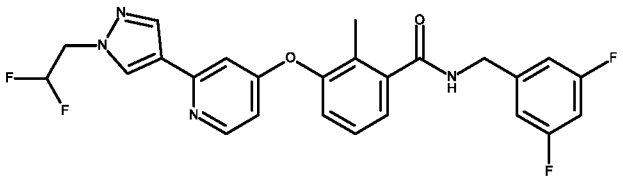

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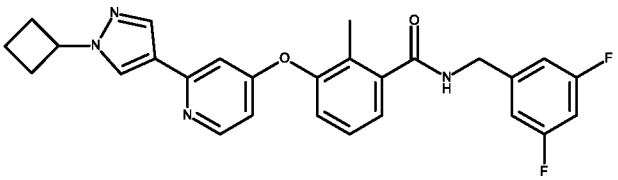

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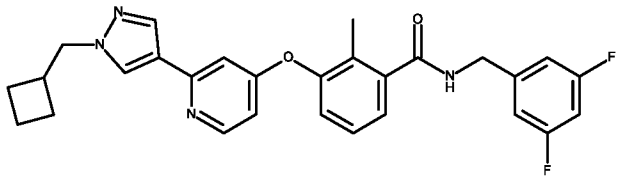

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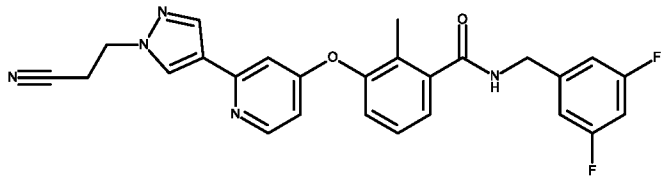
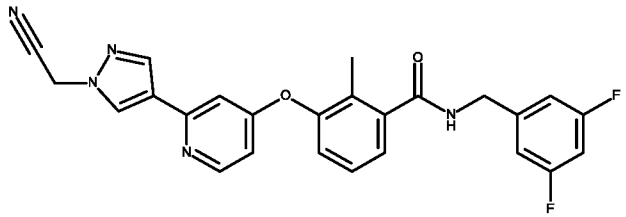
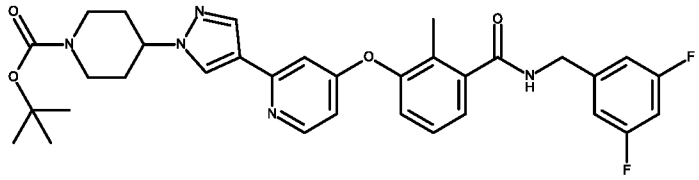


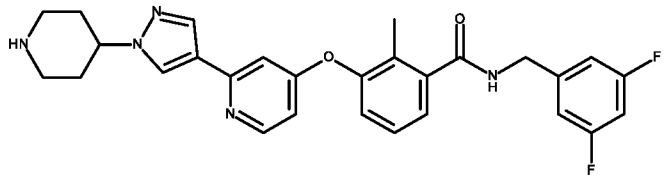
Formula (CLXXX)



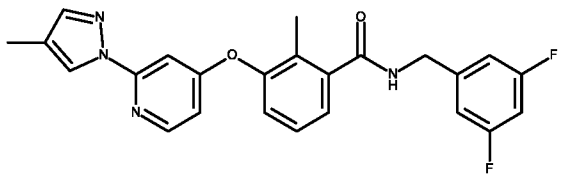
Formula (CLXXXI)



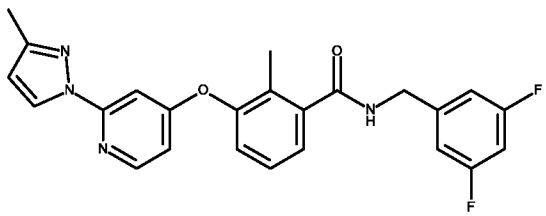
Formula (CLXXXII)



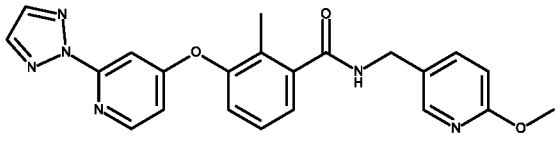
Formula (CLXXXIII)



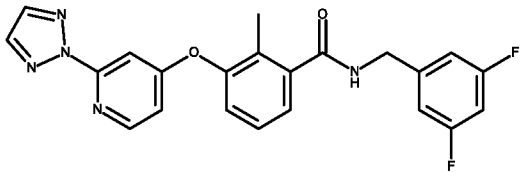
Formula (CLXXXIV)



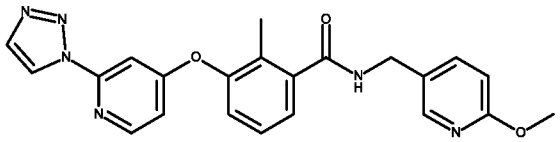
Formula (CLXXXV)



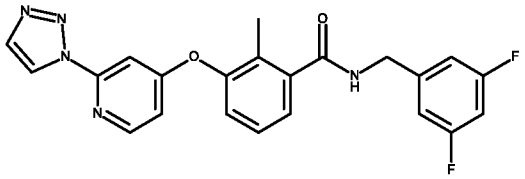
Formula (CLXXXVI)



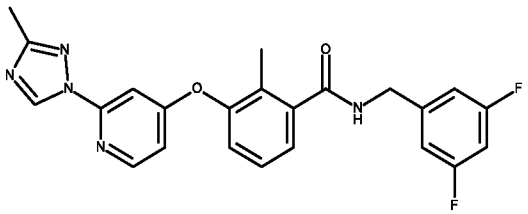
Formula (CLXXXVII)



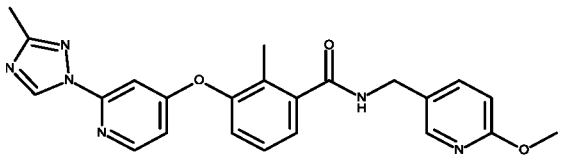
Formula (CLXXXVIII)



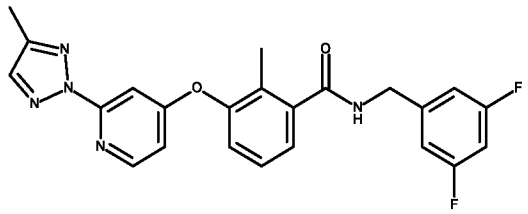
Formula (CLXXXIX)



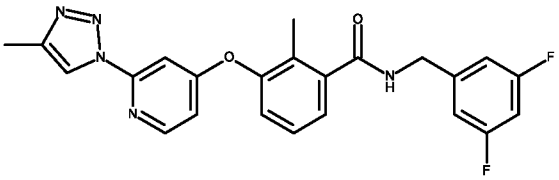
Formula (CXC)



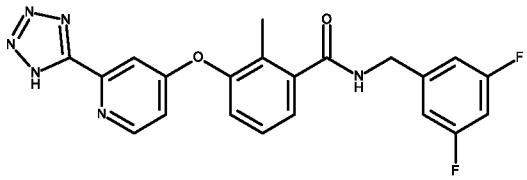
Formula (CXCI)



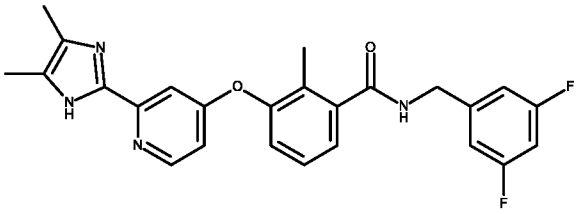
Formula (CXCII)



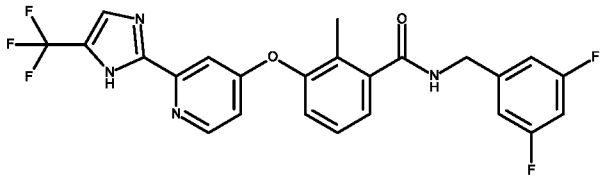
Formula (CXCIII)



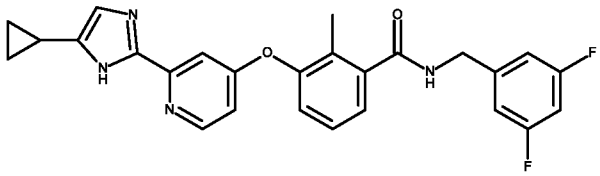
Formula (CXCIV)



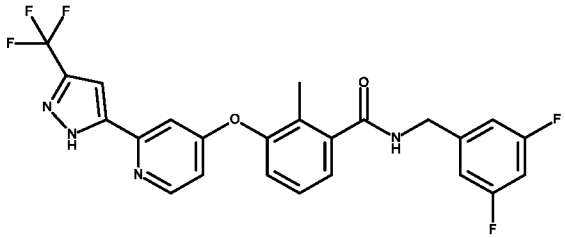
Formula (CXCV)



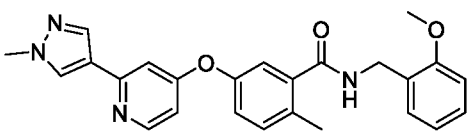
Formula (CXCVI)



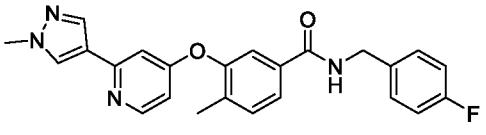
Formula (CXCVII)



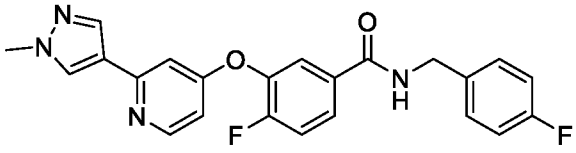
Formula (CXCVIII)



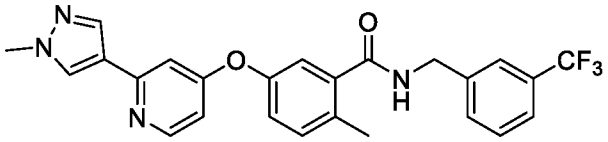
Formula (CXCVIII-1)



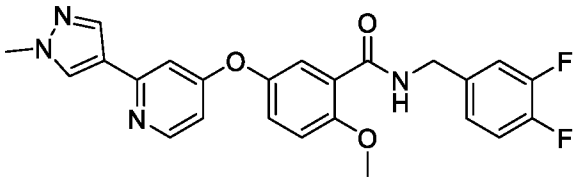
Formula (CXCVIII-2)



Formula (CXCVIII-3)

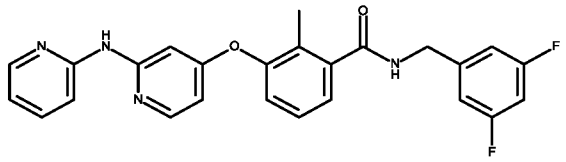


Formula (CXCVIII-4)

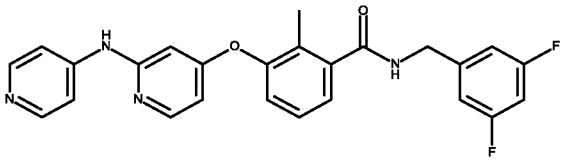


Formula (CXCVIII-5)

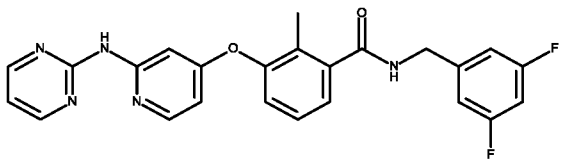
In a preferred embodiment of the present invention, the compound (C) according to general formula (VI-a) is a compound chosen among those of formulae (CXCIX) to (CCXII) herein below:



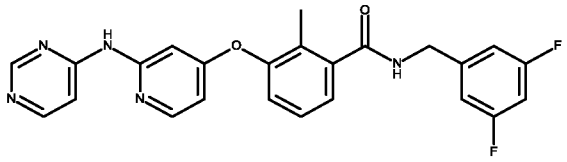
Formula (CXCIX)



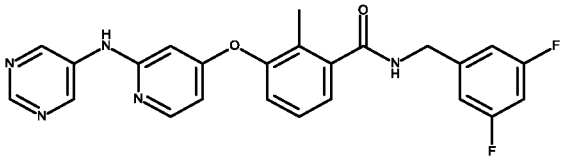
Formula (CC)



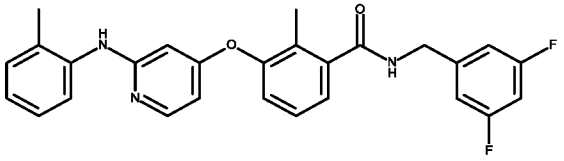
Formula (CCI)



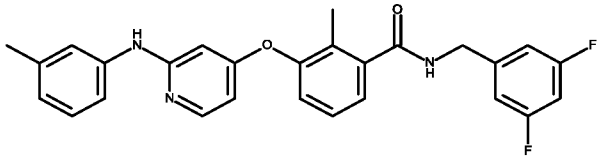
Formula (CCII)



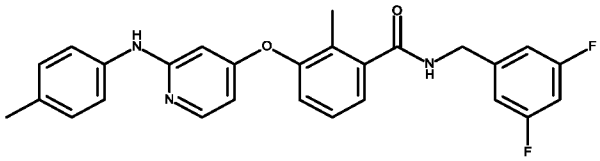
Formula (CCIII)



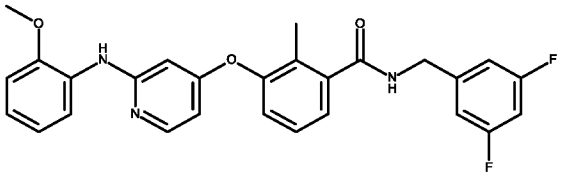
Formula (CCIV)



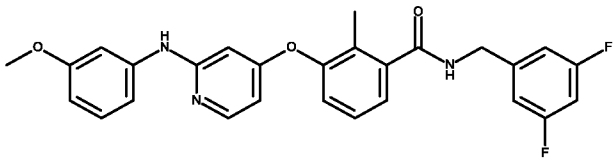
Formula (CCV)



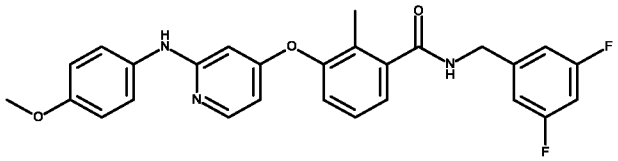
Formula (CCVI)



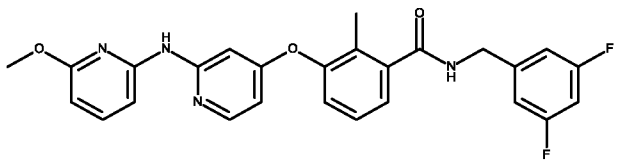
Formula (CCVII)



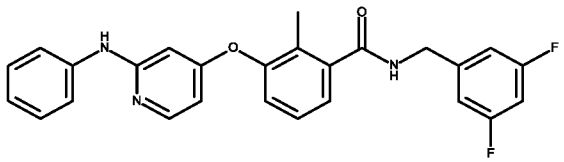
Formula (CCVIII)



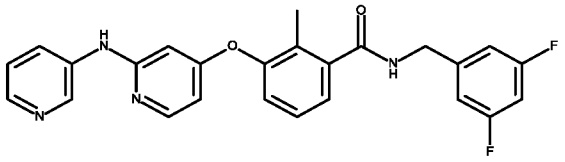
Formula (CCIX)



Formula (CCX)

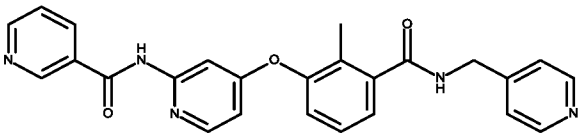


Formula (CCXI)

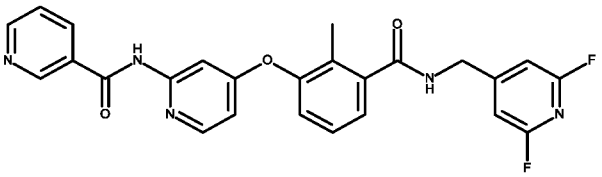


Formula (CCXII)

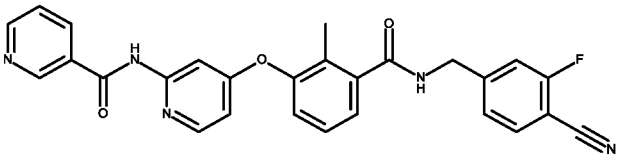
In a preferred embodiment of the present invention, the compound (C) according to general formula (VI-b) is a compound chosen among those of formulae (CCXIII) to (CCXV) herein below:



Formula (CCXIII)

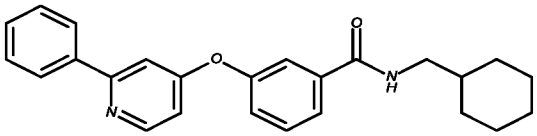


Formula (CCXIV)

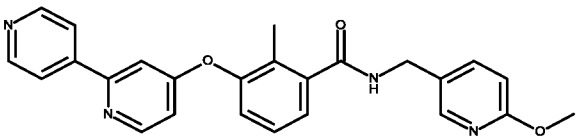


Formula (CCXV)

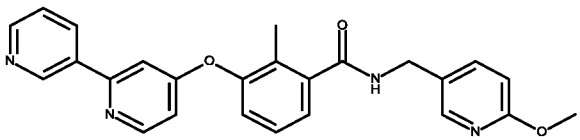
In a preferred embodiment of the present invention, the compound (C) according to general formula (VI-c) is a compound chosen among those of formulae (CCXVI) to (CCLX) herein below:



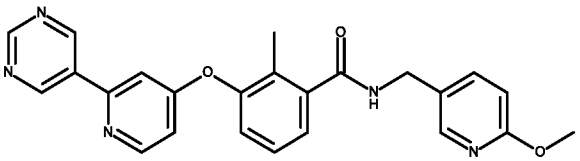
Formula (CCXVI)



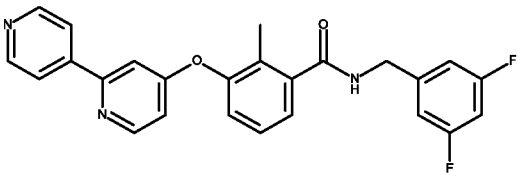
Formula (CCXVII)



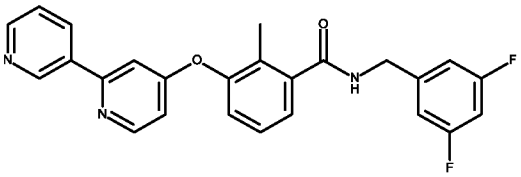
Formula (CCXVIII)



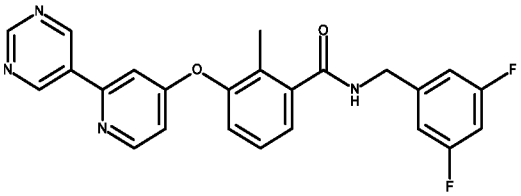
Formula (CCXIX)



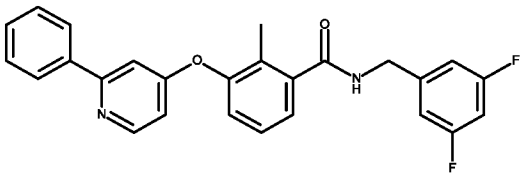
Formula (CCXX)



Formula (CCXXI)



Formula (CCXXII)



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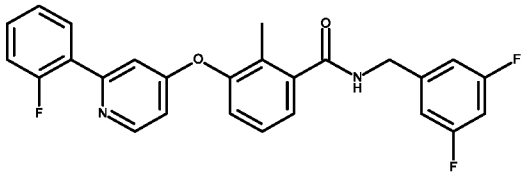

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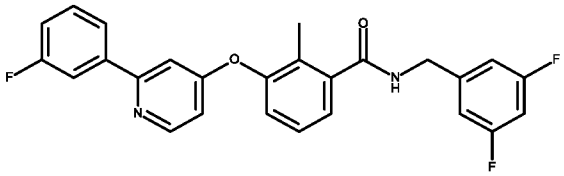

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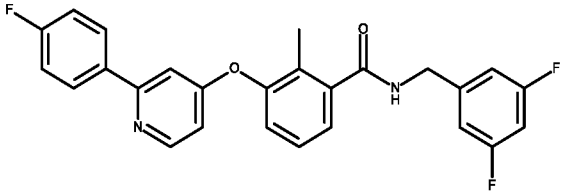

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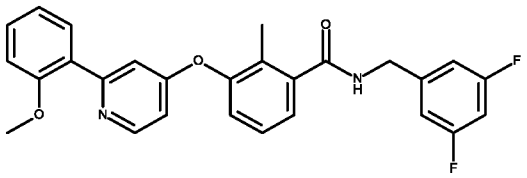

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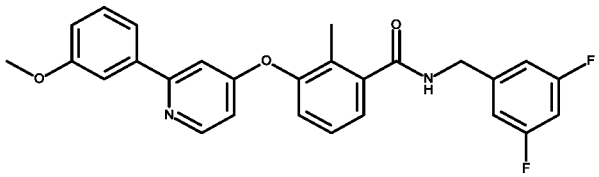

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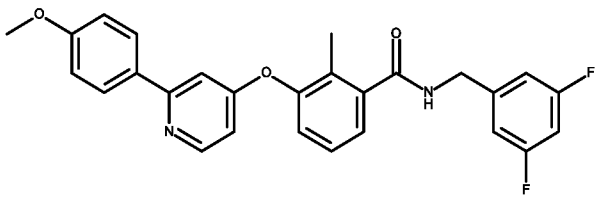

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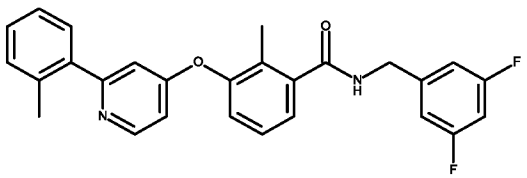

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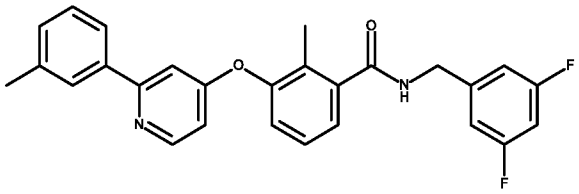

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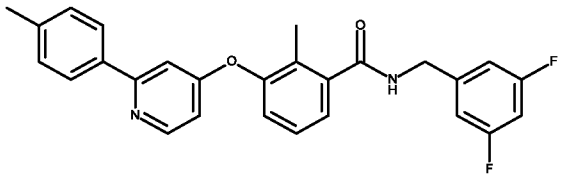

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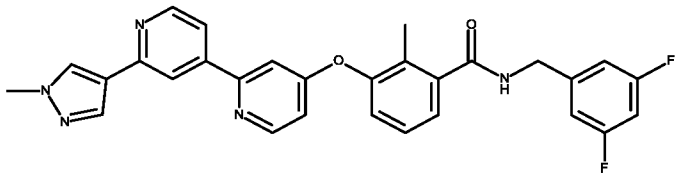

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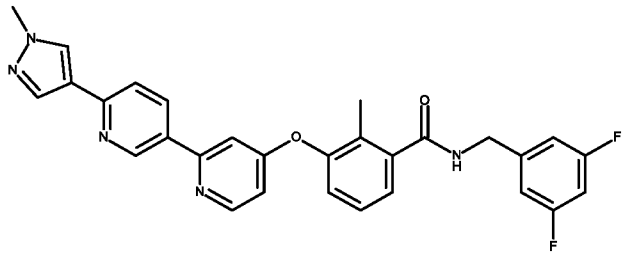

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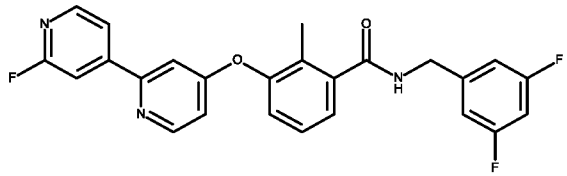

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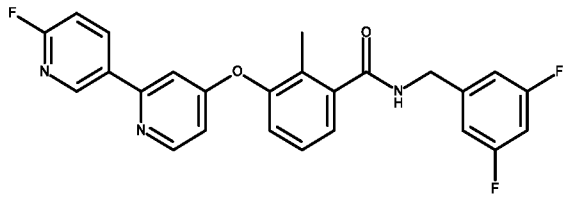

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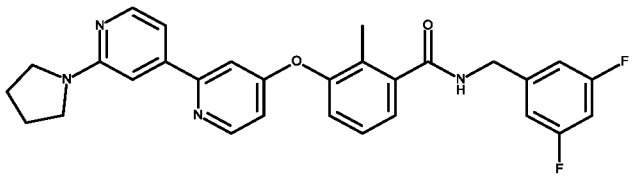

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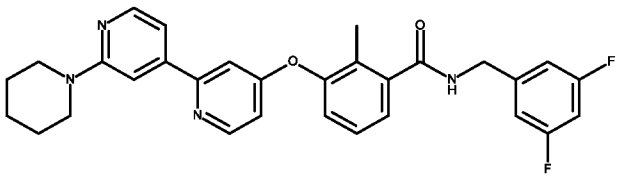

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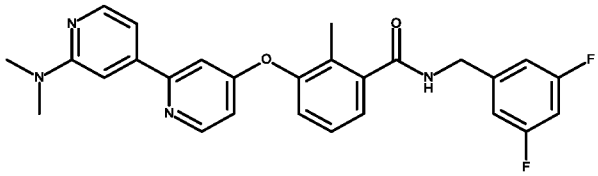

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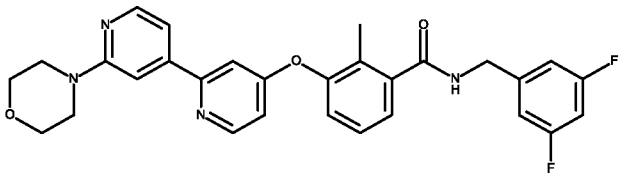

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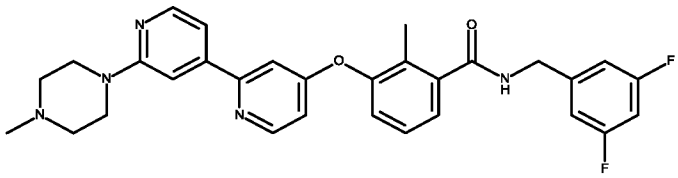

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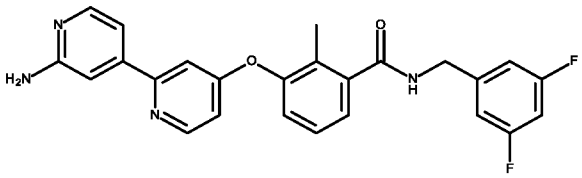

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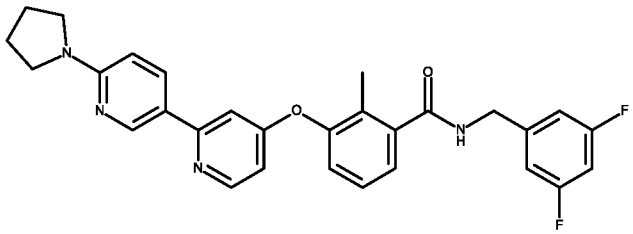

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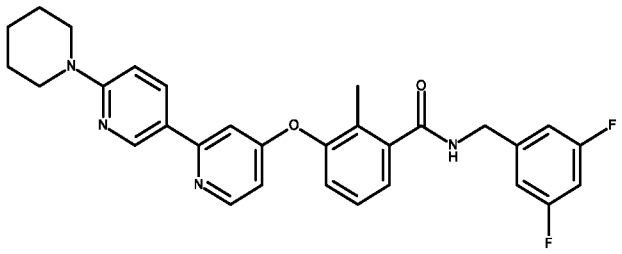

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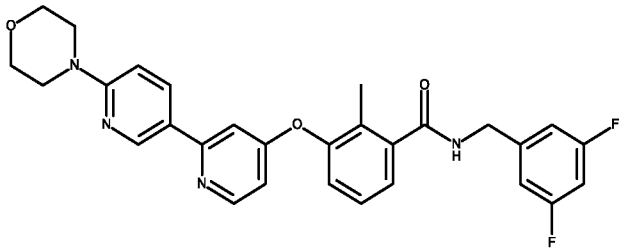

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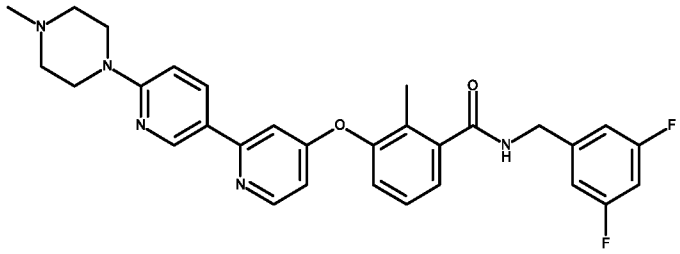

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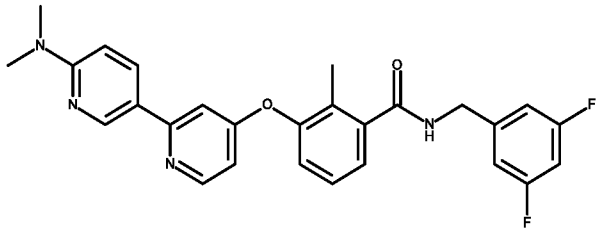

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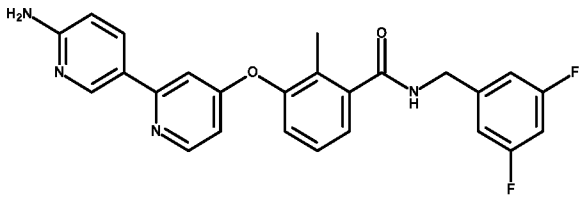

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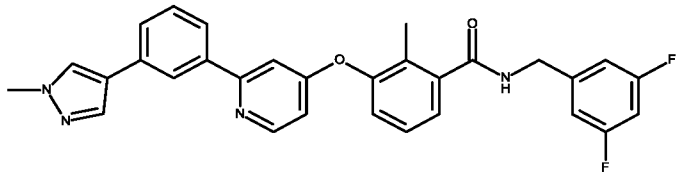

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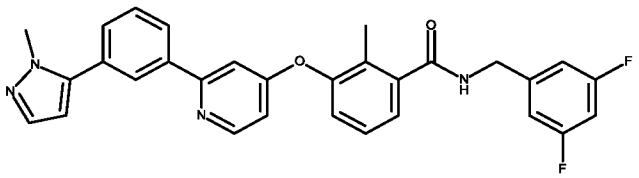

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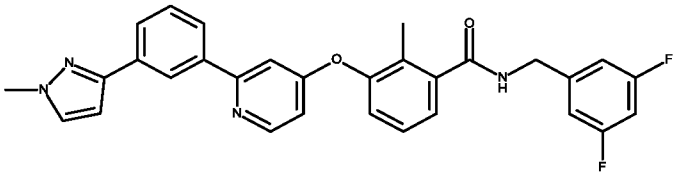

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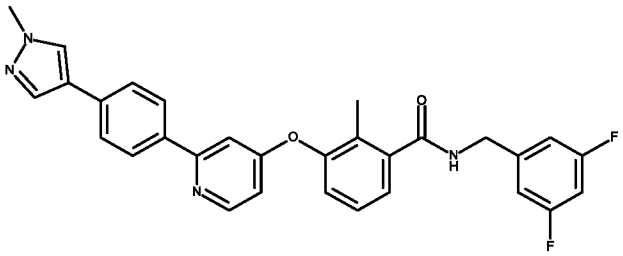

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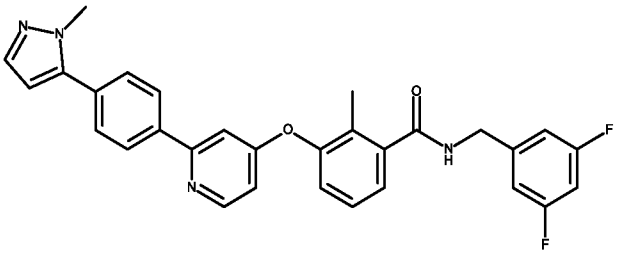

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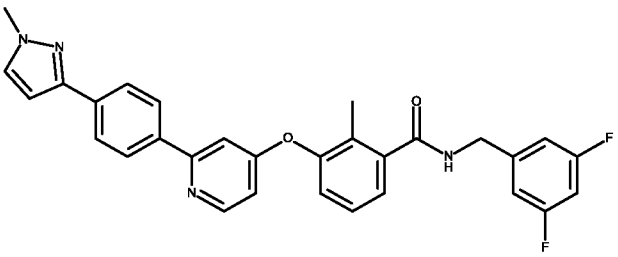

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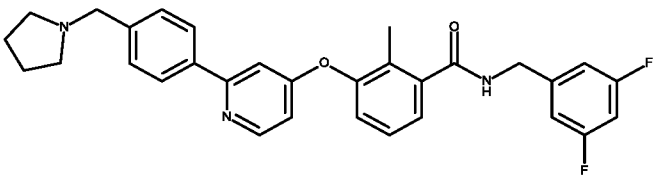

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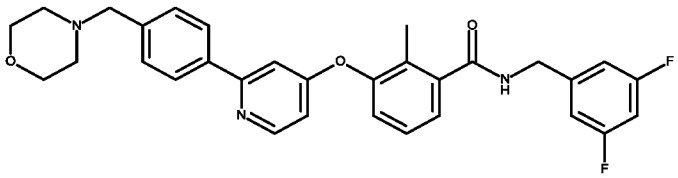
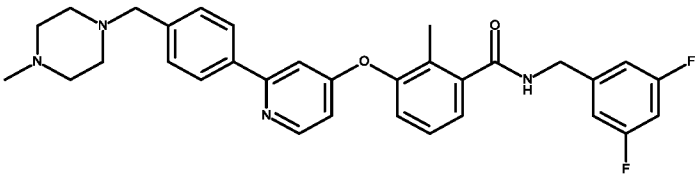
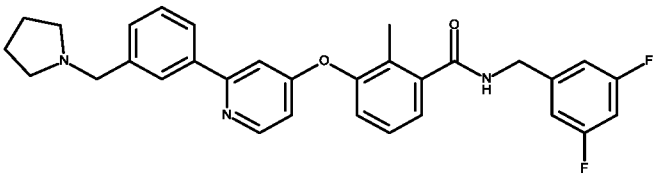


Formula (CCLVI)



Formula (CCLVII)



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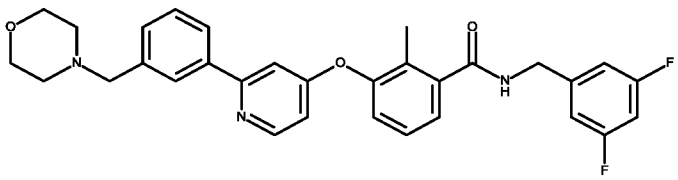
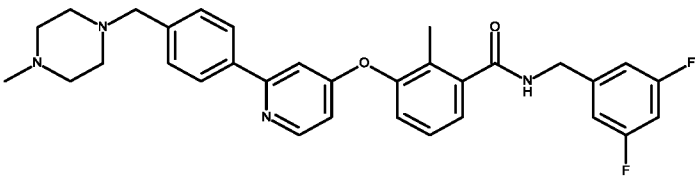
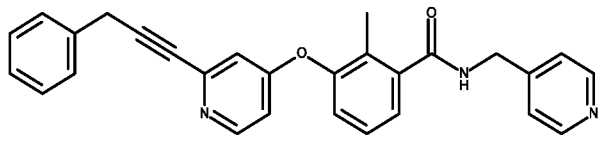


Formula (CCLIX)

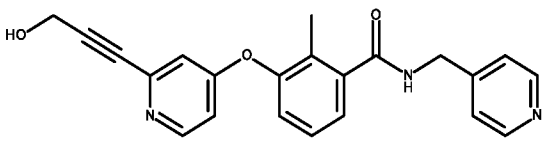


Formula (CCLX)

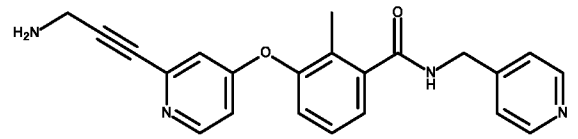
In a preferred embodiment of the present invention, the compound (C) according to general formula (VII-a) is a compound chosen among those of formulae (CCLXI) to (CCLXVII) herein below:



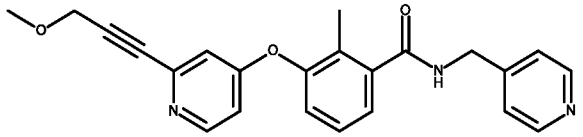
Formula (CCLXI)



Formula (CCLXII)



Formula (CCLXIII)



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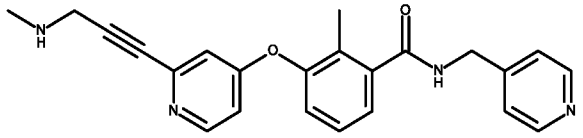
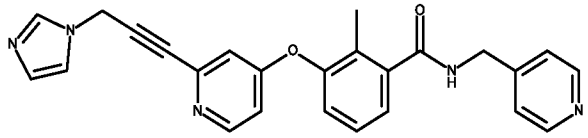
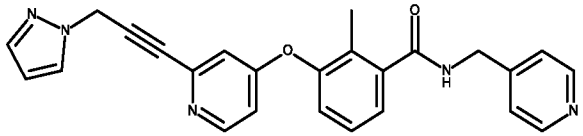


Formula (CCLXV)

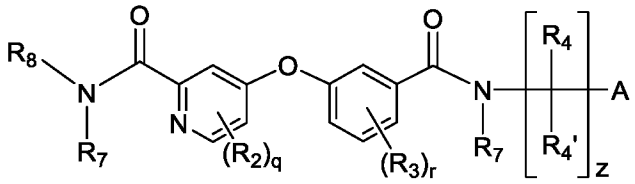


Formula (CCLXVI)

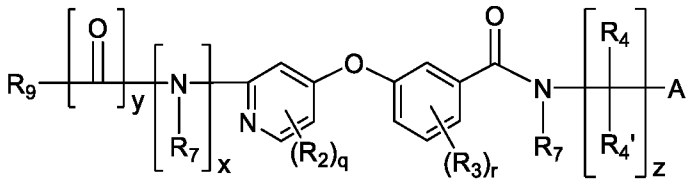


Formula (CCLXVII)

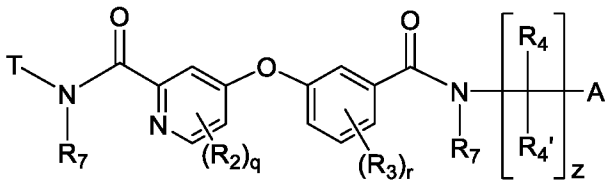
The present invention further relates to an *in vitro* method of inhibiting protein kinase activity which comprises contacting a protein kinase with a compound of formulae (I) to (VII) [compound (C), herein after], as defined above, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof,



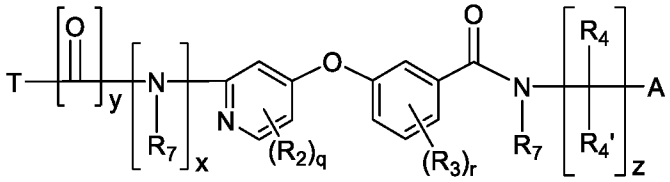
Formula (I)



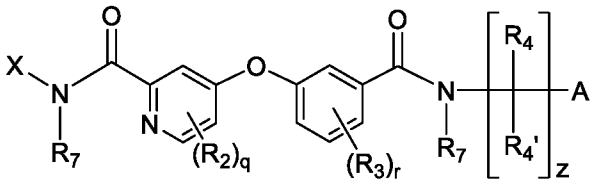
Formula (II)



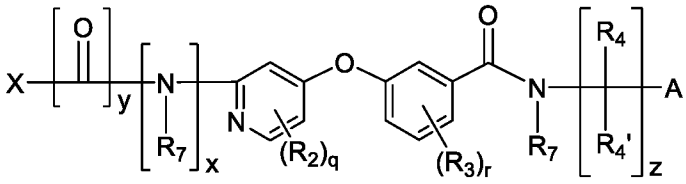
Formula (III)



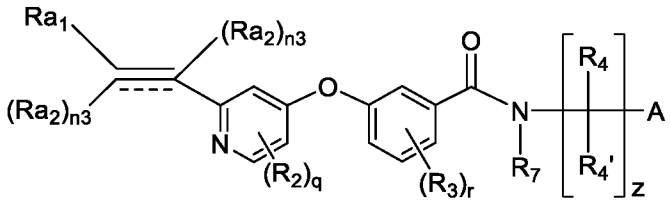
Formula (IV)



Formula (V)



Formula (VI)



Formula (VII)

wherein:

- each of A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}4}$ alkenyl, $C_{2\text{-}4}$ alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $S(O)R_{12}$, SO_2R_{12}, $SO_2N(R_{11})_2$, $S(O)_3R_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$,

and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl substituents is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, COR_{11}, $CON(R_{11})_2$, $OC(O)R_{11}$, CN, or OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, C_{1-6} alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl.

- each of R_4 and R'_4, independently from each other and at each occurrence, are selected from hydrogen or C_{1-6} alkyl, and z is an integer in the range from 0 to 2; with the proviso that when z = 0, then A and R_7 may form together a saturated or unsaturated cyclic moiety;
- each of R_7, independently from each other and at each occurrence is selected from hydrogen, C_{1-6} alkyl, cycloalkyl, wherein said alkyl and cycloalkyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, and CF_3;
- each of R_3, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{21}, SR_{21}, $N(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $OC(R_{21})_2O$, and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl,

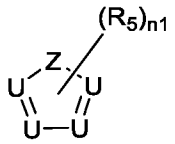
heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of r is an integer in the range from 0 to 3; with the proviso that when $R_3 = NR_{21}$, and $R_7 = H$, then R_3 and NR_7 may form together a saturated or unsaturated cyclic moiety;

- each of R_2, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CF_3, CN, NO_2, OR_{21}, SR_{21}, $N(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, $OC(R_{21})_2O$ and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, CF_3, COR_{21}, $CON(R_{21})_2$, $C(O)OR_{21}$, $N(R_{21})_2$, CN, or OR_{21}, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituent is further optionally substituted with heterocyclyl, $N(R_{11})_2$, or OR_{11}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of q is an integer in the range from 0 to 2;
- each of x and y are independently integers equal to 0 or 1;
- R_8 is independently selected from the group consisting of C_{6-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen

atom, an aryl group, an aralkyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl;

- R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, $N(R_{11})_2$ and CN, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, an heterocyclyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl optionally substituted with a C_{1-4} alkyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl, with the proviso that if x = 1 and y = 0, R_9 is different from heterocyclyl, and from C_{1-6} alkyl wherein said alkyl is optionally substituted with heterocyclyl; and with the proviso that if x=0 and y=0, R_9 is different from hydrogen, and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$; with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.

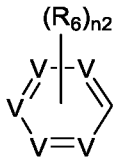
- each of T is independently the moiety of formula (T-a) herein below:



(T-a)

wherein:

- each of U, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen or C_{1-4} alkyl; with the proviso that at least one U is different from N;
- each of Z, independently from each other and at each occurrence is selected from $C(R)_2$, O, S and NR_7, wherein R, independently from each other and at each occurrence is selected from hydrogen or an C_{1-6} alkyl which is optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein R_7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, cycloalkyl, heterocyclyl, aryl, aralkyl and CF_3;
- each of R_5, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n1 is an integer in the range from 0 to 2;
- each of X is independently the moiety of formula (X-a) herein below:



(X-a)

wherein :

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from hydrogen or C_{1-4} alkyl;
- each of R_6, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n2 is an integer in the range from 0 to 4;
- the dash bond represents an optional triple bond;
- R_{a1} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl,

wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl.

- each of R_{a2}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl; and wherein n3 is an integer equal to 0 or 1; with the proviso that when the dash bond represents a triple bond, n3 is 0;

wherein said cycloalkyl is a monocyclic, bicyclic or tricyclic ring system of 3-6 ring members per ring; said heterocyclyl is a saturated, partially saturated or completely saturated monocycle, bicycle or tricycle containing 3 to 12 carbon atoms and 1 or 2 heteroatoms independently selected from O or N; said aryl is phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of 5-7 ring members; said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

It is further understood that all definitions and preferences as described for compound (C) above equally apply for this embodiment and all further embodiments, as described below.

As used in the foregoing and hereinafter, the following definitions apply unless otherwise noted.

The term halo - alone or in combination means all halogens, that is,

chloro (Cl), bromo (Br), fluoro (F), iodo (I).

The term alkyl - alone or in combination means an alkane-derived radical containing from 1 to 15 carbon atoms, unless otherwise specified, for example C_{F-G} alkyl defines a straight or branched alkyl radical having from F to G carbon atoms, e.g. C_{1-4} alkyl defines a straight or branched alkyl radical having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, l-butyl, 2-butyl, 2-methyl-1-propyl. An alkyl group may be a straight chain alkyl or branched alkyl. Preferably, straight or branched alkyl groups containing from 1-10, more preferably 1 to 8, even more preferably 1-6 and most preferably 1-4, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like. Alkyl also includes a straight chain or branched alkyl group that contains or is interrupted by a cycloalkyl portion. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. Examples of this include, but are not limited to, 4-(isopropyl)-cyclohexylethyl or 2-methyl-cyclopropylpentyl.

The term alkenyl - alone or in combination means a straight or branched hydrocarbon containing 2-15 more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms, unless otherwise specified and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Examples of alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, cyclohexenyl, cyclohexenylalkyl and the like. Alkenyl also includes a straight chain or branched alkenyl group that contains or is interrupted by a cycloalkyl portion. Carbon to carbon double bonds may be either contained within a cycloalkyl portion, with the exception of cyclopropyl, or within a straight chain or branched portion.

The term alkynyl - alone or in combination means a straight or branched hydrocarbon containing 2-15 more preferably 2-10, even more preferably 2-8, most preferably 2-4, carbon atoms containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl and the like.

The term aryl - alone or in combination means phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of

preferably 5-7, more preferably 5-6, ring members and/or optionally substituted with 1 to 5 groups or substituent. An aryl may be optionally substituted whereby the substituent is attached at one point to the aryl or whereby the substituent is attached at two points to the aryl to form a bicyclic system e.g. benzodioxole, benzodioxan, benzimidazole.

The term heteroaryl - alone or in combination means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3, heteroatoms independently selected from the group O, S, and N, and optionally substituted with 1 to 5 groups or substituents. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzisoxazolyl, benzothiophenyl, dibenzofuran, and benzodiazepin-2-one-5-yl, and the like.

The term heterocyclyl - alone or in combination is intended to denote a saturated, partially unsaturated or completely unsaturated monocycle, bicycle, or tricycle having 3 to 12 carbon atoms and containing 1 or 2 heteroatoms each independently selected from O, S, P or N, and are optionally benzo fused or fused heteroaryl of 5-6 ring members and/or are optionally substituted as in the case of cycloalkyl. Heterocycyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment is at a carbon or nitrogen atom. In each case the heterocyclyl may be condensed with an aryl to form a bicyclic ring system.

The term cycloalkyl refers to a cyclic or polycyclic alkyl group containing 3 to 7 carbon atoms. Preferably, cycloalkyl groups are monocyclic, bicyclic or tricyclic ring systems of 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl and the like.

The term aralkyl refers to organic compounds containing an aromatic

nucleus to which an alkyl radical is bonded. These alkyl radicals include methyl, ethyl, propyl, butyl, octyl, etc. radicals. The term aralkyl is thus seen to include aralkyl hydrocarbons such as the alkyl benzenes, and the various alkyl naphthalenes. From this definition of the term aralkyl compound it is seen that the term includes compounds such as benzyl, the three isomeric xylyls, the two isomeric trimethyl benzenes, ethyl benzene, p-methyl biphenyl, a-methyl naphthalene, etc.

The present invention further relates to a pharmaceutical composition comprising a carrier, and as active ingredient an effective amount of a compound (C) formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and as defined in any one of the embodiments presented herein.

The present invention relates to a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-c), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2) as specified herein, and as defined in any one of the embodiments presented herein, for use as a medicament.

The present invention relates to a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and as defined in any one of the embodiments presented herein, for use in the treatment of a disease selected from from cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis,

systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases.

The present invention further relates to a method of inhibiting protein kinase activity in a warm-blooded animal said method comprising the administration to an animal in need thereof, of a kinase-inhibitory effective amount of a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and according to any one of the embodiments presented herein.

The present invention further relates to a method of inhibiting protein kinase activity in a warm-blooded animal said method comprising the administration to an animal in need thereof, of a kinase-inhibitory effective amount of a compound (C) formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and according to any one of the embodiments presented herein, wherein the protein kinase is selected from the group consisting of CSF1R, FLT3, Kit, PDGFRB (PDGFR beta), PDGFRA (PDGFR alfa), ABL1, ACVR1B (ALK4), AKT1 (PKB alpha), AMPK A1/B1/G1, AURKA (Aurora A), BTK, CDK1/cyclin B, CHEK1 (CHK1), CSNK1G2 (CK1 gamma 2), CSNK2A1 (CK2 alpha 1), DYRK3, EGFR (ErbB1), EPHA2, ERBB2 (HER2), FGFR1, FRAP1 (mTOR), GSK3B (GSK3

beta), IGF1R, IKBKB (IKK beta), INSR, IRAK4, JAK3, KDR (VEGFR2), LCK, MAP2K1 (MEK1), MAP4K4 (HGK), MAPK1 (ERK2), MAPK14 (p38 alpha), MAPK3 (ERK1), MAPK8 (JNK1), MARK2, MET (cMet), NEK1, PAK4, PHKG2, PIM1, PLK1, PRKACA (PKA), PRKCB1 (PKC beta I), ROCK1, RPS6KA3 (RSK2), RPS6KB1 (p70S6K), SRC, SYK, and TEK (Tie2). Preferably, the protein kinase is selected from the group consisting of CSF1R, FLT3, Kit, PDGFRB (PDGFR beta), PDGFRA (PDGFR alpha).

The present invention further relates to a method of treating a disease selected from cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases, in a warm-blooded animal said method comprising the administration to an animal in need thereof of an effective amount of a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and according to any one of the embodiments presented herein.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible

isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent. Whenever used hereinafter, the term "compounds (C) of formulae (I) to (VII) ", or "the present compounds" or similar terms, it is meant to include all the compounds (C) of formulae (I) to (VII), N-oxides, addition salts, and stereochemically isomeric forms. One embodiment comprises the compounds (C) of formulae (I) to (VII), or any subgroup of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), specified herein, as well as the N-oxides, salts, as the possible stereoisomeric forms thereof. Another embodiment comprises the compounds (C) of formula formulae (I) to (VII), or any subgroup of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), specified herein, as well as the salts as the possible stereoisomeric forms thereof.

The compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, have several centers of chirality and exist as stereochemically isomeric forms. The term "stereochemically isomeric forms" as used herein defines all the possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, may

possess.

Unless otherwise mentioned or indicated, the chemical designation of a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, encompasses the mixture of all possible stereochemically isomeric forms, which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or mixed with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term “stereoisomerically pure” concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms “enantiomerically pure” and “diastereomerically pure” should be understood in a similar way, but then having regard to the enantiomeric excess, and the diastereomeric excess, respectively, of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application procedures known in the art. For

instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphorsulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of the compounds (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

For some of the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, N-oxides, salts, solvates, and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined.

A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present to a compound (C) of formulae (I) to (VII) as specified

herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

For therapeutic use, salts of the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, are those wherein the counter-ion is pharmaceutically acceptable, which salts can be referred to as pharmaceutically acceptable acid and base addition salts. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), or formula (VII-a-2), as specified herein, are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid in an anion form. Appropriate anions comprise, for example, trifluoroacetate, acetate, benzenesulfonate , benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsyiate, carbonate,

chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, and the like. The counterion of choice can be introduced using ion exchange resins. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), or formula (VII-a-2), as specified herein, containing an acidic proton may also be converted into their nontoxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases in a cation form. Appropriate basic salts comprise those formed with organic cations such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and the like; and those formed with metallic cations such as aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and the like. Conversely said salt forms can be converted by treatment with an appropriate acid into the free form.

The term addition salt as used hereinabove also comprises the solvates which the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The N-oxide forms of the present compound (C) of formulae (I) to (VII)

as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called N-oxide.

It will be appreciated that the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, may have metal binding, chelating, complex forming properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, are intended to be included within the scope of the present invention.

Some of the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to

(VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylactically act against, to stabilize or reduce illnesses mediated by protein kinases in ill subjects or subjects being at risk of being ill, in particular a protein kinase selected from the group consisting of CSF1R, FLT3, Kit, PDGFRB (PDGFR beta), PDGFRA (PDGFR alfa), ABL1, ACVR1B (ALK4), AKT1 (PKB alpha), AMPK A1/B1/G1, AURKA (Aurora A), BTK, CDK1/cyclin B, CHEK1 (CHK1), CSNK1G2 (CK1 gamma 2), CSNK2A1 (CK2 alpha 1), DYRK3, EGFR (ErbB1), EPHA2, ERBB2 (HER2), FGFR1, FRAP1 (mTOR), GSK3B (GSK3 beta), IGF1R, IKBKB (IKK beta), INSR, IRAK4, JAK3, KDR (VEGFR2), LCK, MAP2K1 (MEK1), MAP4K4 (HGK), MAPK1 (ERK2), MAPK14 (p38 alpha), MAPK3 (ERK1), MAPK8 (JNK1), MARK2, MET (cMet), NEK1, PAK4, PHKG2, PIM1, PLK1, PRKACA (PKA), PRKCB1 (PKC beta I), ROCK1, RPS6KA3 (RSK2), RPS6KB1 (p70S6K), SRC, SYK, and TEK (Tie2). Preferably, the protein kinase is selected from the group consisting of CSF1R, FLT3, Kit, PDGFRB (PDGFR beta), PDGFRA (PDGFR alpha).

Examples of illnesses mediated by protein kinases include in particular of illnesses mediated by protein kinases include in particular cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases.

In still a further aspect, this invention relates to a process of preparing a

pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound (C) of formulae (I) to (VII), as specified herein, or of a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein.

Therefore, the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets.

Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other

ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to

(IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compound (C) of formulae (I) to (VII) as specified herein, or a compound of any of the subgroups of compounds of formula (II-a) to (II-b), (III-a), (IV-a) to (IV-c), (VI-a) to (VI-c), (VII-a), (VII-b), (II-a-1) to (II-c-1), (IV-a-1) to (IV-c-1), (VI-a-1) to (VI-c-1), (VII-a-1) to (VII-b-1), (II-a-2) to (II-c-2), (IV-a-2-1) to (IV-c-2-4), (IV-a-2) to (VI-c-2), or formula (VII-a-2), as specified herein, show kinase inhibition properties. Illnesses and diseases treatable using the compounds and methods of the present invention include protein kinase mediated diseases like like cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as

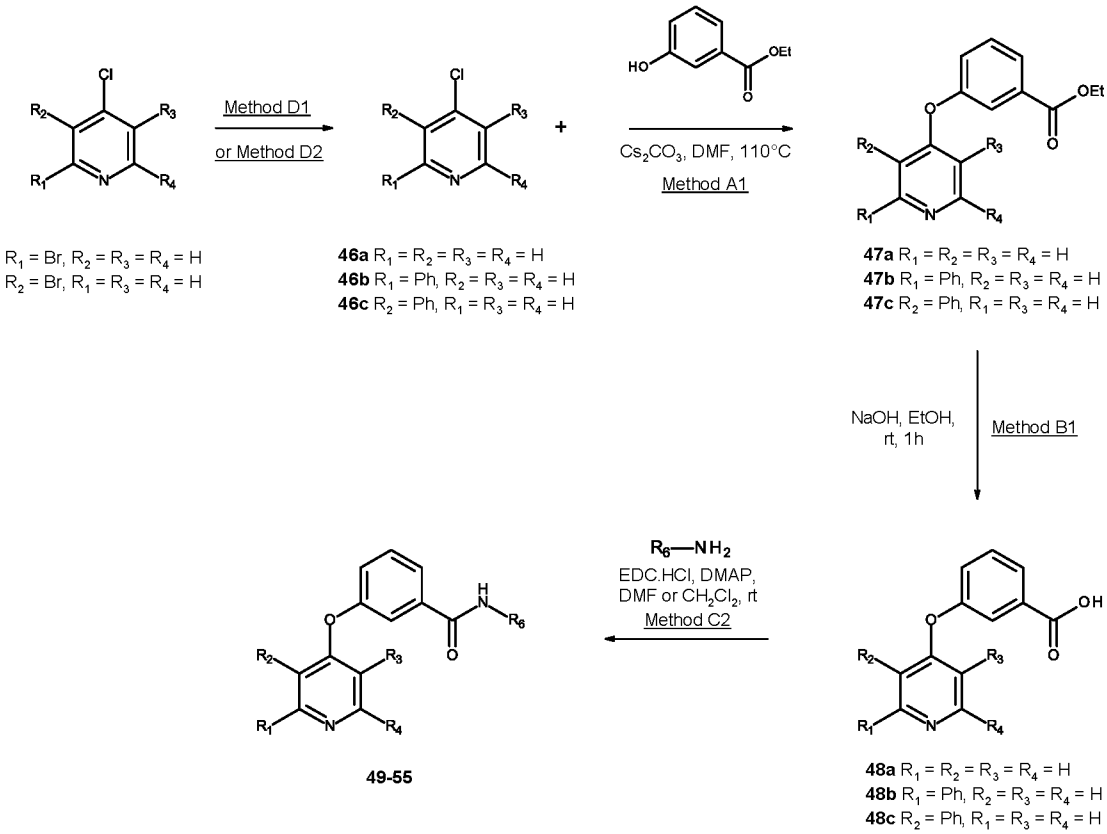
retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases. Many of the compounds of this invention may show a favourable pharmacokinetic profile and have attractive properties in terms of bioavailability, including an acceptable half-life, AUC (area under the curve) and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The combinations of the present invention may be used as medicaments. Said use as a medicine or method of treatment comprises the systemic administration to ill subjects of an amount effective to combat the conditions associated with the illnesses. Consequently, the combinations of the present invention can be used in the manufacture of a medicament useful for treating, preventing or combating illness or disease associated with protein kinases including cancer, metabolic disorders (such as diabetes), inflammatory and autoimmune disorders (such as inflammatory bowel diseases, e.g. Crohn's disease and ulcerative colitis, inflammatory pulmonary diseases, rheumatoid arthritis, lupus nephritis, systemic lupus erythematosus and psoriasis and psoriasis arthritis), neurological disorders (such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, Charcot-Marie-Tooth neuropathy, amyotrophic lateral sclerosis and epilepsy), atherosclerosis and cardiovascular diseases, Sjogren Syndrome, renal allograft rejection, viral induced diseases, circulatory diseases, bone osteolysis and osteoporosis, osteoarthritis, sarcopenia, Langerhans cell histiocytosis, spinal cord injury, endometriosis, asthma and allergic asthma, eye diseases (such as retinopathies, age-related macular degeneration and uveitis) chronic and neuropathic pain, and fibro-proliferative diseases.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought, in the light of the present invention, by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

Examples

Example 1: General procedure for the preparation of analogues 49-55



R_1 = Br, R_2 = R_3 = R_4 = H
R_2 = Br, R_1 = R_3 = R_4 = H

46a R_1 = R_2 = R_3 = R_4 = H
46b R_1 = Ph, R_2 = R_3 = R_4 = H
46c R_2 = Ph, R_1 = R_3 = R_4 = H

47a R_1 = R_2 = R_3 = R_4 = H
47b R_1 = Ph, R_2 = R_3 = R_4 = H
47c R_2 = Ph, R_1 = R_3 = R_4 = H

48a R_1 = R_2 = R_3 = R_4 = H
48b R_1 = Ph, R_2 = R_3 = R_4 = H
48c R_2 = Ph, R_1 = R_3 = R_4 = H

49-55

Method A1: To a solution of phenol derivative (1 equiv.) in DMF (5 mL/mmol) under nitrogen was added solid cesium carbonate (2.5 equiv.) followed by 4-chloropyridine derivative (1 equiv.). The reaction mixture was stirred at 110°C until completion (from 2h to overnight). After cooling at room temperature, a saturated aqueous solution of NH_4Cl was added and the aqueous layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (cyclohexane/EtOAc from100/0 to 50/50) or (DCM/MeOH from 100/0 to 90/10), or reverse phase chromatography (H_2O/MeOH: 0 to 100%) to give the expected compound.

Method B1: To a solution of appropriate intermediate **47** (1 equiv.) in EtOH or MeOH (2.5 mL/mmol) was added a solution of NaOH 1N (2.9 mL/mmol). The

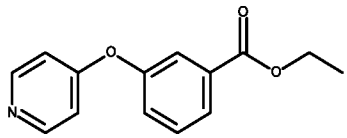
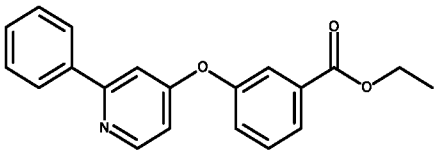
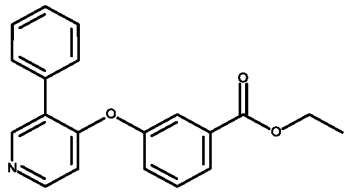
reaction mixture was stirred at rt until completion. EtOH or MeOH was removed under reduce pressure and the crude was acidified with HCl 1N until pH = 2-3. The precipitate was filtered-off, washed with water and dried over P_2O_5 in vacuum to give the expected intermediate **48**.

Method C2: To a suspension of appropriate intermediate **48** (1 equiv.) in DCM or DMF (10 mL/mmol) under nitrogen were added DMAP (2.2 equiv.), EDC.HCl (2 equiv.) and appropriate amine (1.1-1.5 equiv.). The reaction mixture was stirred at room temperature until completion (1h-overnight). The reaction mixture was diluted with DCM and washed twice with a saturated solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH: 0 to 100%) to give the expected compound.

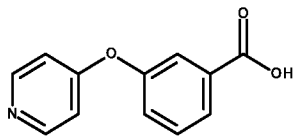
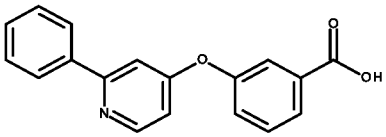
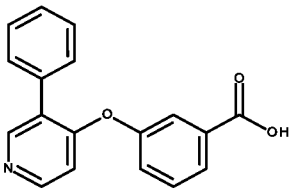
Method D1: To a stirred solution of 2-bromo-4-chloropyridine (192 mg, 1 mmol) in isopropanol/H_2O (4 mL/4 mL) were added phenylboronic acid (128 mg, 1.05 mmol), K_3PO_4 (424 mg, 2 mmol) and $Pd(OAc)_2$ (4 mg, 0.015 mmol). The reaction mixture was stirred at 80°C under air atmosphere for 30 minutes. After cooling at room temperature, the reaction mixture was diluted with EtOAc and washed twice with a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Cyclohexane/EtOAc: 100/0 to 90/10) to give 162 mg of 4-chloro-2-phenylpyridine **46b** in 85% yield.

Method D2: To a stirred solution of 3-bromo-4-chloropyridine (385 mg, 2 mmol) in dioxane (10 mL) were added under nitrogen phenylboronic acid (256 mg, 2.1 mmol), solid K_3PO_4 (849 mg, 4 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.2 mmol). The reaction mixture was stirred at 100°C for 4h. The solvent was removed under vacuum, and the crude was purified by flash column chromatography (cyclohexane/EtOAc from 100/0 to 75/25), , to give 4-chloro-3-phenyl-pyridine **46c** as a yellow oil in 87% yield.

The following table illustrates intermediates **47** prepared from Method A1:

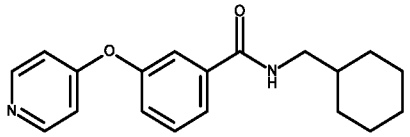
Intermediate	Structure	Synthesis procedure
Compound **47a**		Method A1
Compound **47b**		Method A1
Compound **47c**		Method A1

The following table illustrates intermediates **48** prepared from Method B1:

Intermediate	Structure	Synthesis procedure
Compound **48a**		Method B1
Compound **48b**		Method B1
Compound **48c**		Method B1

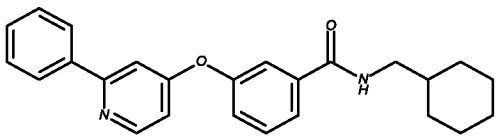
The following compounds are examples illustrating procedure C2:

N-(cyclohexylmethyl)-3-(4-pyridyloxy)benzamide (**49**):



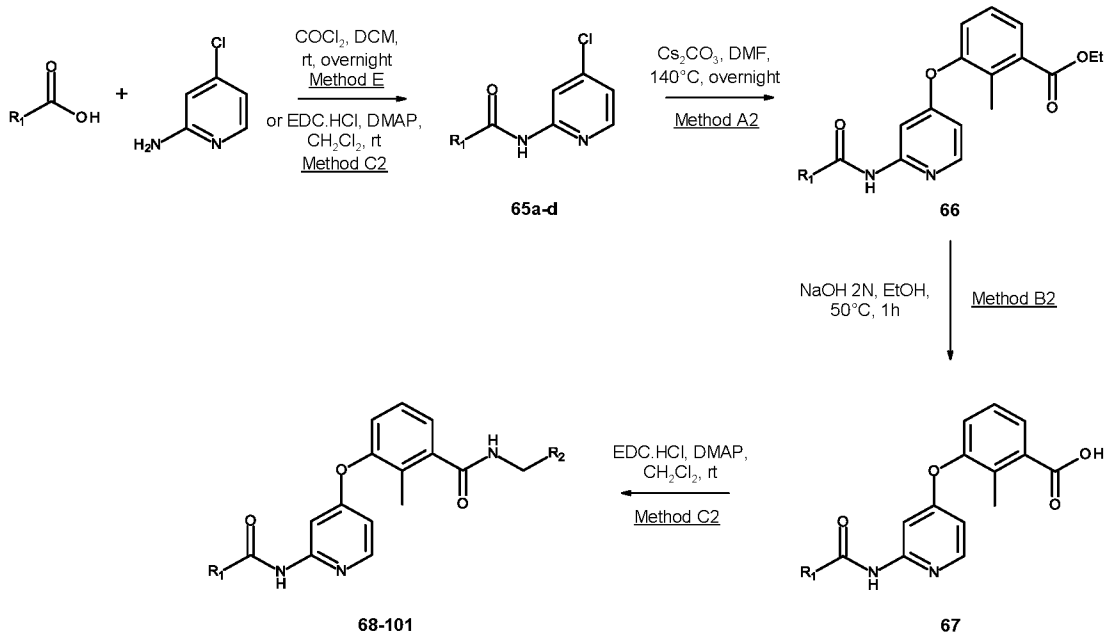
Compound **49** was synthesized from intermediate **48a** (0.20 mmol) and 1-cyclohexylmethanamine (0.34 mmol) as a white solid in 83% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.51 (t, J = 5.8 Hz, 1H), 8.49-8.47 (m, 2H), 7.78 (ddd, J = 7.8 Hz, 1.5 Hz, 1.0 Hz, 1H), 7.64-7.61 (m, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.35 (ddd, J = 8.1 Hz, 2.5 Hz, 1.0 Hz, 1H), 6.96-6.93 (m, 2H), 3.09 (dd, J = 6.8 Hz, 6.0 Hz, 2H), 1.68 (t, J = 13.5 Hz, 4H), 1.63-1.49 (m, 2H), 1.23-1.09 (m, 3H), 0.95-0.84 (m, 2H).

N-(cyclohexylmethyl)-3-[(2-phenyl-4-pyridyl)oxy]benzamide (**50**):



Compound **50** was synthesized from intermediate **48b** (0.20 mmol) and 1-cyclohexylmethanamine (0.30 mmol) as a white solid in 70% yield according to the general method C2. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.56 (d, J = 5.6 Hz, 1H), 7.94-7.88 (m, 2H), 7.66-7.61 (m, 1H), 7.57-7.54 (m, 1H), 7.52-7.39 (m, 4H), 7.28-7.24 (m, 2H), 6.79 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 6.14 (bs, 1H), 3.35-3.28 (m, 2H), 1.83-1.54 (m, 6H), 1.27-1.15 (m, 3H), 1.05-0.94 (m, 2H).

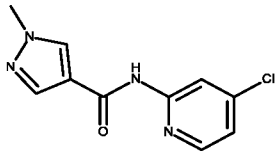
Example 2: General procedure for the synthesis of analogues 68 – 101



Method E: To a solution of carboxylic acid derivative (1 equiv.) in CH_2Cl_2 (5 mL/mmol) under nitrogen were added oxalyl chloride (3 equiv.) and 50 µL of DMF. The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure to give the acyl chloride derivative. To a solution of this previous intermediate in pyridine (3 mL/mmol) under nitrogen was added 2-amino-4-chloropyridine (1 equiv.) and the reaction mixture was stirred at room temperature until completion (from 2h to overnight). The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 95/5) to give the expected compound.

The following compound **65a** is an example illustrating Method E:

Preparation of *N*-(4-chloro-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**65a**):

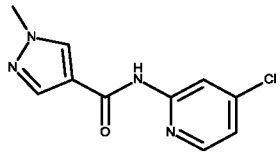
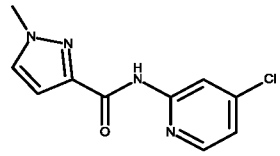
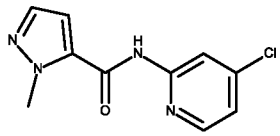
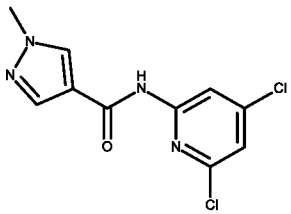


Intermediate **65a** was synthesized from 1-methyl-1*H*-pyrazole-4-carboxylic acid

(2.37 mmol) and 2-amino-4-chloropyridine (2.37 mmol) as a white powder in 84% yield according to the general method E.

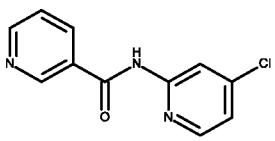
ESI-MS: 237.10 $(M+H)^+$.

The following table illustrates intermediates **65** prepared from method E:

Intermediate	Structure	Synthesis procedure
Compound **65a**		Method E
Compound **65b**		Method E
Compound **65c**		Method E
Compound **65d**		Method E

The following compound **65e** is an example illustrating Method C2:

Preparation of *N*-(4-chloro-2-pyridyl)pyridine-3-carboxamide (**65e**):



Intermediate **65e** was synthesized from nicotinic acid (1.28 mmol) and 2-amino-4-chloropyridine (1.16 mmol) as a white powder in 84% yield according to the

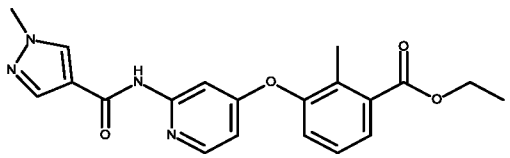
general method C2.

ESI-MS: 234.10 $(M+H)^+$.

Method A2: To a solution of phenol derivative (1 equiv.) in DMF (2 mL/mmol) under nitrogen was added solid cesium carbonate (2.5 equiv.) followed by 4-chloropyridine derivative (1 equiv.). The reaction mixture was stirred at 140°C overnight. The reaction mixture was concentrated under reduced pressure to give the expected compound which was used in the next step without purification.

The following compound **66a** is an example illustrating Method A2:

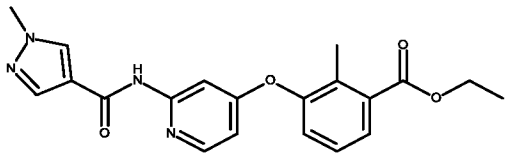
Preparation of ethyl 3-({2-[(1-methylpyrazole-4-carbonyl)amino]-4-pyridyl}oxy) benzoate (**66a**):

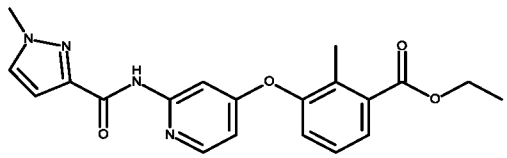
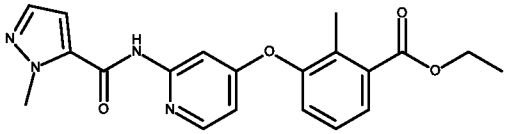
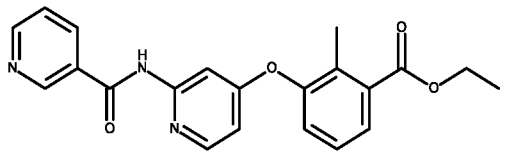


Intermediate **66a** was synthesized from ethyl 3-hydroxy-2-methyl-benzoate (0.91 mmol) and compound **65a** (0.91 mmol) as a brown powder according to the general method A2.

ESI-MS: 381.20 $(M+H)^+$.

The following table illustrates intermediates **66** prepared from method A2:

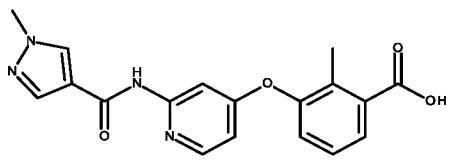
Intermediate	**Structure**	**Synthesis procedure**
Compound **66a**		Method A2

Compound **66b**		Method A2
Compound **66c**		Method A2
Compound **66d**		Method A2

Method B2: To a solution of appropriate intermediate **66** (1 equiv.) in EtOH (2.5 mL/mmol) was added a solution of NaOH 2N (2.5 mL/mmol). The reaction mixture was stirred at 50°C for 1h. EtOH was evaporated under reduced pressure and the residue was dissolved in water and washed 3 times with CH_2Cl_2. The aqueous layer was then acidified with concentrated HCl until pH = 2-3. The resulting precipitate was filtered, washed with H_2O and dried over P_2O_5 to afford the expected compound. If necessary, the filtrate was evaporated under reduced pressure and purified by reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give more expected compound.

The following compound **67a** is an example illustrating Method B2:

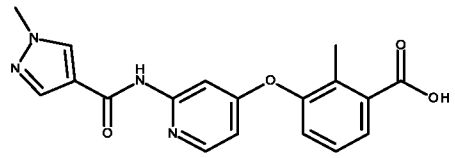
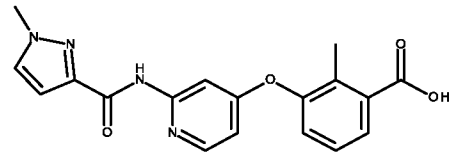
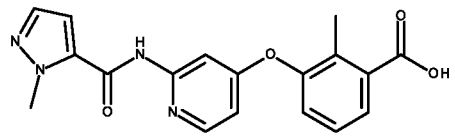
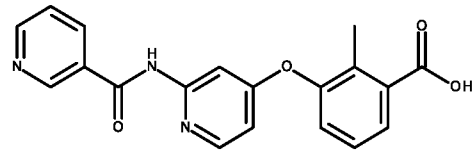
Preparation of 2-methyl-3-({2-[(1-methylpyrazole-4-carbonyl)amino]-4-pyridyl}oxy)benzoic acid (**67a**):



Intermediate **67a** was synthesized from intermediate **66a** (0.91 mmol) as a white solid in 32% yield (over 2 steps) according to the general method B2.

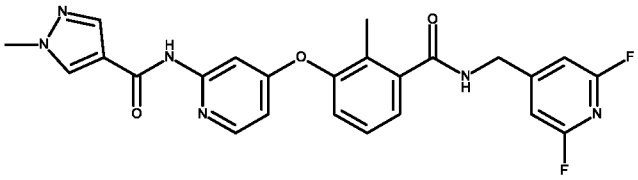
ESI-MS: 353.15 $(M+H)^+$.

The following table illustrates intermediates **67** prepared from method B2:

Intermediate	Structure	Synthesis procedure
Compound **67a**		Method B2
Compound **67b**		Method B2
Compound **67c**		Method B2
Compound **67d**		Method B2

The following compounds are examples illustrating Method C2:

N-(4-{3-[(2,6-difluoro-4-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**68**):

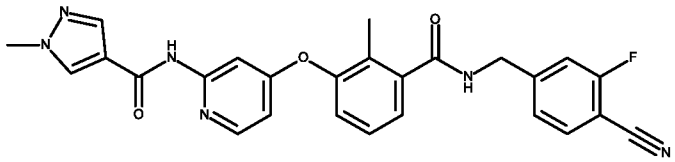


Compound **68** was synthesized from intermediate **67a** (0.42 mmol) and (2,6-difluoro-4-pyridyl)methanamine (0.63 mmol) as a white solid in 23% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):

10.59 (s, 1H), 9.16 (t, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 8.24 (d, *J* = 5.7 Hz, 1H), 8.09 (s, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.50-7.37 (m, 2H), 7.30-7.24 (m, 1H), 7.14 (s, 2H), 6.63 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.57 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 479.20 $(M+H)^+$.

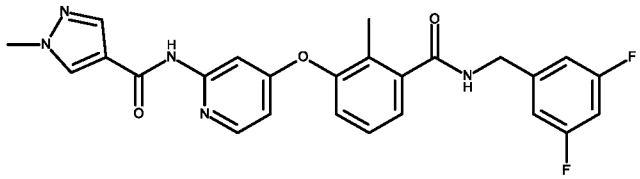
N-(4-{3-[(4-cyano-3-fluoro-phenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**69**):



Compound **69** was synthesized from intermediate **67a** (0.10 mmol) and 4-aminomethyl-2-fluorobenzonitrile (0.11 mmol) as a white solid in 71% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.59 (s, 1H), 9.14 (t, *J* = 6.0 Hz, 1H), 8.40 (s, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 8.09 (d, *J* = 0.6 Hz, 1H), 7.97-7.88 (m, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.48 (d, *J* = 10.4 Hz, 1H), 7.43-7.37 (m, 3H), 7.26 (t, *J* = 4.7 Hz, 1H), 6.63 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).

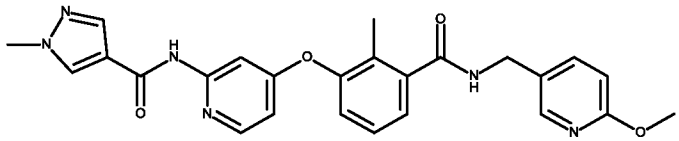
ESI-MS: 485.15 $(M+H)^+$.

N-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**70**):



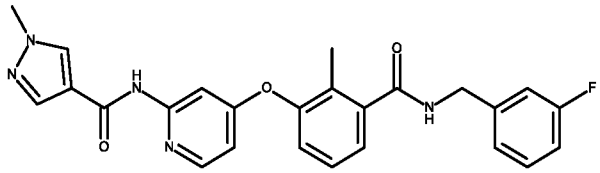
Compound **70** was synthesized from intermediate **67a** (0.10 mmol) and 3,5-difluorobenzylamine (0.11 mmol) as a white solid in 64% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 9.05 (t, *J* = 6.1 Hz, 1H), 8.40 (s, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 8.09 (s, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.44-7.35 (m, 2H), 7.25 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.18-7.03 (m, 3H), 6.62 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).

N-(4-{3-[(6-methoxy-3-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**71**):



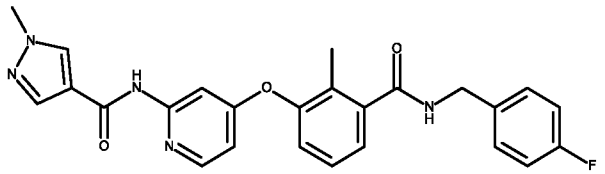
Compound **71** was synthesized from intermediate **67a** (0.10 mmol) and (6-methoxypyridin-3-yl)methanamine (0.11 mmol) as a white solid in 61% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 8.95 (t, *J* = 5.9 Hz, 1H), 8.40 (s, 1H), 8.22 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 8.09 (s, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.40-7.19 (m, 3H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.61 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.11 (s, 3H).

N-(4-{3-[(3-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**72**):



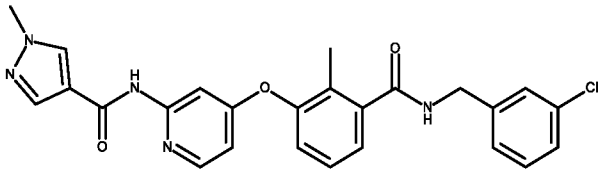
Compound **72** was synthesized from intermediate **67a** (0.09 mmol) and 3-fluorobenzylamine (0.13 mmol) as a white solid in 26% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 1H), 9.01 (t, *J* = 6.1 Hz, 1H), 8.40 (s, 1H), 8.23 (d, *J* = 5.8 Hz, 1H), 8.09 (d, *J* = 0.6 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.45-7.20 (m, 6H), 7.24 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 6.62 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H). ESI-MS: 460.15 $(M+H)^+$.

N-(4-{3-[(4-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**73**):



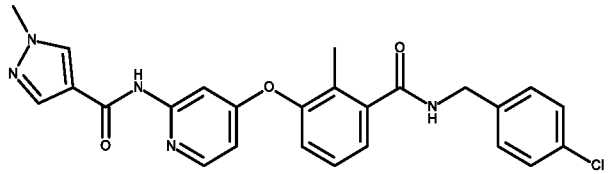
Compound **73** was synthesized from intermediate **67a** (0.09 mmol) and 4-fluorobenzylamine (0.13 mmol) as a white solid in 26% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 9.00 (t, J = 6.0 Hz, 1H), 8.40 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 8.09 (d, J = 0.5 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 7.46-7.32 (m, 3H), 7.26-7.04 (m, 4H), 6.62 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).
ESI-MS: 460.15 $(M+H)^+$.

N-(4-{3-[(3-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**74**):



Compound **74** was synthesized from intermediate **67a** (0.09 mmol) and 3-chlorobenzylamine (0.13 mmol) as a white solid in 30% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 8.97 (t, J = 6.2 Hz, 1H), 8.40 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 8.09 (d, J = 0.5 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 7.47-7.30 (m, 4H), 7.25-7.12 (m, 3H), 6.61 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).
ESI-MS: 476.10 $(M+H)^+$.

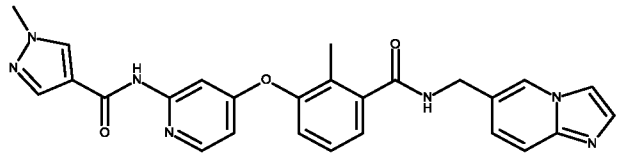
N-(4-{3-[(4-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**75**):



Compound **75** was synthesized from intermediate **67a** (0.09 mmol) and 4-chlorobenzylamine (0.13 mmol) as a white solid in 30% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 9.01 (t, J = 6.0 Hz, 1H), 8.40 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 8.09 (d, J = 0.4 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 7.47-7.31 (m, 6H), 7.23 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 6.62 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

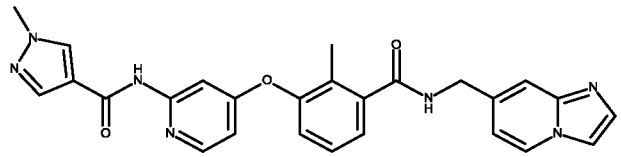
N-{4-[3-(imidazo[1,2-*a*]pyridin-6-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-1-methyl-pyrazole-4-carboxamide (**76**):



Compound **76** was synthesized from intermediate **67a** (0.09 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.13 mmol) as a white solid in 22% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 9.01 (t, J = 5.9 Hz, 1H), 8.50 (s, 1H), 8.40 (s, 1H), 8.23 (d, J = 5.7 Hz, 1H), 8.09 (d, J = 0.5 Hz, 1H), 7.97 (s, 1H), 7.74 (d, J = 2.3 Hz, 1H), 7.58-7.52 (m, 2H), 7.45-7.32 (m, 2H), 7.29-7.19 (m, 2H), 6.62 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 482.20 $(M+H)^+$.

N-{4-[3-(imidazo[1,2-*a*]pyridin-7-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-1-methyl-pyrazole-4-carboxamide (**77**):

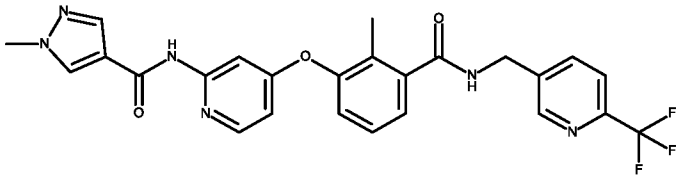


Compound **77** was synthesized from intermediate **67a** (0.09 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.13 mmol) as a white solid in 15% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.56 (s, 1H), 9.05 (t, *J* = 6.1 Hz, 1H), 8.51 (dd, *J* = 7.0 Hz, 0.7 Hz, 1H), 8.40 (s, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 8.09 (d, *J* = 0.5 Hz, 1H), 7.90 (s, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.47-7.35 (m, 3H), 7.25 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 6.89 (dd, *J* = 7.0 Hz, 1.6 Hz, 1H), 6.62 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 482.2

0 $(M+H)^+$.

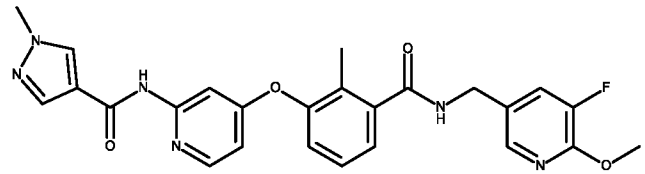
1-methyl-*N*-[4-(2-methyl-3-{[6-(trifluoromethyl)-3-pyridyl]methylcarbamoyl} phenoxy)-2-pyridyl]pyrazole-4-carboxamide (**78**):



Compound **78** was synthesized from intermediate **67a** (0.09 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.13 mmol) as a white solid in 44% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.88 (s, 1H), 9.12 (t, *J* = 5.9 Hz, 1H), 8.76 (s, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 8.05 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.46-7.35 (m, 2H), 7.30-7.23 (m, 2H), 6.65 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.04 (s, 3H), 2.14 (s, 3H).

ESI-MS: 511.15 $(M+H)^+$.

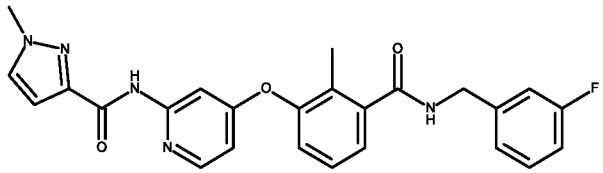
N-(4-{3-[(5-fluoro-6-methoxy-3-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-4-carboxamide (**79**):



Compound **79** was synthesized from intermediate **67a** (0.09 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.13 mmol) as a white solid in 38% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.54 (s, 1H), 8.95 (t, *J* = 5.9 Hz, 1H), 8.40 (s, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 8.09 (d, *J* = 0.4 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.65 (dd, *J* = 11.4 Hz, 1.9 Hz, 1H), 7.41-7.30 (m, 2H), 7.23 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 6.61 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.12 (s, 3H).

ESI-MS: 491.05 $(M+H)^+$.

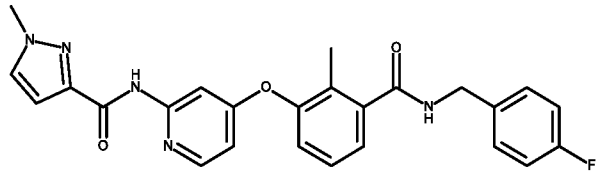
N-(4-{3-[(3-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**80**):



Compound **80** was synthesized from intermediate **67b** (0.11 mmol) and 3-fluorobenzylamine (0.17 mmol) as a white solid in 37% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 9.03 (t, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.45-7.34 (m, 3H), 7.29-7.14 (m, 3H), 7.09 (td, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 2.14 (s, 3H).

ESI-MS: 460.30 $(M+H)^+$.

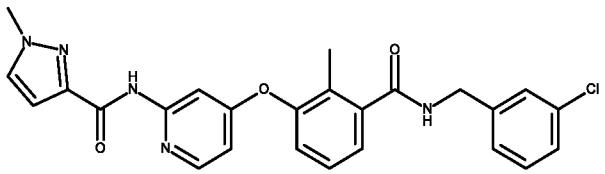
N-(4-{3-[(4-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**81**):



Compound **81** was synthesized from intermediate **67b** (0.11 mmol) and 4-fluorobenzylamine (0.17 mmol) as a white solid in 37% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 8.99 (t, J = 6.1 Hz, 1H), 8.23 (d, J = 5.7 Hz, 1H), 7.88 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.42-7.33 (m, 4H), 7.25 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 7.22-7.12 (m, 2H), 6.81 (d, J = 2.3 Hz, 1H), 6.65 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.95 (s, 3H), 2.13 (s, 3H).

ESI-MS: 460.25 $(M+H)^+$.

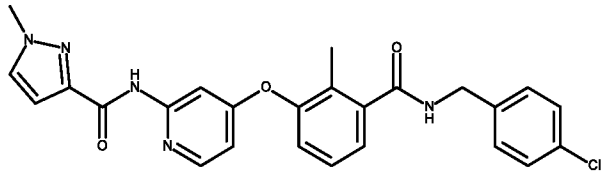
N-(4-{3-[(3-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**82**):



Compound **82** was synthesized from intermediate **67b** (0.11 mmol) and 3-chlorobenzylamine (0.17 mmol) as a white solid in 41% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 9.03 (t, J = 6.1 Hz, 1H), 8.23 (d, J = 5.7 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.45-7.30 (m, 6H), 7.26 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.65 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.95 (s, 3H), 2.14 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

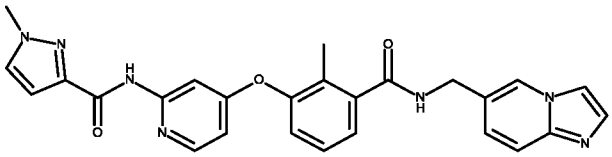
N-(4-{3-[(4-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**83**):



Compound **83** was synthesized from intermediate **67b** (0.11 mmol) and 4-chlorobenzylamine (0.17 mmol) as a white solid in 48% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H), 8.99 (t, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.44-7.32 (m, 6H), 7.25 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 2.13 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

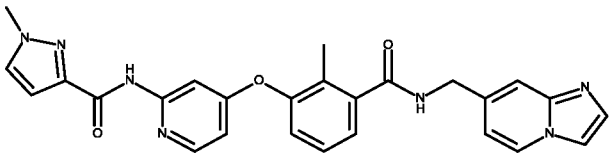
N-{4-[3-(imidazo[1,2-*a*]pyridin-6-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-1-methyl-pyrazole-3-carboxamide (**84**):



Compound **84** was synthesized from intermediate **67b** (0.11 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.17 mmol) as a white solid in 35% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H), 8.99 (t, *J* = 6.0 Hz, 1H), 8.50 (s, 1H), 8.22 (d, *J* = 5.8 Hz, 1H), 7.96 (s, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.59-7.52 (m, 2H), 7.44-7.34 (m, 2H), 7.28-7.22 (m, 2H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 3.95 (s, 3H), 2.14 (s, 3H).

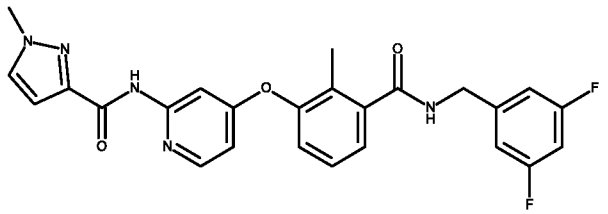
ESI-MS: 482.20 $(M+H)^+$.

N-{4-[3-(imidazo[1,2-*a*]pyridin-7-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-1-methyl-pyrazole-3-carboxamide (**85**):



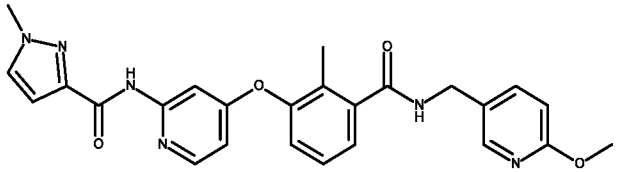
Compound **85** was synthesized from intermediate **67b** (0.11 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.17 mmol) as a white solid in 22% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H), 9.04 (t, *J* = 6.0 Hz, 1H), 8.51 (dd, *J* = 7.0 Hz, 0.7 Hz, 1H), 8.23 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 1.1 Hz, 1H), 7.45-7.37 (m, 3H), 7.26 (dd, *J* = 7.1 Hz, 2.2 Hz, 1H), 6.89 (dd, *J* = 7.0 Hz, 1.6 Hz, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 2.16 (s, 3H).
ESI-MS: 482.15 $(M+H)^+$.

N-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**86**):



Compound **86** was synthesized from intermediate **67b** (0.09 mmol) and 3,5-difluorobenzylamine (0.13 mmol) as a white solid in 49% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.53 (s, 1H), 9.03 (t, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.44-7.35 (m, 2H), 7.26 (dd, *J* = 7.2 Hz, 2.1 Hz, 1H), 7.17-7.02 (m, 3H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 2.14 (s, 3H).
ESI-MS: 478.15 $(M+H)^+$.

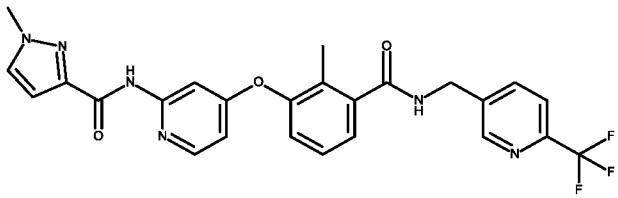
N-(4-{3-[(6-methoxy-3-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-1-methyl-pyrazole-3-carboxamide (**87**):



Compound **87** was synthesized from intermediate **67b** (0.09 mmol) and (6-methoxypyridin-3-yl)methanamine (0.13 mmol) as a white solid in 45% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.52 (s, 1H), 8.93 (t, *J* = 5.9 Hz, 1H), 8.22 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 2.3 Hz, 1H), 7.71-7.69 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.24 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 6.82-6.80 (m, 2H), 6.64 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 2.12 (s, 3H).

ESI-MS: 473.15 $(M+H)^+$.

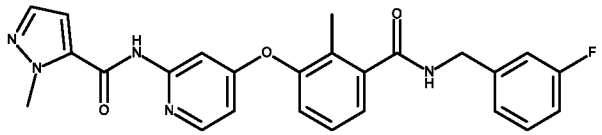
1-methyl-*N*-[4-(2-methyl-3-{[6-(trifluoromethyl)-3-pyridyl]methylcarbamoyl}phenoxy)-2-pyridyl]pyrazole-3-carboxamide (**88**):



Compound **88** was synthesized from intermediate **67b** (0.09 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.13 mmol) as a white solid in 48% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.54 (s, 1H), 9.13 (t, J = 5.9 Hz, 1H), 8.77 (d, J = 1.2 Hz, 1H), 8.23 (d, J = 5.7 Hz, 1H), 8.05 (dd, J = 8.1 Hz, 1.4 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.44-7.36 (m, 2H), 7.31-7.24 (m, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.58 (d, J = 5.8 Hz, 2H), 3.95 (s, 3H), 2.14 (s, 3H).

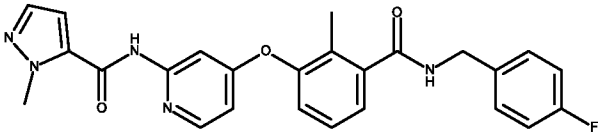
ESI-MS: 511.15 $(M+H)^+$.

N-(4-{3-[(3-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**89**):



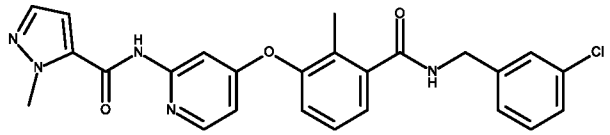
Compound **89** was synthesized from intermediate **67c** (0.09 mmol) and 3-fluorobenzylamine (0.13 mmol) as a white solid in 33% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 9.00 (t, J = 6.1 Hz, 1H), 8.27 (d, J = 5.8 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.41-7.35 (m, 3H), 7.26-7.24 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 10.2 Hz, 1H), 7.09 (td, J = 8.3 Hz, 2.0 Hz, 1H), 6.65 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 4.05 (s, 3H), 2.15 (s, 3H).
ESI-MS: 460.20 $(M+H)^+$.

N-(4-{3-[(4-fluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**90**):



Compound **90** was synthesized from intermediate **67c** (0.09 mmol) and 4-fluorobenzylamine (0.13 mmol) as a white solid in 32% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 8.96 (t, J = 6.1 Hz, 1H), 8.29-8.24 (m, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.41-7.37 (m, 3H), 7.33 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 7.27-7.23 (m, 2H), 7.20-7.14 (m, 2H), 6.64 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 4.05 (s, 3H), 2.14 (s, 3H).
ESI-MS: 460.20 $(M+H)^+$.

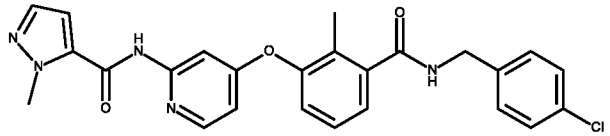
N-(4-{3-[(3-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**91**):



Compound **91** was synthesized from intermediate **67c** (0.09 mmol) and 3-chlorobenzylamine (0.13 mmol) as a white solid in 37% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 9.00 (t, *J* = 6.0 Hz, 1H), 8.31-8.23 (m, 1H), 7.72 (d, *J* = 2.3, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.43-7.30 (m, 6H), 7.25 (m, 2H), 6.65 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.05 (s, 3H), 2.15 (s, 3H).

ESI-MS: 476.15 $(M+H)^+$.

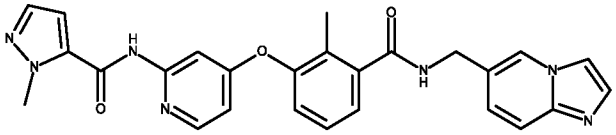
N-(4-{3-[(4-chlorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**92**):



Compound **92** was synthesized from intermediate **67c** (0.09 mmol) and 4-chlorobenzylamine (0.13 mmol) as a white solid in 35% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 8.98 (t, *J* = 6.1 Hz, 1H), 8.29-8.24 (m, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.42-7.33 (m, 5H), 7.26 (d, *J* = 2.1 Hz, 2H), 7.25 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H) 6.64 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.05 (s, 3H), 2.14 (s, 3H).

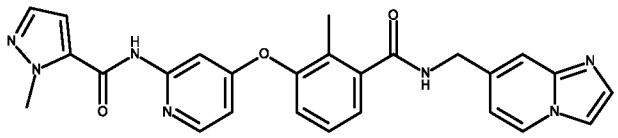
ESI-MS: 476.15 $(M+H)^+$.

N-{4-[3-(imidazo[1,2-*a*]pyridin-6-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-2-methyl-pyrazole-3-carboxamide (**93**):



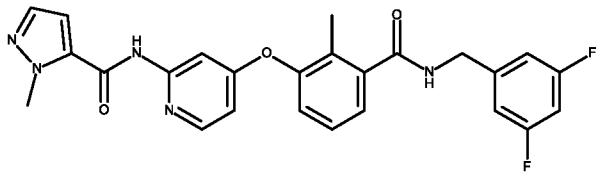
Compound **93** was synthesized from intermediate **67c** (0.09 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.13 mmol) as a white solid in 15% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 8.52-8.49 (m, 1H), 8.26 (d, *J* = 5.7 Hz, 1H), 7.98-7.95 (m, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.58-7.54 (m, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.41-7.34 (m, 2H), 7.27-7.22 (m, 3H), 6.64 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.04 (s, 3H), 2.14 (s, 3H).
ESI-MS: 482.20 $(M+H)^+$.

N-{4-[3-(imidazo[1,2-*a*]pyridin-7-ylmethylcarbamoyl)-2-methyl-phenoxy]-2-pyridyl}-2-methyl-pyrazole-3-carboxamide (**94**):



Compound **94** was synthesized from intermediate **67c** (0.09 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.13 mmol) as a white solid in 20% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 9.03 (t, *J* = 6.0 Hz, 1H), 8.51 (dd, *J* = 7.0 Hz, 0.9 Hz, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 7.91-7.88 (m, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.45-7.36 (m, 3H), 7.28-7.24 (m, 2H), 6.89 (dd, *J* = 7.0 Hz, 1.7 Hz, 1H), 6.65 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 4.05 (s, 3H), 2.17 (s, 3H).
ESI-MS: 482.20 $(M+H)^+$.

N-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**95**):

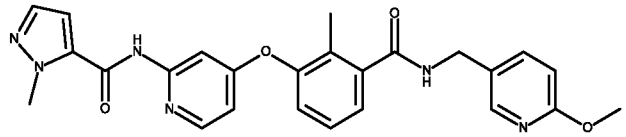


Compound **95** was synthesized from intermediate **67c** (0.09 mmol) and 3,5-difluorobenzylamine (0.13 mmol) as a white solid in 42% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 9.02

(t, *J* = 6.1 Hz, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.43-7.36 (m, 2H), 7.27-7.25 (m, 2H), 7.12 (tt, *J* = 9.3 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 6.65 (dd, *J* = 5.5 Hz, 2.3 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.05 (s, 3H), 2.15 (s, 3H).

ESI-MS: 478.15 $(M+H)^+$.

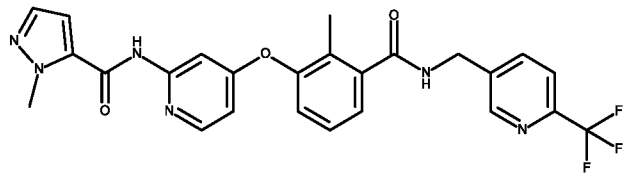
N-(4-{3-[(6-methoxy-3-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**96**):



Compound **96** was synthesized from intermediate **67c** (0.09 mmol) and (6-methoxypyridin-3-yl)methanamine (0.13 mmol) as a white solid in 38% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.85 (s, 1H), 8.92 (t, *J* = 5.9 Hz, 1H), 8.33-8.22 (m, 1H), 8.14 (dd, *J* = 2.4 Hz, 0.6 Hz, 1H), 7.76-7.64 (m, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.39-7.36 (m, 1H), 7.31 (dd, *J* = 7.6 Hz, 1.1 Hz, 1H), 7.26-7.22 (m, 2H), 6.81 (dd, *J* = 8.5 Hz, 0.6 Hz, 1H), 6.63 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 2.12 (s, 3H).

ESI-MS: 473.20 $(M+H)^+$.

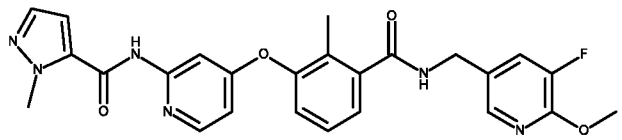
2-methyl-*N*-[4-(2-methyl-3-{[6-(trifluoromethyl)-3-pyridyl]methylcarbamoyl}phenoxy)-2-pyridyl]pyrazole-3-carboxamide (**97**):



Compound **97** was synthesized from intermediate **67c** (0.09 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.13 mmol) as a white solid in 44% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.88 (s, 1H), 9.12 (t, *J* = 5.9 Hz, 1H), 8.76 (s, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 8.05 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.44-7.36 (m, 2H), 7.28-7.25 (m, 2H), 6.65 (dd, *J* = 5.7

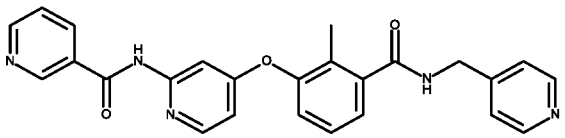
Hz, 2.3 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 4.04 (s, 3H), 2.14 (s, 3H).
ESI-MS: 511.15 $(M+H)^+$.

N-(4-{3-[(5-fluoro-6-methoxy-3-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)-2-methyl-pyrazole-3-carboxamide (**98**):



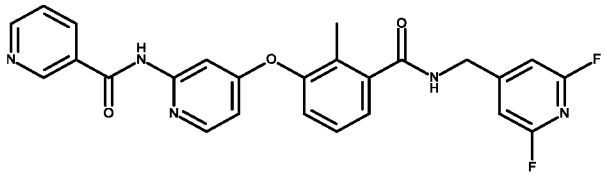
Compound **98** was synthesized from intermediate **67c** (0.09 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.13 mmol) as a white solid in 36% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.86 (s, 1H), 8.95 (t, *J* = 5.8 Hz, 1H), 8.27 (d, *J* = 5.7 Hz, 1H), 7.98 (d, *J* = 1.7 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.65 (dd, *J* = 11.4 Hz, 1.9 Hz, 1H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.44-7.31 (m, 2H), 7.26-7.23 (m, 2H), 6.64 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 4.05 (s, 3H), 3.93 (s, 3H), 2.13 (s, 3H).
ESI-MS: 491.10 $(M+H)^+$.

N-{4-[2-methyl-3-(4-pyridylmethylcarbamoyl)phenoxy]-2-pyridyl}pyridine-3-carboxamide (**99**):



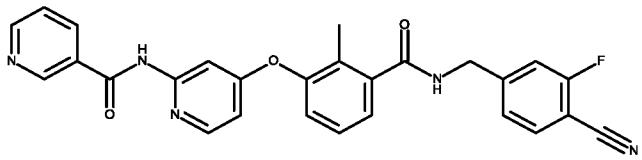
Compound **99** was synthesized from intermediate **67d** (0.13 mmol) and 4-(aminomethyl)pyridine (0.19 mmol) as a white solid in 7% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.14 (s, 1H), 9.08-9.05 (m, 2H), 8.73 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 8.53 (dd, *J* = 4.4 Hz, 1.5 Hz, 2H), 8.35-8.24 (m, 2H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.52 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 7.45-7.39 (m, 2H), 7.35 (d, *J* = 5.9 Hz, 2H), 7.31-7.24 (m, 1H), 6.70 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.17 (s, 3H).
ESI-MS: 440.15 $(M+H)^+$.

N-(4-{3-[(2,6-difluoro-4-pyridyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl) pyridine-3-carboxamide (**100**):



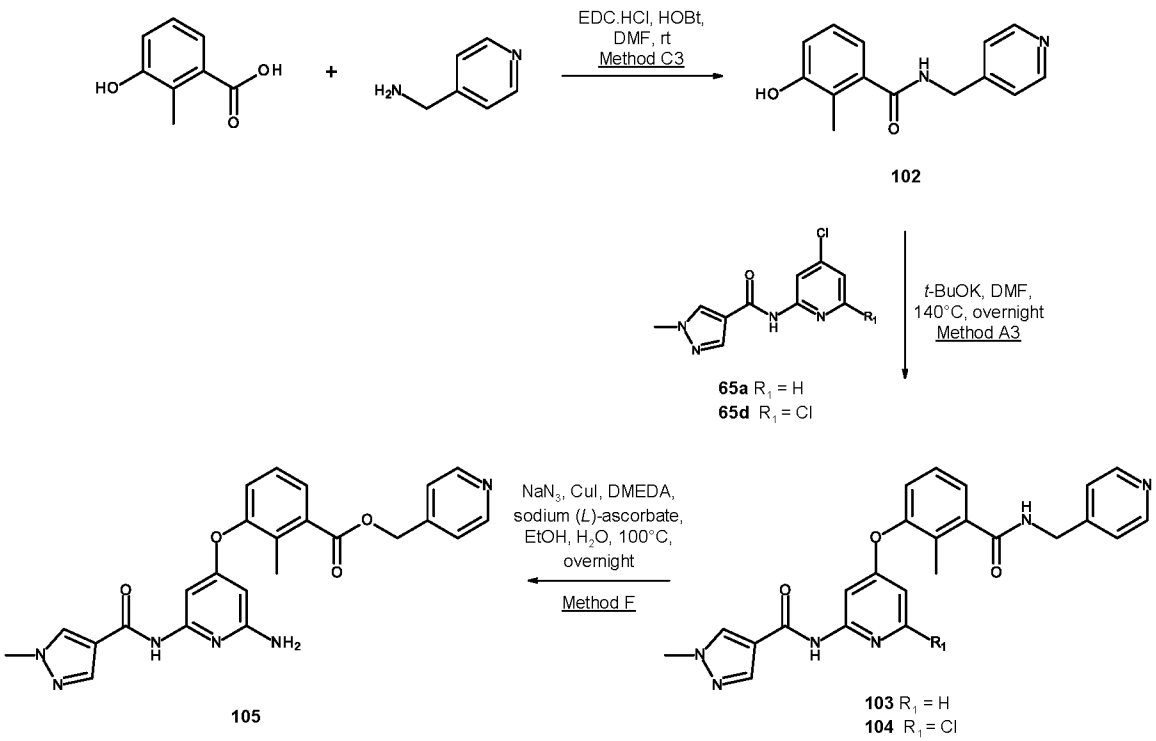
Compound **100** was synthesized from intermediate **67d** (0.13 mmol) and (2,6-difluoro-4-pyridyl)methanamine (0.38 mmol) as a white solid in 14% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.14 (s, 1H), 9.12 (t, *J* = 5.8 Hz, 1H), 9.08 (d, *J* = 1.7 Hz, 1H), 8.73 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.34-8.24 (m, 2H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.52 (dd, *J* = 7.5 Hz, 4.8 Hz, 1H), 7.48-7.40 (m, 2H), 7.28 (dd, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.13 (s, 2H), 6.71 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.57 (d, *J* = 5.9 Hz, 2H), 2.17 (s, 3H).
ESI-MS: 476.20 $(M+H)^+$.

N-(4-{3-[(4-cyano-3-fluoro-phenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)pyridine-3-carboxamide (**101**):

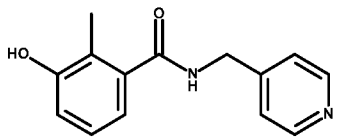


Compound **101** was synthesized from intermediate **67d** (0.13 mmol) and 4-aminomethyl-2-fluorobenzonitrile (0.14 mmol) as a white solid in 8% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1H NMR (400 MHz, DMSO) δ 11.14 (s, 1H), 9.15-9.05 (m, 2H), 8.73 (dd, *J* = 4.7 Hz, 1.5 Hz, 1H), 8.34-8.26 (m, 2H), 7.97-7.88 (m, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.55-7.38 (m, 5H), 7.30-7.25 (m, 1H), 6.70 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.55 (d, *J* = 5.9 Hz, 2H), 2.16 (s, 3H).
ESI-MS: 482.15 $(M+H)^+$.

Example 3: General procedure for the synthesis of analogues 103 – 105



Preparation of 3-hydroxy-2-methyl-*N*-(4-pyridylmethyl)benzamide (**102**):



Intermediate **102** was synthesized from 3-hydroxy-2-methylbenzoic acid (19.6 mmol) and 4-(aminomethyl)pyridine (19.6 mmol) as a white solid in 93% yield according to the general method C3.

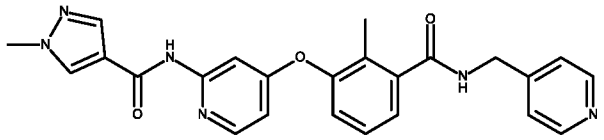
Method A3: To a solution of phenol derivative (1 equiv.) in DMF (5 mL/mmol) under nitrogen was added *t*-BuOK (1.5 equiv.). 4-Chloropyridine derivative (1 equiv.) was added and the reaction mixture was stirred at 140°C until completion (from 24 to 48 hours). The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

Method F: To a stirred solution of **104** (30 mg, 0.063 mmol) in EtOH/H_2O (0.75 mL/0.25 mL) were added sodium (*L*)-ascorbate (2 mg, 0.006 mmol), sodium azide (9 mg, 0.126 mmol), copper iodide (3 mg, 0.013 mmol) and DMEDA (2 µL, 0.019 mmol). The reaction mixture was stirred at 100°C overnight. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 80/20) and reverse phase chromatography (H_2O/MeOH: 0 to 100%) to give 6 mg of *N*-{6-amino-4-[2-methyl-3-(4-pyridylmethylcarbamoyl)phenoxy]-2-pyridyl}-1-methyl-pyrazole-4-carboxamide **105** in 21% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.94 (s, 1H), 9.05 (t, *J* = 6.1 Hz, 1H), 8.54-8.52 (m, 2H), 8.36 (s, 1H), 8.05 (d, *J* = 0.6 Hz, 1H), 7.40-7.29 (m, 4H), 7.19 (dd, *J* = 7.0 Hz, 2.3 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 5.79 (bs, 2H), 5.56 (d, *J* = 2.0 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 2.16 (s, 3H).

ESI-MS: 458.15 $(M+H)^+$.

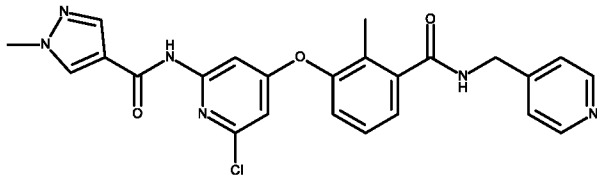
The following compounds are examples illustrating Method A3:

<u>1-methyl-*N*-{4-[2-methyl-3-(4-pyridylmethylcarbamoyl)phenoxy]-2-pyridyl} pyrazole-4-carboxamide (**103**):</u>



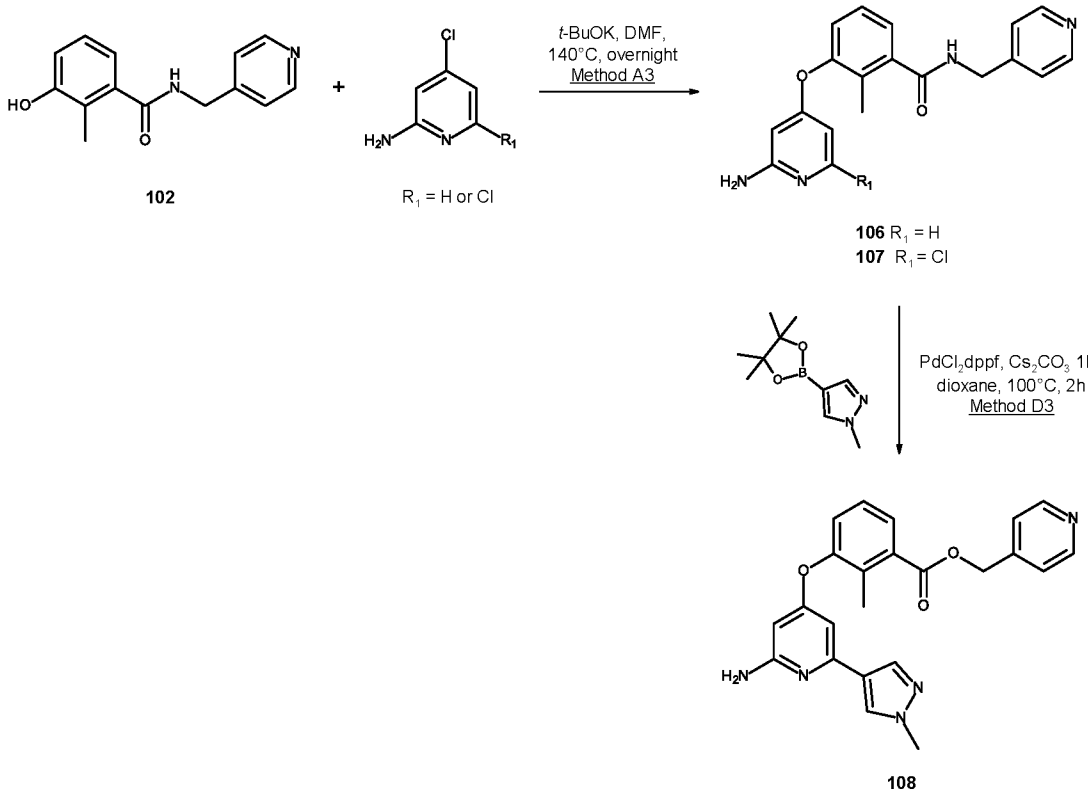
Compound **103** was synthesized from intermediate **102** (0.22 mmol) and **65a** (0.22 mmol) as a white solid in 19% yield according to the general method A3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.53 (s, 1H), 9.05 (t, *J* = 6.0 Hz, 1H), 8.53 (dd, *J* = 4.5 Hz, 1.5 Hz, 2H), 8.40 (s, 1H), 8.23 (d, *J* = 5.7 Hz, 1H), 8.09 (s, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.42-7.33 (m, 4H), 7.28-7.20 (m, 1H), 6.62 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.16 (s, 3H).

N-{6-chloro-4-[2-methyl-3-(4-pyridylmethylcarbamoyl)phenoxy]-2-pyridyl}-1-methyl-pyrazole-4-carboxamide (**104**):



Compound **104** was synthesized from intermediate **102** (0.22 mmol) and **65d** (0.22 mmol) as a white solid in 23% yield according to the general method A3. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.84 (s, 1H), 9.10 (t, J = 6.1 Hz, 1H), 8.53 (dd, J = 4.4 Hz, 1.6 Hz, 2H), 8.41 (s, 1H), 8.10 (d, J = 0.5 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.44-7.40 (m, 2H), 7.35 (d, J = 6.0 Hz, 2H), 7.33-7.28 (m, 1H), 6.73 (d, J = 2.0 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.85 (s, 3H), 2.16 (s, 3H). ESI-MS: 477.15 $(M+H)^+$.

Example 4: General procedure for the synthesis of analogues 106 – 108

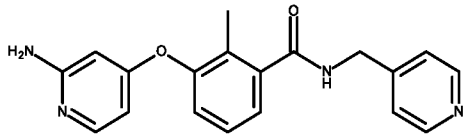


102 R_1 = H or Cl

106 R_1 = H
107 R_1 = Cl

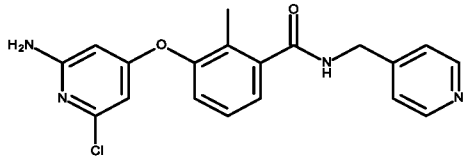
108

3-[(2-amino-4-pyridyl)oxy]-2-methyl-*N*-(4-pyridylmethyl)benzamide (**106**):



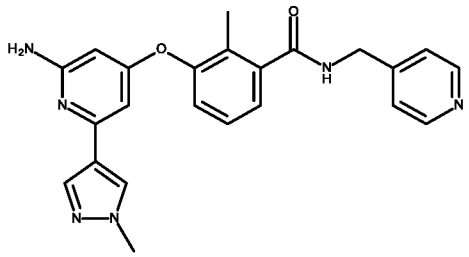
Compound **106** was synthesized from intermediate **102** (0.39 mmol) and 2-amino-4-chloropyridine (0.39 mmol) as a white solid in 23% yield according to the general method A3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m, 2H), 7.79 (d, J = 5.8 Hz, 1H), 7.36-7.33 (m, 4H), 7.17 (dd, J = 6.4 Hz, 2.9 Hz, 1H), 6.08 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 5.92 (s, 2H), 5.74 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.13 (s, 3H).

3-[(2-amino-4-pyridyl)oxy]-2-methyl-*N*-(4-pyridylmethyl)benzamide (**107**):



Compound **107** was synthesized from intermediate **102** (0.61 mmol) and 2-amino-4,6-dichloropyridine (0.61 mmol) as a white solid in 30% yield according to the general method A3. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, J = 6.0 Hz, 1H), 8.53 (d, J = 5.4 Hz, 2H), 7.40-7.31 (m, 4H), 7.25-7.20 (m, 1H), 6.45 (s, 2H), 6.13 (d, J = 1.9 Hz, 1H), 5.65 (d, J = 1.9 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.12 (s, 3H).

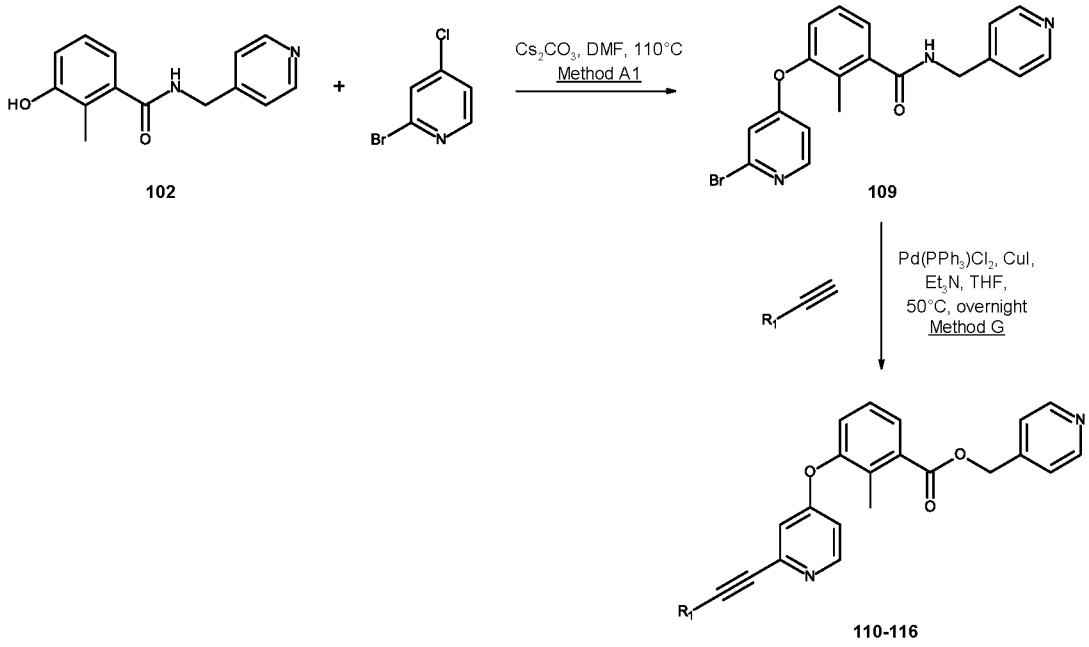
3-{[2-amino-6-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-2-methyl-*N*-(4-pyridyl methyl)benzamide (**108**):



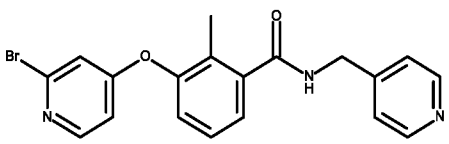
Method D3: To a stirred solution of **107** (32 mg, 0.086 mmol) in dioxane (1 mL) under nitrogen were added $PdCl_2$dppf (7 mg, 0.009 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-1*H*-pyrazole (27 mg, 0.13 mmol) and Cs_2CO_3

1M (0.215 mL, 0.215 mmol). The reaction mixture was stirred at 100°C for 2h. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH) and reverse phase chromatography (H_2O/MeOH: 0 to 100%) to give 18 mg of **108** in 51% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.03 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m 2H), 8.06 (s, 1H), 7.83 (d, J = 0.6 Hz, 1H), 7.41-7.32 (m, 4H), 7.20 (dd, J = 6.7 Hz, 2.6 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 5.92 (s, 2H), 5.49 (d, J = 2.0 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 2.16 (s, 3H).

Example 5: General procedure for the synthesis of analogues 110 – 116



Preparation of 3-[(2-bromo-4-pyridyl)oxy]-2-methyl-*N*-(4-pyridylmethyl) benzamide (**109**):

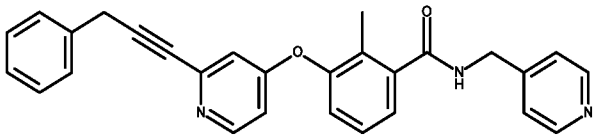


Intermediate **109** was synthesized from intermediate **102** (5.87 mmol) and 2-bromo-4-chloropyridine (5.87 mmol) as a white solid in 84% yield according to the general method A1.

ESI-MS: 398.10-400.10 $(M+H)^+$.

Method G: To a solution of **109** (1 equiv.) in THF (20 mL/mmol) under nitrogen were added alkyne derivative (3 equiv.), $Pd(PPh_3)Cl_2$ (0.1 equiv.), CuI (0.2 equiv.) and triethylamine (3 equiv.). The mixture was stirred at 50°C overnight. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

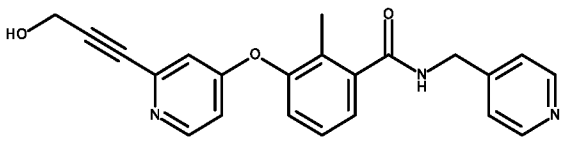
2-methyl-3-{[2-(3-phenylprop-1-ynyl)-4-pyridyl]oxy}-*N*-(4-pyridylmethyl) benzamide (**110**):



Compound **110** was synthesized from intermediate **109** (0.10 mmol) and 3-phenyl-1-propyne (0.30 mmol) as a white solid in 21% yield according to the general method G. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.03 (t, J = 6.0 Hz, 1H), 8.55-8.52 (m, 2H), 8.41 (d, J = 5.7 Hz, 1H), 7.44-7.32 (m, 9H), 7.28-7.23 (m, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.90 (s, 2H), 2.12 (s, 3H).

ESI-MS: 434.25 $(M+H)^+$.

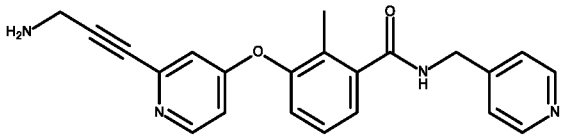
3-{[2-(3-hydroxyprop-1-ynyl)-4-pyridyl]oxy}-2-methyl-*N*-(4-pyridylmethyl) benzamide (**111**):



Compound **111** was synthesized from intermediate **109** (0.10 mmol) and propargyl alcohol (0.30 mmol) as a white solid in 22% yield according to the general method G. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m, 2H), 8.43 (d, J = 5.7 Hz, 1H), 7.44-7.39 (m, 2H), 7.34 (d, J = 6.0 Hz, 2H), 7.29-7.23 (m, 1H), 6.91 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 5.41 (bs, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.28 (s, 2H), 2.11 (s, 3H).

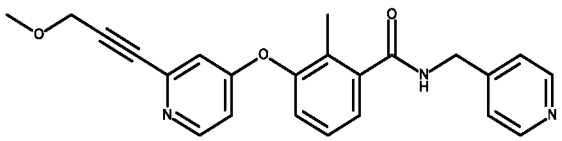
ESI-MS: 374.20 $(M+H)^+$.

3-{[2-(3-aminoprop-1-ynyl)-4-pyridyl]oxy}-2-methyl-*N*-(4-pyridylmethyl) benzamide (**112**):



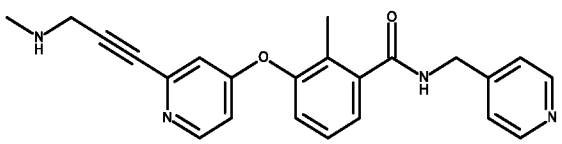
Compound **112** was synthesized from intermediate **109** (0.10 mmol) and propargylamine (0.30 mmol) as a white solid in 22% yield according to the general method G. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m, 2H), 8.41 (d, J = 5.7 Hz, 1H), 7.44-7.39 (m, 2H), 7.34 (d, J = 5.9 Hz, 2H), 7.26 (dd, J = 8.7 Hz, 4.3 Hz, 1H), 6.90 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 3H), 3.47 (s, 2H), 2.11 (s, 4H).
ESI-MS: 373.20 $(M+H)^+$.

3-{[2-(3-methoxyprop-1-ynyl)-4-pyridyl]oxy}-2-methyl-*N*-(4-pyridylmethyl) benzamide (**113**):



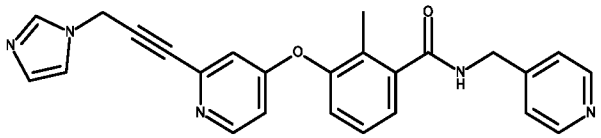
Compound **113** was synthesized from intermediate **109** (0.10 mmol) and methyl propargyl ether (0.30 mmol) as a white solid in 31% yield according to the general method G. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (t, J = 5.9 Hz, 1H), 8.54-8.52 (m, 2H), 8.44 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 4.5 Hz, 2H), 7.35 (d, J = 5.7 Hz, 2H), 7.25 (t, J = 4.7 Hz, 1H), 6.93-6.86 (m, 2H), 4.48 (d, J = 5.9 Hz, 2H), 4.32 (s, 2H), 3.31 (s, 3H), 2.12 (s, 3H).
ESI-MS: 388.20 $(M+H)^+$.

2-methyl-3-({2-[3-(methylamino)prop-1-ynyl]-4-pyridyl}oxy)-*N*-(4-pyridylmethyl) benzamide (**114**):



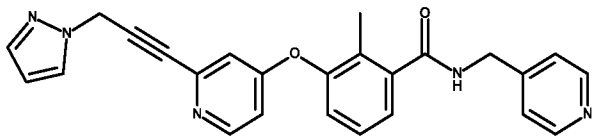
Compound **114** was synthesized from intermediate **109** (0.10 mmol) and *N*-methyl-*N*-prop-2-ynylamine (0.30 mmol) as a white solid in 18% yield according to the general method G. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, *J* = 5.9 Hz, 1H), 8.54-8.52 (m, 2H), 8.41 (d, *J* = 5.8 Hz, 1H), 7.41-7.38 (m, 3H), 7.34 (d, *J* = 5.8 Hz, 2H), 7.25 (t, *J* = 4.7 Hz, 1H), 6.87 (dd, *J* = 5.7 Hz, 2.5 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 2H), 3.48 (d, *J* = 5.7 Hz, 2H), 2.30 (d, *J* = 5.0 Hz, 3H), 2.11 (s, 3H).
ESI-MS: 387.25 $(M+H)^+$.

3-{[2-(3-imidazol-1-ylprop-1-ynyl)-4-pyridyl]oxy}-2-methyl-*N*-(4-pyridylmethyl) benzamide (**115**):



Compound **115** was synthesized from intermediate **109** (0.20 mmol) and 1-(2-propyn-1-yl)-1*H*-imidazole (0.40 mmol) as a white solid in 4% yield according to the general method G. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (t, *J* = 5.9 Hz, 1H), 8.54-8.52 (m, 2H), 8.44 (d, *J* = 5.7 Hz, 1H), 7.73 (s, 1H), 7.41 (d, *J* = 4.3 Hz, 2H), 7.34 (d, *J* = 5.8 Hz, 2H), 7.27-7.23 (m, 2H), 6.94-6.93 (m, 2H), 6.89 (dd, *J* = 5.7 Hz, 2.5 Hz, 1H), 5.19 (s, 2H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.11 (s, 3H).
ESI-MS: 424.30 $(M+H)^+$.

2-methyl-3-({2-[3-(methylamino)prop-1-ynyl]-4-pyridyl}oxy)-*N*-(4-pyridylmethyl) benzamide (**116**):

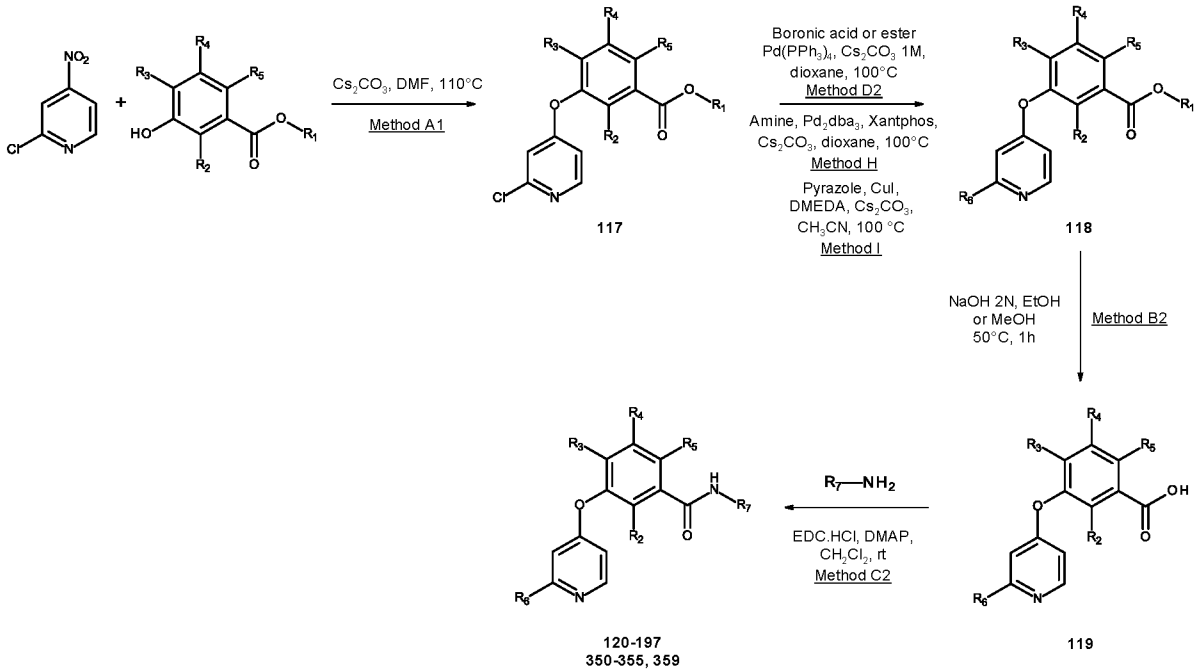


Compound **116** was synthesized from intermediate **109** (0.20 mmol) and 1-(2-propyn-1-yl)-1*H*-pyrazole (0.30 mmol) as a white solid in 12% yield according to

the general method G. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m, 2H), 8.46-8.41 (m, 1H), 7.83 (d, J = 1.8 Hz, 1H), 7.49 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 4.2 Hz, 2H), 7.34 (d, J = 6.0 Hz, 2H), 7.25 (t, J = 4.7 Hz, 1H), 6.98-6.88 (m, 2H), 6.30-6.29 (m, 1H), 5.30 (s, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.11 (s, 3H).

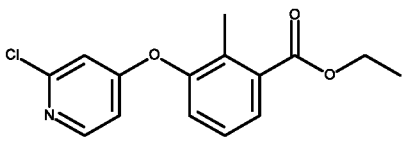
ESI-MS: 424.25 $(M+H)^+$.

Example 6: General procedure for the synthesis of analogues 120 – 197, 350-355, and 359



The following compound **117a** is an example illustrating Method A1:

Preparation of ethyl 3-[(2-chloro-4-pyridyl)oxy]-2-methyl-benzoate (**117a**):

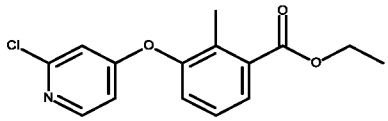
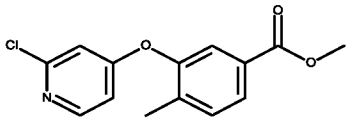
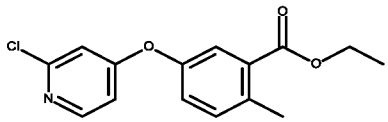
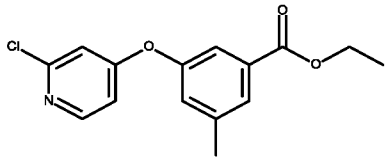
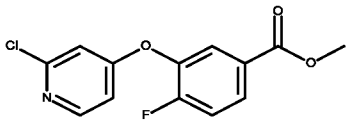
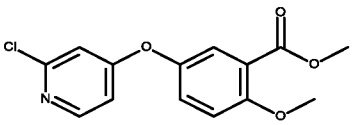
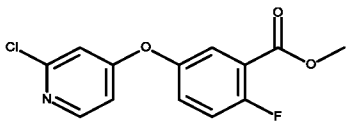


Intermediate **117a** was synthesized from ethyl 3-hydroxy-2-methyl-benzoate (6.30 mmol) and 2-chloro-4-nitropyridine (6.30 mmol) as a colorless oil in 95%

yield according to the general method A1.

ESI-MS: 292.00 $(M+H)^+$.

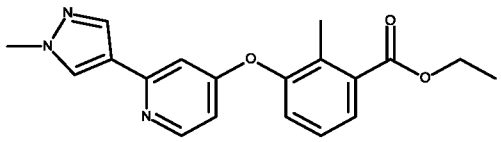
The following table illustrates intermediates **117** prepared from method A1:

Intermediate	Structure	Synthesis procedure
Compound **117a**		Method A1
Compound **117b**		Method A1
Compound **117c**		Method A1
Compound **117d**		Method A1
Compound **117e**		Method A1
Compound **117f**		Method A1
Compound **117g**		Method A1

5

The following compound **118a** is an example illustrating Method D2:

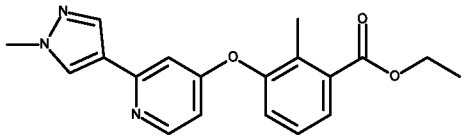
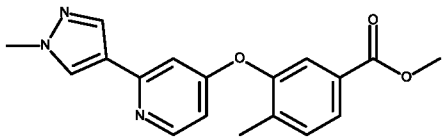
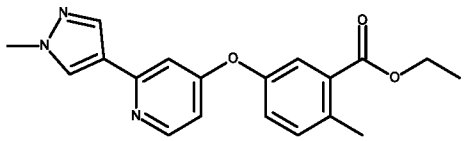
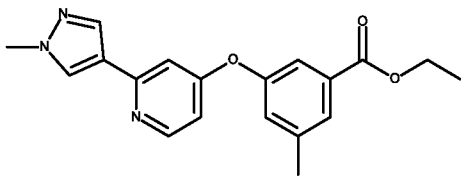
Preparation of ethyl 2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzoate (**118a**):

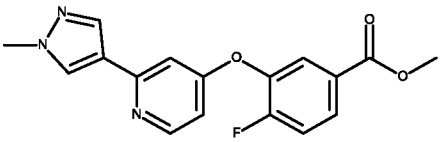
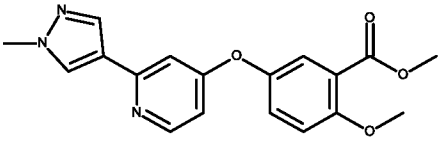


Intermediate **118a** was synthesized from **117a** (1.71 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (2.05 mmol) as a colorless oil in quantitative yield according to the general method D2.

ESI-MS: 338.15 $(M+H)^+$.

The following table illustrates intermediates **118** prepared from method D2:

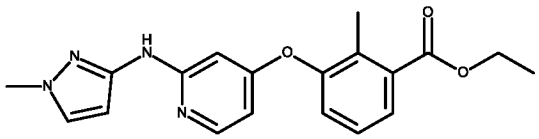
Intermediate	**Structure**	**Synthesis procedure**
Compound **118a**		Method D2
Compound **118b**		Method D2
Compound **118c**		Method D2
Compound **118d**		Method D2

Compound **118h**		Method D2
Compound **118i**		Method D2

Method H: To a solution of **117** (1 equiv.) in dioxane (10 mL/mmol) under nitrogen were added amine derivative (2 equiv.), Pd_2dba_3 (0.1 equiv.), Xantphos (0.2 equiv.) and Cs_2CO_3 (2 equiv.). The mixture was stirred at 100°C until completion (from 2 h to overnight). The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) to give the expected compound.

The following compound **118e** is an example illustrating Method H:

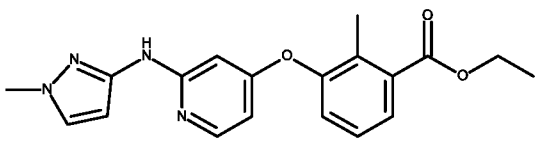
Preparation of ethyl 2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy) benzoate (**118e**):

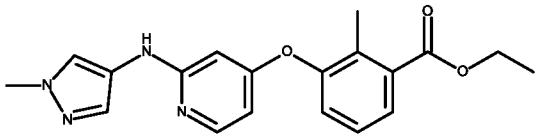
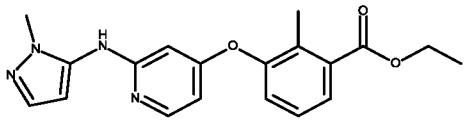
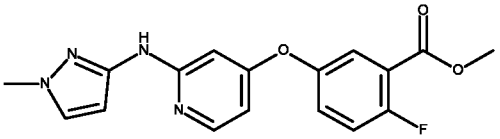
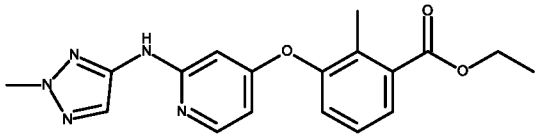


Intermediate **118e** was synthesized from **117a** (1.37 mmol) and 1-methylpyrazol-3-amine (2.74 mmol) as a yellow oil in 90% yield according to the general method H.

ESI-MS: 353.05 $(M+H)^+$.

The following table illustrates intermediates **113** prepared from method H:

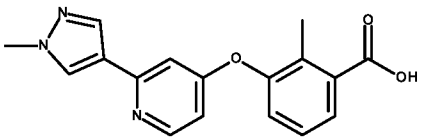
Intermediate	**Structure**	**Synthesis procedure**
Compound **118e**		Method H

Compound **118f**		Method H
Compound **118g**		Method H
Compound **118j**		Method H
Compound **118k**		Method H

Method I: To a stirred solution of **117a** (250 mg, 0.86 mmol) in CH_3CN (6 mL) were added pyrazole (123 mg, 1.79 mmol), Cs_2CO_3 (1.12 g, 3.42 mmol), CuI (360 mg, 1.88 mmol) and DMEDA (0.323 mL, 3 mmol). The reaction mixture was stirred at 100°C for 48h. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (Cyclohexane/EtOAc from 100/0 to 75/25) to give 58 mg of ethyl 2-methyl-3-[(2-pyrazol-1-yl-4-pyridyl)oxy]benzoate **118h** in 11% yield.

The following compound **119a** is an example illustrating Method B2:

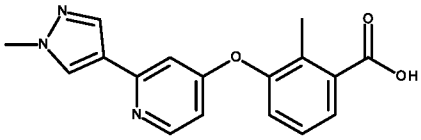
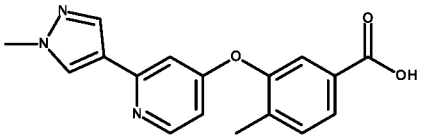
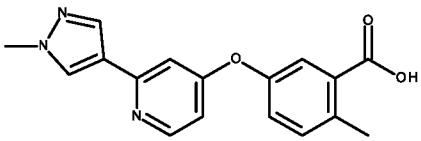
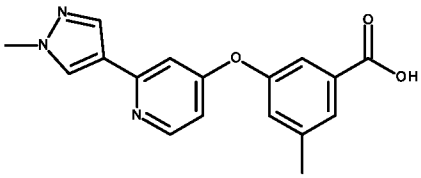
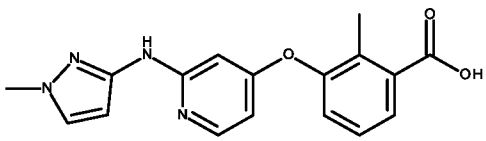
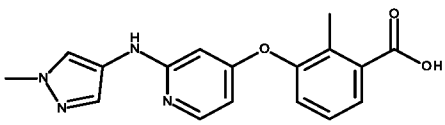
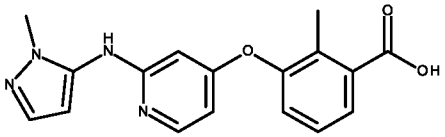
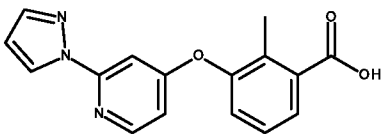
Preparation of 2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzoic acid (**119a**):

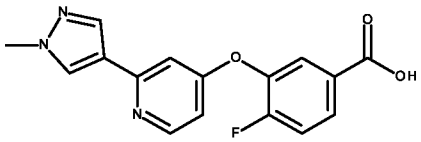
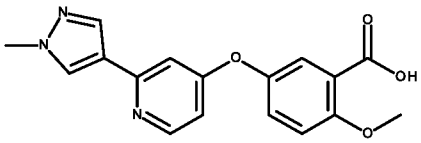
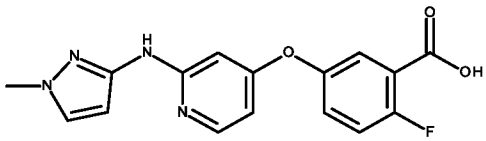
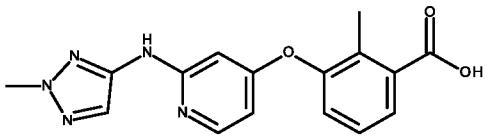


Intermediate **119a** was synthesized from **118a** (1.88 mmol) as a white powder in 79% yield according to the general method B2.

ESI-MS: 292.00 $(M+H)^+$.

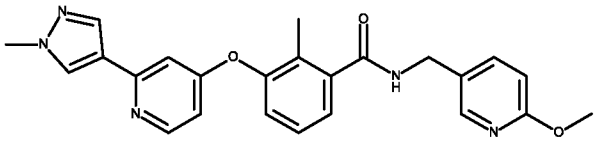
The following table illustrates intermediates **119** prepared from method B2:

Intermediate	Structure	Synthesis procedure
Compound **119a**		Method B2
Compound **119b**		Method B2
Compound **119c**		Method B2
Compound **119d**		Method B2
Compound **119e**		Method B2
Compound **119f**		Method B2
Compound **119g**		Method B2
Compound **119h**		Method B2

Compound **119i**		Method B2
Compound **119j**		Method B2
Compound **119k**		Method B2
Compound **119l**		Method B2

The following compounds are examples illustrating Method C2:

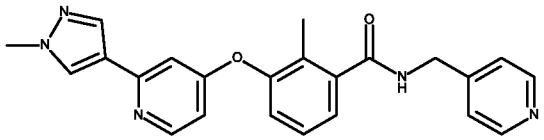
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**120**):



Compound **120** was synthesized from intermediate **119a** (0.10 mmol) and (6-methoxypyridin-3-yl)methanamine (0.12 mmol) as a white solid in 60% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.96 (s, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 7.39-7.28 (m, 2H), 7.24 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.47 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.11 (s, 3H).

ESI-MS: 430.10 $(M+H)^+$.

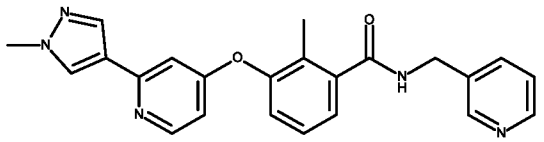
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-(4-pyridylmethyl) benzamide (**121**):



Compound **121** was synthesized from intermediate **119a** (0.10 mmol) and 4-(aminomethyl)pyridine (0.12 mmol) as a white solid in 69% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (t, J = 6.0 Hz, 1H), 8.54-8.52 (m, 2H), 8.36 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.43-7.32 (m, 4H), 7.25-7.22 (m, 2H), 6.49 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 400.05 $(M+H)^+$.

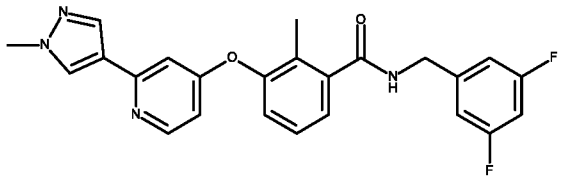
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-(3-pyridylmethyl) benzamide (**122**):



Compound **122** was synthesized from intermediate **119a** (0.10 mmol) and 3-(aminomethyl)pyridine (0.12 mmol) as a white solid in 59% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 5.9 Hz, 1H), 8.57 (d, J = 1.7 Hz, 1H), 8.48 (dd, J = 4.7 Hz, 1.4 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.76 (dt, J = 7.8 Hz, 1.8 Hz, 1H) 7.43-7.30 (m, 3H), 7.27-7.20 (m, 2H), 6.47 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.12 (s, 3H).

ESI-MS: 400.10 $(M+H)^+$.

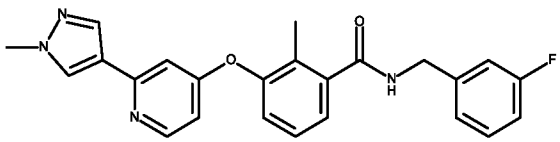
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**123**):



Compound **123** was synthesized from intermediate **119a** (0.10 mmol) and 3,5-difluorobenzylamine (0.12 mmol) as a white solid in 85% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.42-7.34 (m, 2H), 7.26-7.22 (m, 2H), 7.17-7.03 (m, 3H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).

ESI-MS: 435.15 $(M+H)^+$.

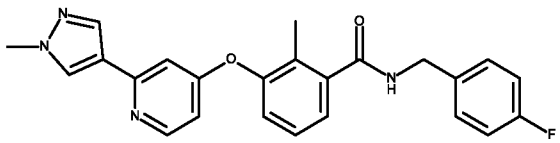
N-[(3-fluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**124**):



Compound **124** was synthesized from intermediate **119a** (0.10 mmol) and 3-fluorobenzylamine (0.12 mmol) as a white solid in 82% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (d, J = 0.5 Hz, 1H), 7.43-7.31 (m, 3H), 7.26-7.13 (m, 4H), 7.09 (td, J = 8.4 Hz, 2.3 Hz, 1H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).

ESI-MS: 417.20 $(M+H)^+$.

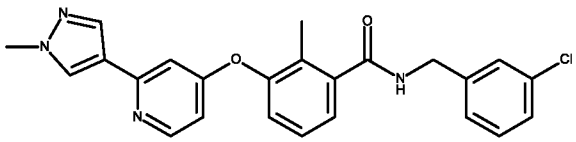
N-[(4-fluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**125**):



Compound **125** was synthesized from intermediate **119a** (0.10 mmol) and 4-fluorobenzylamine (0.12 mmol) as a white solid in 92% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (d, J = 0.5 Hz, 1H), 7.43-7.30 (m, 4H), 7.26-7.14 (m, 4H), 6.47 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.12 (s, 3H).

ESI-MS: 417.15 $(M+H)^+$.

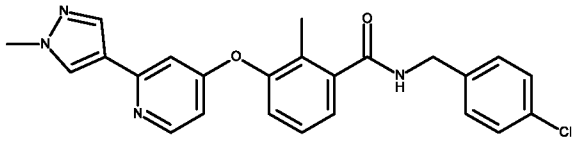
N-[(3-chlorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**126**):



Compound **126** was synthesized from intermediate **119a** (0.10 mmol) and 3-chlorobenzylamine (0.12 mmol) as a white solid in 72% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.44-7.30 (m, 6H), 7.25 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 433.15 $(M+H)^+$.

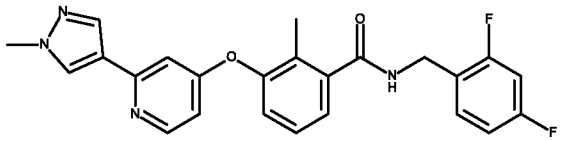
N-[(4-chlorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**127**):



Compound **127** was synthesized from intermediate **119a** (0.10 mmol) and 4-chlorobenzylamine (0.12 mmol) as a white solid in 83% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.97 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.45-7.30 (m, 6H), 7.25-7.20 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 433.05 $(M+H)^+$.

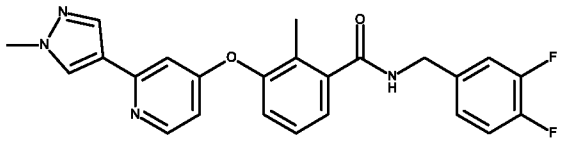
N-[(2,4-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**128**):



Compound **128** was synthesized from intermediate **119a** (0.065 mmol) and 2,4-difluorobenzylamine (0.097 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.93 (t, J = 5.6 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.51-7.43 (m, 1H), 7.40-7.18 (m, 5H), 7.09 (dd, J = 8.5 Hz, 7.0 Hz, 1H), 6.47 (dd, J = 5.6 Hz, 2.2 Hz, 1H), 4.46 (d, J = 5.5 Hz, 2H), 3.86 (s, 3H), 2.11 (s, 3H).

ESI-MS: 435.15 $(M+H)^+$.

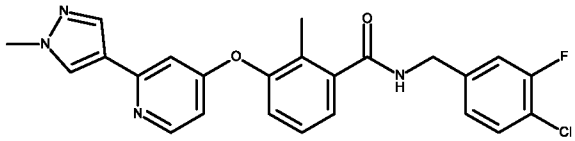
N-[(3,4-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**129**):



Compound **129** was synthesized from intermediate **119a** (0.065 mmol) and 3,4-difluorobenzylamine (0.097 mmol) as a white solid in 57% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.47-7.30 (m, 4H), 7.27-7.17 (m, 3H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 435.15 $(M+H)^+$.

N-[(4-chloro-3-fluoro-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**130**):

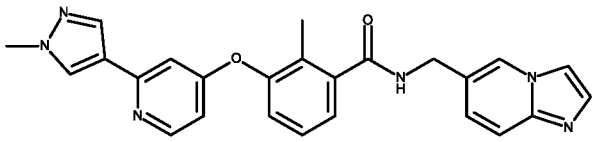


Compound **130** was synthesized from intermediate **119a** (0.065 mmol) and 4-

chloro-3-fluorobenzylamine (0.097 mmol) as a white solid in 34% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.43-7.32 (m, 3H), 7.28-7.18 (m, 3H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 451.10 $(M+H)^+$.

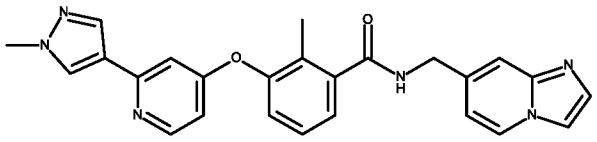
N-(imidazo[1,2-*a*]pyridin-6-ylmethyl)-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**131**):



Compound **131** was synthesized from intermediate **119a** (0.065 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.097 mmol) as a white solid in 57% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.97 (t, J = 5.9 Hz, 1H), 8.51 (s, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.97-7.95 (m, 2H), 7.57-5.55 (m, 2H), 7.41-7.32 (m, 2H), 7.26-7.20 (m, 3H), 6.47 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.45 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 439.15 $(M+H)^+$.

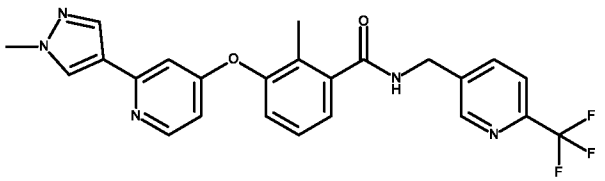
N-(imidazo[1,2-*a*]pyridin-7-ylmethyl)-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**132**):



Compound **132** was synthesized from intermediate **119a** (0.065 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.097 mmol) as a white solid in 50% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.51 (d, J = 7.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.90 (s, 1H), 7.53 (d, J = 1.0 Hz, 1H), 7.44 (s, 1H), 7.41-7.34 (m, 2H), 7.28-7.20 (m, 2H), 6.89 (dd, J = 7.0 Hz , Hz 1.5, 1H), 6.49 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.49 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 439.15 $(M+H)^+$.

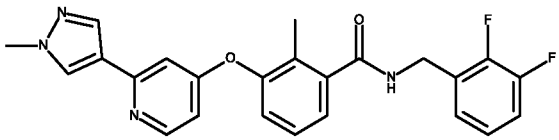
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-{[6-(trifluoromethyl)-3-pyridyl]methyl}benzamide (**133**):



Compound **133** was synthesized from intermediate **119a** (0.065 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.097 mmol) as a white solid in 79% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, J = 5.9 Hz, 1H), 8.76 (s, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 8.08-8.02 (m, 1H), 7.96 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.43-7.35 (m, 2H), 7.27-7.20 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.59 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H).

ESI-MS: 468.15 $(M+H)^+$.

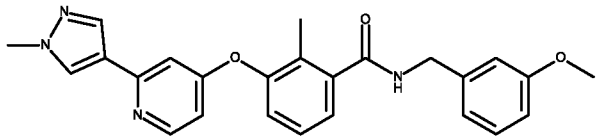
N-[(2,3-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**134**):



Compound **134** was synthesized from intermediate **119a** (0.074 mmol) and 2,3-difluorobenzylamine (0.111 mmol) as a white solid in 60% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.97 (t, J = 5.8 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.40-7.29 (m, 3H), 7.28-7.18 (m, 4H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.53 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

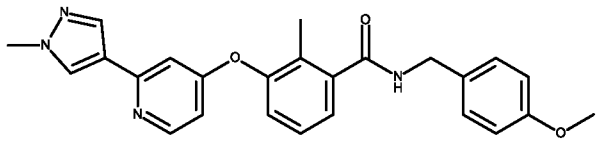
ESI-MS: 435.15 $(M+H)^+$.

N-[(3-methoxyphenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl] oxy}benzamide (**135**):



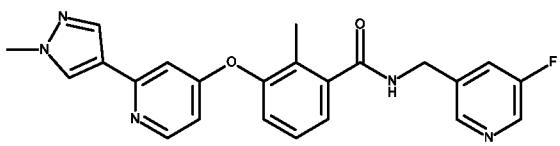
Compound **135** was synthesized from intermediate **119a** (0.074 mmol) and 3-methoxybenzylamine (0.111 mmol) as a white solid in 78% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (t, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6 Hz, 1H), 7.43-7.16 (m, 5H), 6.98-6.90 (m, 2H), 6.86-6.80 (m, 1H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.14 (s, 3H).
ESI-MS: 429.20 $(M+H)^+$.

N-[(4-methoxyphenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl] oxy}benzamide (**136**):



Compound **136** was synthesized from intermediate **119a** (0.074 mmol) and 4-methoxybenzylamine (0.111 mmol) as a white solid in 63% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.83 (t, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30-7.18 (m, 5H), 6.92-6.88 (m, 2H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 2.12 (s, 3H).
ESI-MS: 429.15 $(M+H)^+$.

N-[(5-fluoro-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl] oxy}benzamide (**137**):

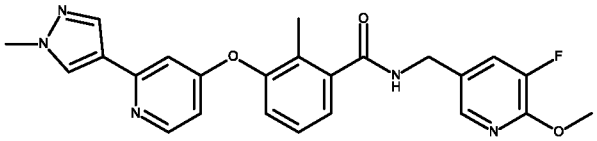


Compound **137** was synthesized from intermediate **119a** (0.10 mmol) and 5-

fluoro-3-pyridinemethanamine (0.15 mmol) as a white solid in 50% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 5.9 Hz, 1H), 8.52-8.45 (m, 2H), 8.36 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.71-7.64 (m, 1H), 7.41-7.33 (m, 2H), 7.27-7.20 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.53 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.13 (s, 3H).

ESI-MS: 418.15 $(M+H)^+$.

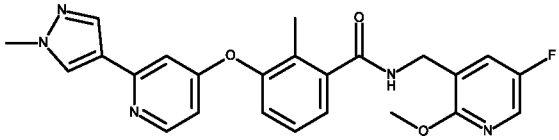
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**138**):



Compound **138** was synthesized from intermediate **119a** (0.10 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.15 mmol) as a white solid in 62% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (t, J = 5.9 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.98-7.95 (m, 2H), 7.65 (dd, J = 11.4 Hz, 1.9 Hz, 1H), 7.42-7.31 (m, 2H), 7.26-7.19 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H), 3.93 (s, 3H), 3.86 (s, 3H), 2.12 (s, 3H).

ESI-MS: 448.15 $(M+H)^+$.

N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (139):

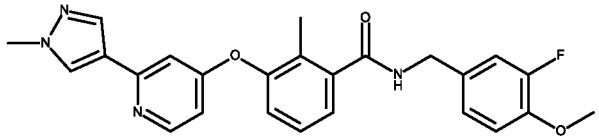


Compound **139** was synthesized from intermediate **119a** (0.10 mmol) and 5-fluoro-2-methoxy-3-pyridinemethanamine (0.24 mmol) as a white solid in 40% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85 (t, J = 5.7 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 8.07 (d, J = 3.0 Hz, 1H), 7.96 (d, J = 0.6 Hz, 1H), 7.57 (dd, J = 8.6 Hz, 3.0 Hz, 1H), 7.41-7.36 (m, 2H), 7.24-7.21 (m, 2H), 6.49 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, J =

5.7 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 448.20 $(M+H)^+$.

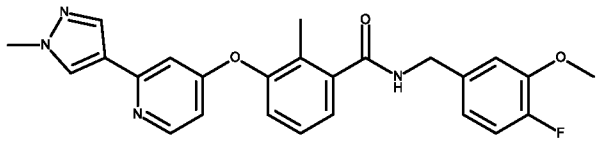
N-[(3-fluoro-4-methoxy-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (140):



Compound **140** was synthesized from intermediate **119a** (0.10 mmol) and (3-fluoro-4-methoxyphenyl)methanamine (0.15 mmol) as a white solid in 58% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.31 (dd, J = 7.6 Hz, 1.3 Hz, 1H), 7.24-7.09 (m, 5H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.13 (s, 3H).

ESI-MS: 447.20 $(M+H)^+$.

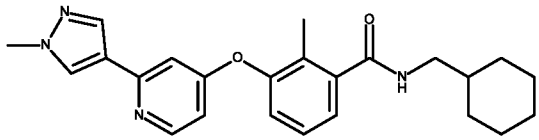
N-[(4-fluoro-3-methoxy-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**141**):



Compound **141** was synthesized from intermediate **119a** (0.10 mmol) and 5-(aminomethyl)-2-fluoroanisole (0.15 mmol) as a white solid in 70% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (t, J = 6.0 Hz, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 0.6 Hz, 1H), 7.42-7.30 (m, 2H), 7.25-7.12 (m, 4H), 6.92-6.88 (m, 1H), 6.49 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 2.14 (s, 3H).

ESI-MS: 447.20 $(M+H)^+$.

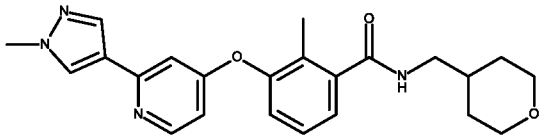
N-(cyclohexylmethyl)-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**142**):



Compound **142** was synthesized from intermediate **119a** (0.10 mmol) and 1-cyclohexylmethanamine (0.15 mmol) as a white solid in 69% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.36-3.81 (m, 2H), 8.24 (s, 1H), 7.96 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.27-7.22 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.87 (s, 3H), 3.09 (t, *J* = 6.4 Hz, 2H), 2.13 (s, 3H), 1.77-1.47 (m, 6H), 1.27-1.12 (m, 3H), 0.99-0.89 (m, 2H).

ESI-MS: 405.20 $(M+H)^+$.

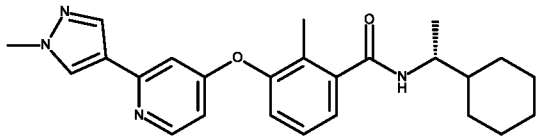
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-(tetrahydropyran-4-ylmethyl)benzamide (**143**):



Compound **143** was synthesized from intermediate **119a** (0.10 mmol) and 4-(aminomethyl)tetrahydropyran (0.15 mmol) as a white solid in 71% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.39 (t, *J* = 5.8 Hz, 1H), 8.36 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.96 (d, *J* = 0.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.28-7.21 (m, 2H), 7.19 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.89-3.82 (m, 5H), 3.27-3.24 (m, 2H), 3.18-3.12 (m, 2H), 2.13 (s, 3H), 1.80-1.74 (m, 1H), 1.63-1.60 (m, 2H), 1.26-1.16 (m, 2H).

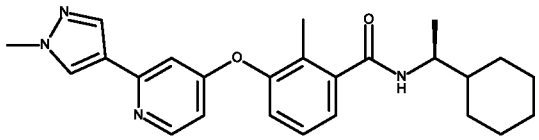
ESI-MS: 407.15 $(M+H)^+$.

N-[(1*R*)-1-cyclohexylethyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**144**):



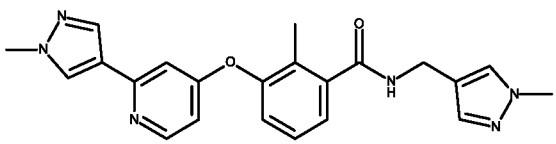
Compound **144** was synthesized from intermediate **119a** (0.10 mmol) and (*R*)-1-cyclohexylethanamine (0.15 mmol) as a white solid in 60% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.36 (d, *J* = 5.7 Hz, 1H), 8.25 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 0.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.27-7.14 (m, 3H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.92-3.76 (m, 4H), 2.12 (s, 3H), 1.83-1.57 (m, 5H), 1.38-1.33 (m, 1H), 1.24-0.92 (m, 8H). ESI-MS: 419.20 $(M+H)^+$.

N-[(1*S*)-1-cyclohexylethyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**145**):



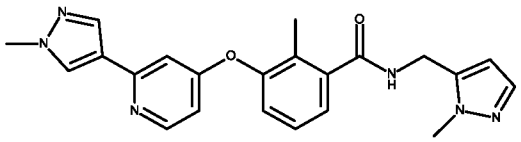
Compound **145** was synthesized from intermediate **119a** (0.10 mmol) and (*S*)-1-cyclohexylethanamine (0.15 mmol) as a white solid in 54% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.36 (d, *J* = 5.7 Hz, 1H), 8.25 (s, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.96 (s, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.26-7.15 (m, 3H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.90-3.75 (m, 4H), 2.12 (s, 3H), 1.82-1.58 (m, 5H), 1.42-1.33 (m, 1H), 1.24-1.06 (m, 6H), 1.03-0.94 (m, 2H). ESI-MS: 419.20 $(M+H)^+$.

2-methyl-*N*-[(1-methylpyrazol-4-yl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**146**):



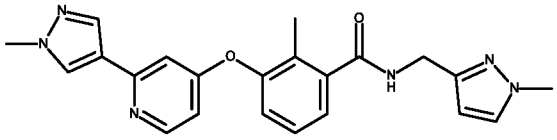
Compound **146** was synthesized from intermediate **119a** (0.10 mmol) and *C*-(1-methyl-1*H*-pyrazol-4-yl)-methylamine (0.15 mmol) as a white solid in 62% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.69 (t, *J* = 5.7 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6 Hz, 1H), 7.61 (s, 1H), 7.37-7.32 (m, 2H), 7.27 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.18 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 6.47 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.27 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 2.12 (s, 3H).
ESI-MS: 403.15 $(M+H)^+$.

2-methyl-*N*-[(2-methylpyrazol-3-yl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**147**):



Compound **147** was synthesized from intermediate **119a** (0.10 mmol) and *C*-(2-methyl-2*H*-pyrazol-3-yl)-methylamine (0.15 mmol) as a white solid in 69% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.89 (t, *J* = 5.7 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.32-7.28 (m, 2H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 6.19 (d, *J* = 1.8 Hz, 1H), 4.51 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 2.13 (s, 3H).
ESI-MS: 403.20 $(M+H)^+$.

2-methyl-*N*-[(1-methylpyrazol-3-yl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**148**):

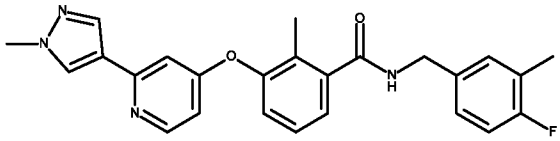


Compound **148** was synthesized from intermediate **119a** (0.10 mmol) and (1-methyl-1*H*-pyrazol-3-yl)methanamine (0.15 mmol) as a white solid in 72% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.74 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6

Hz, 1H), 7.59 (d, *J* = 2.1 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.27 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.18 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.13 (s, 3H).

ESI-MS: 403.15 $(M+H)^+$.

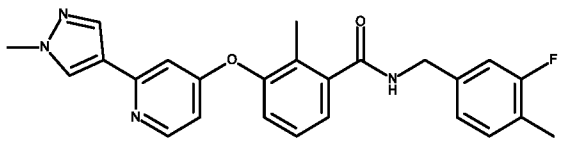
N-[(4-fluoro-3-methyl-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**149**):



Compound **149** was synthesized from intermediate **119a** (0.10 mmol) and (4-fluoro-3-methylphenyl)methanamine (0.15 mmol) as a white solid in 67% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (t, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (s, 1H), 7.42-7.29 (m, 2H), 7.28-7.16 (m, 4H), 7.13-7.06 (m, 1H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.40 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.22 (d, *J* = 1.5 Hz, 3H), 2.13 (s, 3H).

ESI-MS: 431.15 $(M+H)^+$.

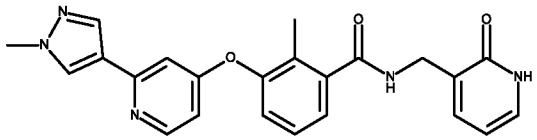
N-[(3-fluoro-4-methyl-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**150**):



Compound **150** was synthesized from intermediate **119a** (0.10 mmol) and 3-fluoro-4-methylbenzylamine (0.15 mmol) as a white solid in 69% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (t, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, *J* = 0.6 Hz, 1H), 7.40-7.30 (m, 2H), 7.27-7.17 (m, 3H), 7.13-7.07 (m, 2H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.21 (d, *J* = 1.2 Hz, 3H), 2.13 (s, 3H).

ESI-MS: 431.15 $(M+H)^+$.

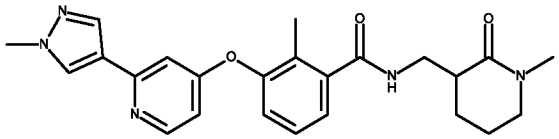
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-[(2-oxo-1*H*-pyridin-3-yl)methyl]benzamide (**151**):



Compound **151** was synthesized from intermediate **119a** (0.10 mmol) and 3-(aminomethyl)-2(1*H*)-pyridinone (0.24 mmol) as a white solid in 40% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.62 (bs, 1H), 8.66 (t, *J* = 5.8 Hz, 1H), 8.36 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.96 (d, *J* = 0.6 Hz, 1H), 7.37-7.35 (m, 3H), 7.30 (dd, *J* = 6.5 Hz, 2.0 Hz, 1H), 7.25-7.18 (m, 2H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 6.20 (t, *J* = 6.6 Hz, 1H), 4.21 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H), 2.15 (s, 3H).

ESI-MS: 416.15 $(M+H)^+$.

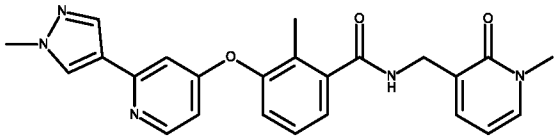
2-methyl-*N*-[(1-methyl-2-oxo-3-piperidyl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide(**152**):



Compound **152** was synthesized from intermediate **119a** (0.10 mmol) and 3-(aminomethyl)-1-methyl-2-piperidinone (0.24 mmol) as a white solid in 69% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.36 (d, *J* = 5.7 Hz, 1H), 8.30 (t, *J* = 5.8 Hz, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 6.6 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 3.87 (s, 3H), 3.67-3.61 (m, 1H), 3.41-3.33 (m, 2H), 3.27-3.20 (m, 2H), 2.81 (s, 3H), 2.13 (s, 3H), 1.92-1.84 (m, 2H), 1.72-1.54 (m, 2H).

ESI-MS: 434.20 $(M+H)^+$.

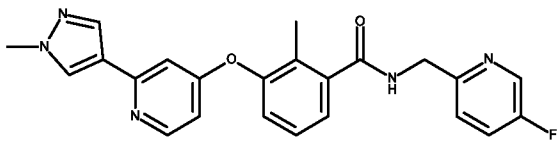
2-methyl-*N*-[(1-methyl-2-oxo-3-pyridyl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide(**153**):



Compound **153** was synthesized from intermediate **119a** (0.07 mmol) and 3-(aminomethyl)-1-methyl-2(1*H*)-pyridinone (0.15 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.69 (t, *J* = 5.8 Hz, 1H), 8.36 (d, *J* = 5.8 Hz, 1H), 8.25 (s, 1H), 7.96 (d, *J* = 0.7 Hz, 1H), 7.63 (dd, *J* = 6.7 Hz, 1.9 Hz, 1H), 7.41-7.33 (m, 3H), 7.27-7.18 (m, 2H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 6.24 (t, *J* = 6.8 Hz, 1H), 4.24 (d, *J* = 5.8 Hz, 2H), 3.86 (s, 3H), 3.46 (s, 3H), 2.15 (s, 3H).

ESI-MS: 430.20 $(M+H)^+$.

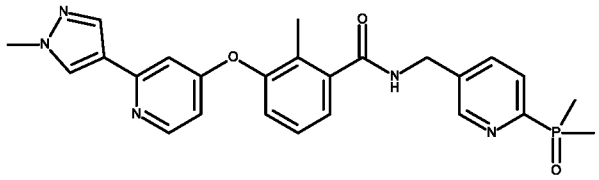
N-[(5-fluoro-2-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**154**):



Compound **154** was synthesized from intermediate **119a** (0.06 mmol) and 5-fluoro-2-pyridinemethanamine (0.10 mmol) as a white solid in 41% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.52 (d, *J* = 2.9 Hz, 1H), 8.36 (d, *J* = 5.7 Hz, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.73 (td, *J* = 8.8 Hz, 3.0 Hz, 1H), 7.47 (dd, *J* = 8.7 Hz, 4.5 Hz, 1H), 7.43-7.35 (m, 2H), 7.28-7.19 (m, 2H), 6.49 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 3.86 (s, 3H), 2.16 (s, 3H).

ESI-MS: 418.20 $(M+H)^+$.

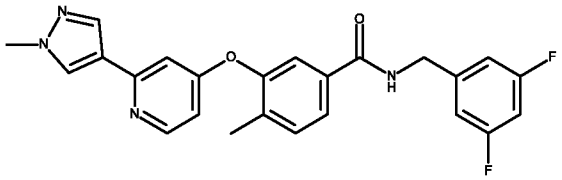
N-[(6-dimethylphosphoryl-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide(**155**):



Compound **155** was synthesized from intermediate **119a** (0.10 mmol) and (5-(aminomethyl)pyridin-2-yl)dimethylphosphine oxide (0.29 mmol) as a white solid in 78% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (t, J = 5.9 Hz, 1H), 8.75 (s, 1H), 8.35 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.98-7.90 (m, 3H), 7.44-7.33 (m, 2H), 7.24-7.21 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.54 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.14 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H). ^{31}P NMR (162 MHz, DMSO-d_6) δ (ppm): 33.89.

ESI-MS: 476.10 $(M+H)^+$.

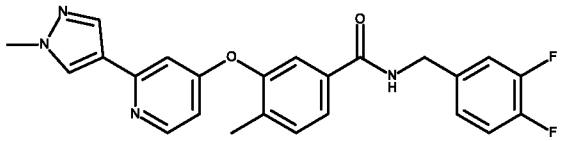
N-[(3,5-difluorophenyl)methyl]-4-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**156**):



Compound **156** was synthesized from intermediate **119b** (0.10 mmol) and 3,5-difluorobenzylamine (0.15 mmol) as a white solid in 67% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.10 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.97 (d, J = 0.7 Hz, 1H), 7.79 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.64 (d, J = 1.7 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.29-7.20 (m, 1H), 7.13-7.05 (m, 1H), 7.04-6.98 (m, 2H), 6.55 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.46 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.20 (s, 3H).

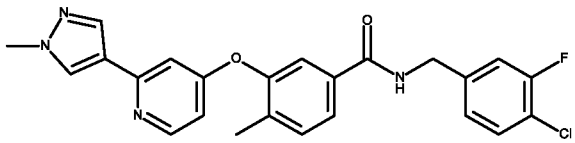
ESI-MS: 435.00 $(M+H)^+$.

N-[(3,4-difluorophenyl)methyl]-4-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**157**):



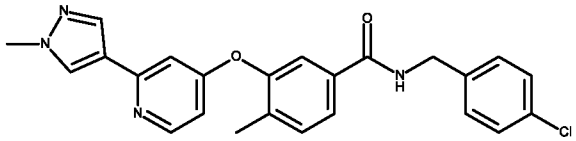
Compound **157** was synthesized from intermediate **119b** (0.10 mmol) and 3,4-difluorobenzylamine (0.15 mmol) as a white solid in 45% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, J = 5.9 Hz, 1H), 8.40-8.33 (m, 1H), 8.25 (s, 1H), 7.97 (d, J = 0.7 Hz, 1H), 7.78 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.42-7.31 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.16-7.13 (m, 1H), 6.54 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.42 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.20 (s, 3H).
ESI-MS: 435.00 $(M+H)^+$.

N-[(4-chloro-3-fluoro-phenyl)methyl]-4-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**158**):



Compound **158** was synthesized from intermediate **119b** (0.10 mmol) and 4-chloro-3-fluorobenzylamine (0.15 mmol) as a white solid in 57% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, J = 6.0 Hz, 1H), 8.39-8.34 (m, 1H), 8.25 (s, 1H), 7.97 (d, J = 0.7 Hz, 1H), 7.79 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.55-7.47 (m, 2H), 7.33 (dd, J = 10.4 Hz, 1.9 Hz, 1H), 7.27-7.21 (m, 1H), 7.17 (dd, J = 8.2 Hz, 1.3 Hz, 1H), 6.54 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.20 (s, 3H).
ESI-MS: 451.05 $(M+H)^+$.

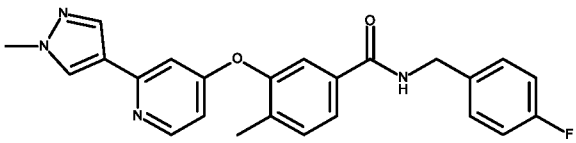
N-[(4-chlorophenyl)methyl]-4-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**159**):



Compound **159** was synthesized from intermediate **119b** (0.10 mmol) and 4-chlorobenzylamine (0.15 mmol) as a white solid in 92% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, J = 6.0 Hz, 1H), 8.38-8.34 (m, 1H), 8.25 (s, 1H), 7.97 (d, J = 0.7 Hz, 1H), 7.78 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.40-7.29 (m, 4H), 7.23 (d, J = 2.1 Hz, 1H), 6.54 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.20 (s, 3H).

ESI-MS: 433.00 $(M+H)^+$.

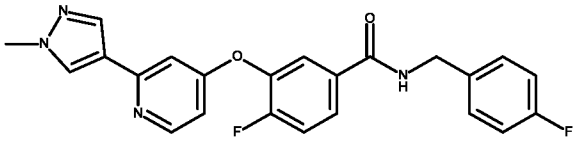
N-[(4-fluorophenyl)methyl]-4-methyl-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**352**):



Compound **352** was synthesized from intermediate **119b** (0.08 mmol) and 4-fluorobenzylamine (0.12 mmol) as a white solid in 80% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.25 (s, 1H), 7.97 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.36-7.31 (m, 2H), 7.23 (d, J = 2.4 Hz, 1H), 7.16-7.10 (m, 2H), 6.54 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.20 (s, 3H).

ESI-MS: 417.10 $(M+H)^+$.

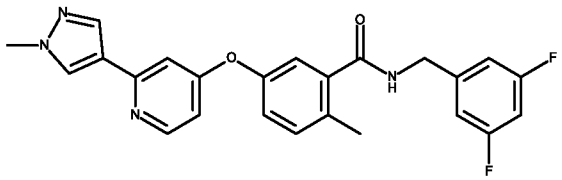
4-fluoro-*N*-[(4-fluorophenyl)methyl]-3-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**353**):



Compound **353** was synthesized from intermediate **119i** (0.08 mmol) and 4-fluorobenzylamine (0.12 mmol) as a white solid in 63% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.14 (t, J = 5.9 Hz, 1H), 8.40 (d, J = 5.7 Hz, 1H), 8.28 (s, 1H), 7.99 (s, 1H), 7.94-7.87 (m, 2H), 7.61-7.56 (m, 1H), 7.37-7.30 (m, 3H), 7.19-7.10 (m, 2H), 6.71 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H).

ESI-MS: 421.05 $(M+H)^+$.

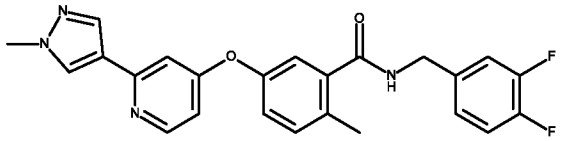
N-[(3,5-difluorophenyl)methyl]-2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl] oxy}benzamide (**160**):



Compound **160** was synthesized from intermediate **119c** (0.10 mmol) and 3,5-difluorobenzylamine (0.15 mmol) as a white solid in 90% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (t, J = 6.0 Hz, 1H), 8.40-8.35 (m, 1H), 8.25 (s, 1H), 7.96 (d, J = 0.7 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.27-7.23 (m, 2H), 7.19 (dd, J = 8.2 Hz, 2.6 Hz, 1H), 7.14-7.07 (m, 1H), 7.07-7.02 (m, 2H), 6.66 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.44 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.36 (s, 3H).

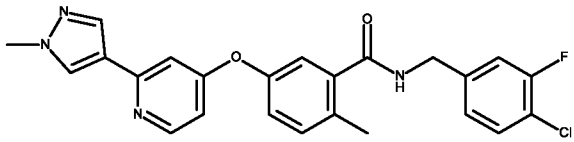
ESI-MS: 435.00 $(M+H)^+$.

N-[(3,4-difluorophenyl)methyl]-2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**161**):



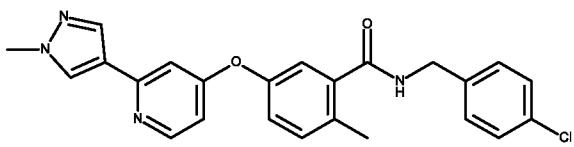
Compound **161** was synthesized from intermediate **119c** (0.10 mmol) and 3,4-difluorobenzylamine (0.15 mmol) as a white solid in 41% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (t, J = 6.0 Hz, 1H), 8.39-8.35 (m, 1H), 8.25 (s, 1H), 7.96 (d, J = 0.7 Hz, 1H), 7.44-7.34 (m, 3H), 7.25 (d, J = 2.1 Hz, 1H), 7.22 (d, J = 2.6 Hz, 1H), 7.20-7.15 (m, 2H), 6.65 (dd, J = 5.7 Hz , 2.4 Hz, 1H), 4.41 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.35 (s, 3H).
ESI-MS: 435.05 $(M+H)^+$.

N-[(4-chloro-3-fluoro-phenyl)methyl]-2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**162**):



Compound **162** was synthesized from intermediate **119c** (0.10 mmol) and 4-chloro-3-fluorobenzylamine (0.15 mmol) as a white solid in 60% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (t, J = 6.0 Hz, 1H), 8.40-8.35 (m, 1H), 8.25 (s, 1H), 7.96 (d, J = 0.7 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.37-7.33 (m, 2H), 7.28-7.15 (m, 4H), 6.65 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.35 (s, 3H).
ESI-MS: 451.05 $(M+H)^+$.

N-[(4-chlorophenyl)methyl]-2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**163**):

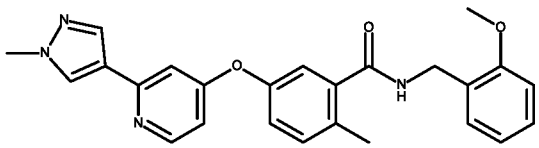


Compound **163** was synthesized from intermediate **119c** (0.10 mmol) and 4-

chlorobenzylamine (0.15 mmol) as a white solid in 79% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 (t, J = 6.0 Hz, 1H), 8.48-8.45 (m, 1H), 8.34 (s, 1H), 8.05 (d, J = 0.7 Hz, 1H), 7.51-7.41 (m, 5H), 7.34 (d, J = 2.1 Hz, 1H), 7.30-7.23 (m, 2H), 6.74 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H), 3.95 (s, 3H), 2.44 (s, 3H).

ESI-MS: 433.00 $(M+H)^+$.

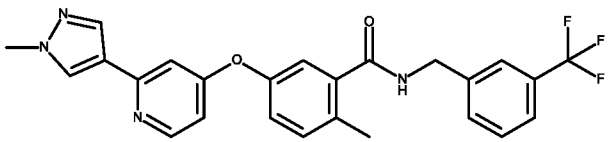
N-[(2-methoxyphenyl)methyl]-2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl] oxy}benzamide (**351**):



Compound **351** was synthesized from intermediate **119c** (0.07 mmol) and 2-methoxybenzylamine (0.10 mmol) as a white solid in 71% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.70 (t, J = 5.8 Hz, 1H), 8.37 (d, J = 5.7 Hz, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.28-7.21 (m, 3H), 7.20-7.16 (m, 2H), 6.98 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.66 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 2.36 (s, 3H).

ESI-MS: 429.10 $(M+H)^+$.

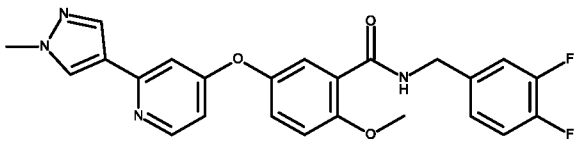
2-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-{[3-(trifluoromethyl) phenyl]methyl}benzamide (**354**):



Compound **354** was synthesized from intermediate **119c** (0.07 mmol) and 3-trifluoromethylbenzylamine (0.10 mmol) as a white solid in 73% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.97 (t, J = 6.0 Hz, 1H), 8.37 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.72-7.53 (m, 4H), 7.36 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.21-7.16 (m, 2H), 6.66 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.86 (s, 3H), 2.35 (s, 3H).

ESI-MS: 467.10 $(M+H)^+$.

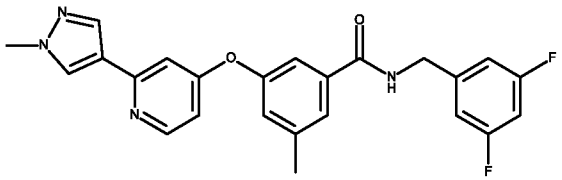
N-[(3,4-difluorophenyl)methyl]-2-methoxy-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**359**):



Compound **359** was synthesized from intermediate **119j** (0.08 mmol) and 3,4-difluorobenzylamine (0.12 mmol) as a white solid in 72% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.87 (t, J = 6.1 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.24 (s, 1H), 7.95 (d, J = 0.7 Hz, 1H), 7.49 (d, J = 3.1 Hz, 1H), 7.43-7.32 (m, 3H), 7.28-7.15 (m, 3H), 6.61 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 6.1 Hz, 2H), 3.94 (s, 3H), 3.86 (s, 3H).

ESI-MS: 451.10 $(M+H)^+$.

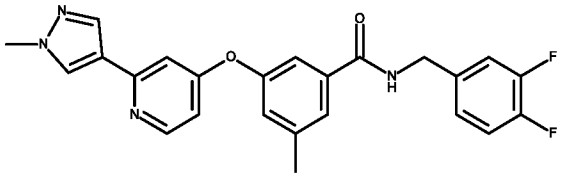
N-[(3,5-difluorophenyl)methyl]-3-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**164**):



Compound **164** was synthesized from intermediate **119d** (0.10 mmol) and 3,5-difluorobenzylamine (0.15 mmol) as a white solid in 43% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.12 (t, J = 5.9 Hz, 1H), 8.39 (d, J = 5.7 Hz, 1H), 8.27 (s, 1H), 7.97 (d, J = 0.5 Hz, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.22 (s, 1H), 7.13-7.07 (m, 1H), 7.04-6.99 (m, 2H), 6.68 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.40 (s, 3H).

ESI-MS: 435.00 $(M+H)^+$.

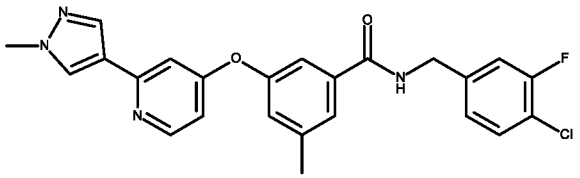
N-[(3,4-difluorophenyl)methyl]-3-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**165**):



Compound **165** was synthesized from intermediate **119d** (0.10 mmol) and 3,4-difluorobenzylamine (0.15 mmol) as a white solid in 29% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, *J* = 5.9 Hz, 1H), 8.39 (d, *J* = 5.7 Hz, 1H), 8.26 (s, 1H), 7.97 (d, *J* = 0.7 Hz, 1H), 7.66-7.64 (m, 1H), 7.48-7.47 (m, 1H), 7.42-7.32 (m, 2H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.22-7.21 (m, 1H), 7.19-7.11 (m, 1H), 6.67 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, *J* = 5.9 Hz, 2H), 3.86 (s, 3H), 2.39 (s, 3H).

ESI-MS: 435.00 $(M+H)^+$.

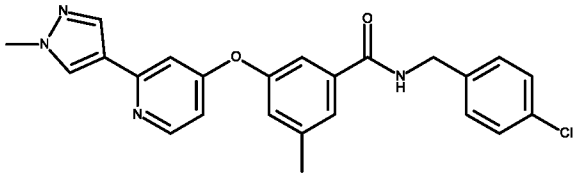
N-[(4-chloro-3-fluoro-phenyl)methyl]-3-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**166**):



Compound **166** was synthesized from intermediate **119d** (0.10 mmol) and 4-chloro-3-fluorobenzylamine (0.15 mmol) as a white solid in 46% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.11 (t, *J* = 5.9 Hz, 1H), 8.41-8.36 (m, 1H), 8.26 (s, 1H), 7.97 (d, *J* = 0.7 Hz, 1H), 7.66-7.65 (m, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.48-7.47 (m, 1H), 7.33 (dd, *J* = 10.4 Hz, 1.9 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.22-7.21 (m, 1H), 7.18 (dd, *J* = 8.3 Hz, 1.3 Hz, 1H), 6.67 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.45 (d, *J* = 5.9, 2H), 3.86 (s, 3H), 2.39 (s, 3H).

ESI-MS: 451.05 $(M+H)^+$.

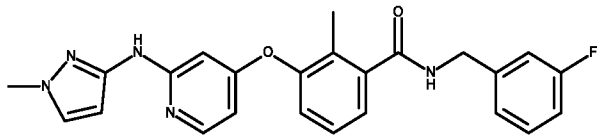
N-[(4-chlorophenyl)methyl]-3-methyl-5-{[2-(1-methylpyrazol-4-yl)-4-pyridyl]oxy} benzamide (**167**):



Compound **167** was synthesized from intermediate **119d** (0.10 mmol) and 4-chlorobenzylamine (0.15 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, J = 5.9 Hz, 1H), 8.41-8.37 (m, 1H), 8.26 (s, 1H), 7.97 (d, J = 0.7 Hz, 1H), 7.66-7.65 (m, 1H), 7.49-7.45 (m, 1H), 7.40-7.30 (m, 4H), 7.28 (d, J = 2.0 Hz, 1H), 7.22-7.21 (m, 1H), 6.66 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.43 (d, J = 5.9 Hz, 2H), 3.86 (s, 3H), 2.39 (s, 3H).

ESI-MS: 433.00 $(M+H)^+$.

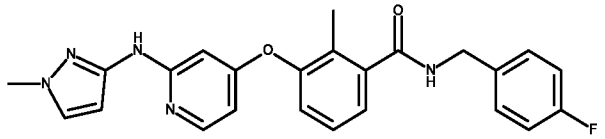
N-[(3-fluorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**168**):



Compound **168** was synthesized from intermediate **119e** (0.09 mmol) and 3-fluorobenzylamine (0.14 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.94 (t, J = 6.0 Hz, 1H), 7.98 (d, J = 5.7 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.42-7.31 (m, 3H), 7.22-7.13 (m, 3H), 7.08 (td, J = 8.3 Hz, 2.1 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H), 6.18 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.67 (s, 3H), 2.14 (s, 3H).

ESI-MS: 432.15 $(M+H)^+$.

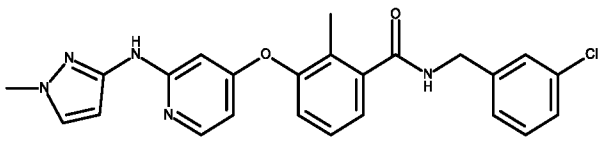
N-[(4-fluorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**169**):



Compound **169** was synthesized from intermediate **119e** (0.09 mmol) and 4-fluorobenzylamine (0.14 mmol) as a white solid in 50% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.91 (t, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.42-7.27 (m, 4H), 7.21-7.13 (m, 3H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.17 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.13 (s, 3H).

ESI-MS: 432.15 $(M+H)^+$.

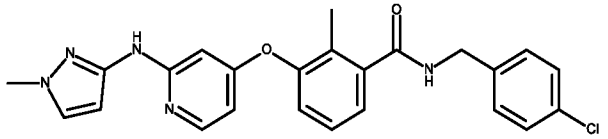
N-[(3-chlorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**170**):



Compound **170** was synthesized from intermediate **119e** (0.09 mmol) and 3-chlorobenzylamine (0.14 mmol) as a white solid in 63% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.95 (t, *J* = 6.1 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.43-7.28 (m, 6H), 7.18 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.14 (s, 3H).

ESI-MS: 448.15 $(M+H)^+$.

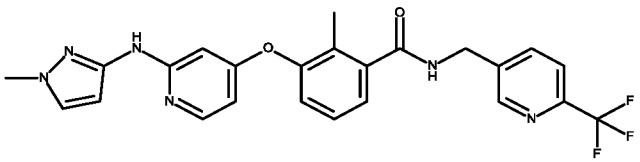
N-[(4-chlorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**171**):



Compound **171** was synthesized from intermediate **119e** (0.09 mmol) and 4-chlorobenzylamine (0.14 mmol) as a white solid in 49% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.93 (t, *J* = 6.0 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.43-7.28 (m, 6H), 7.18 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.17 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.43 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.13 (s, 3H).

ESI-MS: 448.15 $(M+H)^+$.

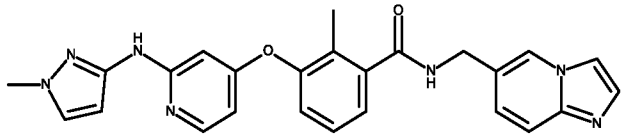
2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)-*N*-{[6-(trifluoromethyl)-3-pyridyl]methyl}benzamide (**172**):



Compound **172** was synthesized from intermediate **119e** (0.09 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.14 mmol) as a white solid in 57% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 9.05 (t, *J* = 5.9 Hz, 1H), 8.76-8.75 (m, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.40-7.33 (m, 2H), 7.19 (dd, *J* = 7.0 Hz, 2.4 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 2H), 3.67 (s, 3H), 2.14 (s, 3H).

ESI-MS: 483.15 $(M+H)^+$.

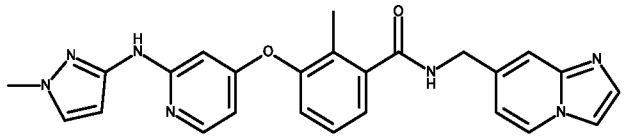
N-(imidazo[1,2-*a*]pyridin-6-ylmethyl)-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**173**):



Compound **173** was synthesized from intermediate **119e** (0.09 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.14 mmol) as a white solid in 50% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.93 (t, *J* = 5.9 Hz, 1H), 8.50-8.49 (m, 1H), 7.99-7.95 (m, 2H), 7.57-7.54 (m, 2H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.38-7.31 (m, 2H), 7.25 (dd, *J* = 9.3 Hz, 1.7 Hz, 1H), 7.18 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.17 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.44 (d, *J* = 5.8 Hz, 2H), 3.67 (s, 3H), 2.13 (s, 3H).

ESI-MS: 454.15 $(M+H)^+$.

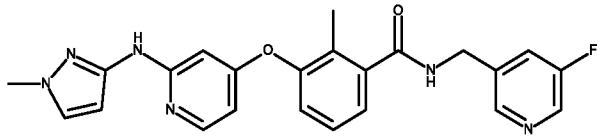
N-(imidazo[1,2-*a*]pyridin-7-ylmethyl)-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**174**):



Compound **174** was synthesized from intermediate **119e** (0.09 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.14 mmol) as a white solid in 41% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 8.51 (dd, *J* = 7.0 Hz, 0.7 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.53 (d, *J* = 1.1 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.44 (s, 1H), 7.40-7.33 (m, 2H), 7.19 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 6.90-6.87 (m, 2H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.67 (s, 3H), 2.16 (s, 3H).

ESI-MS: 454.15 $(M+H)^+$.

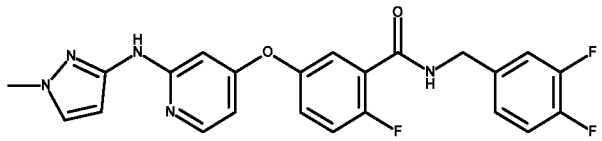
N-[(5-fluoro-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**175**):



Compound **175** was synthesized from intermediate **119e** (0.06 mmol) and 5-fluoro-3-pyridinemethanamine (0.09 mmol) as a white solid in 37% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 9.00 (t, *J* = 5.9 Hz, 1H), 8.49 (d, *J* = 2.8 Hz, 1H), 8.47-8.46 (m, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.69-7.65 (m, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.39-7.32 (m, 2H), 7.19 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 3.67 (s, 3H), 2.13 (s, 3H).

ESI-MS: 433.20 $(M+H)^+$.

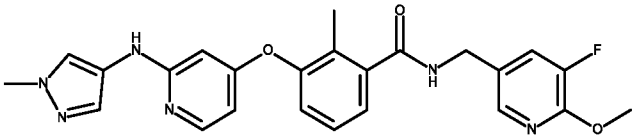
N-[(3,4-difluorophenyl)methyl]-2-fluoro-5-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**355**):



Compound **355** was synthesized from intermediate **119k** (0.08 mmol) and 3,4-difluorobenzylamine (0.11 mmol) as a white solid in 30% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 1H), 8.98 (t, *J* = 5.0 Hz, 1H), 8.01 (d, *J* = 5.7 Hz, 1H), 7.49-7.33 (m, 6H), 7.22-7.14 (m, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.30 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 4.44 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H).

ESI-MS: 454.00 $(M+H)^+$.

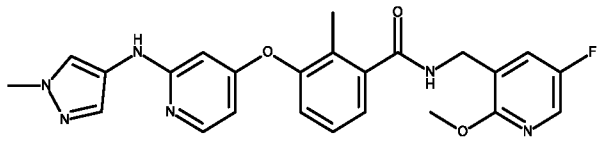
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**176**):



Compound **176** was synthesized from intermediate **119e** (0.06 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.09 mmol) as a white solid in 59% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.90 (t, *J* = 5.9 Hz, 1H), 7.98-7.96 (m, 2H), 7.64 (dd, *J* = 11.4 Hz, 1.9 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.37-7.28 (m, 2H), 7.17 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.17 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.14 (d, *J* = 2.2 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H), 3.67 (s, 3H), 2.12 (s, 3H).

ESI-MS: 463.25 $(M+H)^+$.

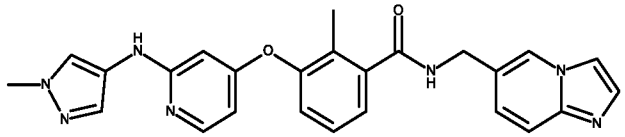
N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**177**):



Compound **177** was synthesized from intermediate **119e** (0.06 mmol) and 5-fluoro-3-pyridinemethanamine (0.09 mmol) as a white solid in 48% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.84 (t, *J* = 5.8 Hz, 1H), 8.07 (d, *J* = 3.0 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.55 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.39-7.34 (m, 2H), 7.21-7.17 (m, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.15 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H), 3.67 (s, 3H), 2.14 (s, 3H).

ESI-MS: 463.20 $(M+H)^+$.

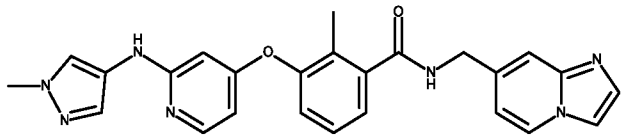
N-(imidazo[1,2-*a*]pyridin-6-ylmethyl)-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**178**):



Compound **178** was synthesized from intermediate **119f** (0.09 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.14 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.95 (t, *J* = 5.9 Hz, 1H), 8.74 (s, 1H), 8.50 (s, 1H), 7.99-7.96 (m, 2H), 7.86 (s, 1H), 7.57-7.55 (m, 2H), 7.38-7.31 (m, 3H), 7.24 (dd, *J* = 9.3 Hz, 1.6 Hz, 1H), 7.19 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 6.23 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 4.44 (d, *J* = 5.9 Hz, 2H), 3.76 (s, 3H), 2.12 (s, 3H).

ESI-MS: 454.15 $(M+H)^+$.

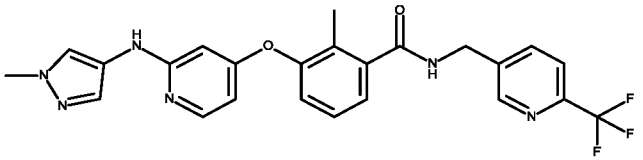
N-(imidazo[1,2-*a*]pyridin-7-ylmethyl)-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**179**):



Compound **179** was synthesized from intermediate **119f** (0.09 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.14 mmol) as a white solid in 46% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.0 Hz, 1H), 8.75 (s, 1H), 8.51 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 7.53 (d, *J* = 1.1 Hz, 1H), 7.44 (s, 1H), 7.40-7.33 (m, 2H), 7.31 (s, 1H), 7.21 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 6.88 (dd, *J* = 7.0 Hz, 1.6 Hz, 1H), 6.24 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.94 (d, *J* = 2.2 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.76 (s, 3H), 2.15 (s, 3H).

ESI-MS: 454.15 $(M+H)^+$.

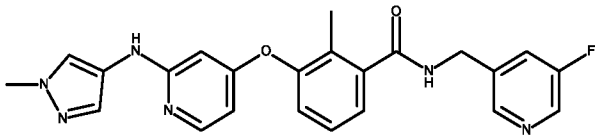
2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)-*N*-{[6-(trifluoro methyl)-3-pyridyl]methyl}benzamide (**180**):



Compound **180** was synthesized from intermediate **119f** (0.09 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.14 mmol) as a white solid in 58% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, *J* = 5.9 Hz, 1H), 8.76-8.74 (m, 2H), 8.04 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.86 (s, 1H), 7.39-7.34 (m, 2H), 7.31 (s, 1H), 7.21 (dd, *J* = 6.7 Hz, 2.6 Hz, 1H), 6.24 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.93 (d, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 5.9 Hz, 2H), 3.76 (s, 3H), 2.12 (s, 3H).

ESI-MS: 483.15 $(M+H)^+$.

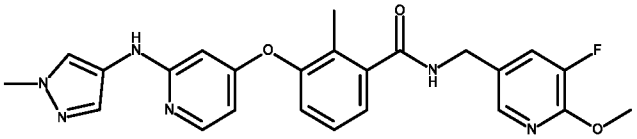
N-[(5-fluoro-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**181**):



Compound **181** was synthesized from intermediate **119f** (0.09 mmol) and 5-fluoro-3-pyridinemethanamine (0.14 mmol) as a white solid in 73% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 5.9 Hz, 1H), 8.73 (s, 1H), 8.49 (d, *J* = 2.8 Hz, 1H), 8.47-8.46 (m, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.86 (s, 1H), 7.69-7.65 (m, 1H), 7.39-7.33 (m, 2H), 7.31 (d, *J* = 0.6 Hz, 1H), 7.20 (dd, *J* = 7.2 Hz, 2.1 Hz, 1H), 6.23 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.94 (d, *J* = 2.2 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 3.77 (s, 3H), 2.12 (s, 3H).

ESI-MS: 433.20 $(M+H)^+$.

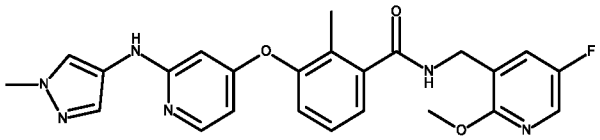
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**182**):



Compound **182** was synthesized from intermediate **119f** (0.09 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.14 mmol) as a white solid in 86% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90 (t, *J* = 5.8 Hz, 1H), 8.72 (s, 1H), 7.99-7.97 (m, 2H), 7.86 (s, 1H), 7.64 (dd, *J* = 11.4 Hz, 1.9 Hz, 1H), 7.37-7.29 (m, 3H), 7.19 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 6.23 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 2.11 (s, 3H).

ESI-MS: 463.20 $(M+H)^+$.

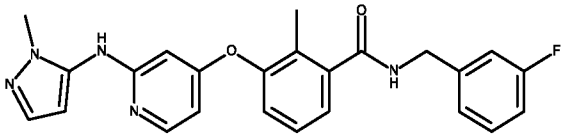
N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**183**):



Compound **183** was synthesized from intermediate **119f** (0.09 mmol) and 5-fluoro-2-methoxy-3-pyridinemethanamine (0.14 mmol) as a white solid in 70% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.84 (t, *J* = 5.8 Hz, 1H), 8.73 (s, 1H), 8.07 (d, *J* = 3.0 Hz, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.86 (s, 1H), 7.55 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 7.39-7.34 (m, 2H), 7.31 (d, *J* = 0.5 Hz, 1H), 7.22-7.18 (m, 1H), 6.24 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.94 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 2.13 (s, 3H).

ESI-MS: 463.20 $(M+H)^+$.

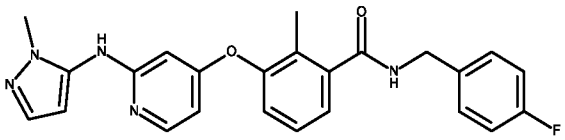
N-[(3-fluorophenyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**184**):



Compound **184** was synthesized from intermediate **119g** (0.15 mmol) and 3-fluorobenzylamine (0.23 mmol) as a white solid in 18% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.95 (t, J = 6.1 Hz, 1H), 8.75 (s, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.43-7.32 (m, 3H), 7.27 (d, J = 1.9 Hz, 1H), 7.23-7.13 (m, 3H), 7.09 (td, J = 8.4 Hz, 2.4 Hz, 1H), 6.36 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, J = 1.9 Hz, 1H), 6.12 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.61 (s, 3H), 2.13 (s, 3H).

ESI-MS: 432.15 $(M+H)^+$.

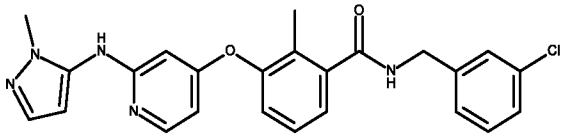
N-[(4-fluorophenyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**185**):



Compound **185** was synthesized from intermediate **119g** (0.15 mmol) and 4-fluorobenzylamine (0.23 mmol) as a white solid in 21% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92 (t, J = 6.0 Hz, 1H), 8.75 (s, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.40-7.34 (m, 3H), 7.31 (dd, J = 7.6 Hz, 1.3 Hz, 1H), 7.27 (d, J = 1.9 Hz, 1H), 7.22-7.14 (m, 3H), 6.36 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, J = 1.9 Hz, 1H), 6.11 (d, J = 2.2 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.61 (s, 3H), 2.12 (s, 3H).

ESI-MS: 432.15 $(M+H)^+$.

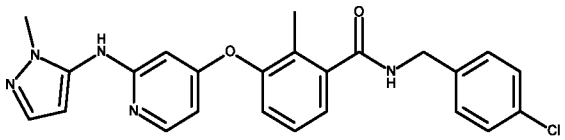
N-[(3-chlorophenyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**186**):



Compound **186** was synthesized from intermediate **119g** (0.15 mmol) and 3-chlorobenzylamine (0.23 mmol) as a white solid in 13% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.96 (t, J = 6.0 Hz, 1H), 8.75 (s, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.41-7.36 (m, 3H), 7.34-7.30 (m, 3H), 7.27 (d, J = 1.9 Hz, 1H), 7.22 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 6.36 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, J = 1.9 Hz, 1H), 6.12 (d, J = 2.2 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.61 (s, 3H), 2.13 (s, 3H).

ESI-MS: 448.10 $(M+H)^+$.

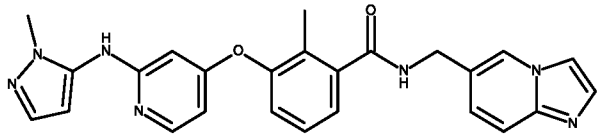
N-[(4-chlorophenyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**187**):



Compound **187** was synthesized from intermediate **119g** (0.15 mmol) and 4-chlorobenzylamine (0.23 mmol) as a white solid in 18% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.17 (s, 1H), 8.94 (t, J = 6.0 Hz, 1H), 8.75 (s, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.43-7.30 (m, 6H), 7.27 (d, J = 1.9 Hz, 1H), 7.21 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 6.36 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, J = 1.9 Hz, 1H), 6.11 (d, J = 2.2 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 3.61 (s, 3H), 2.12 (s, 3H).

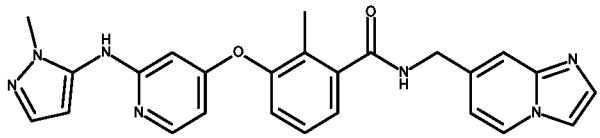
ESI-MS: 448.15 $(M+H)^+$.

N-(imidazo[1,2-*a*]pyridin-6-ylmethyl)-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**188**):



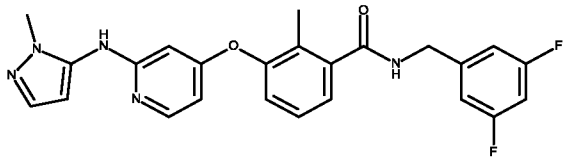
Compound **188** was synthesized from intermediate **119g** (0.15 mmol) and imidazo[1,2-*a*]pyridin-6-ylmethanamine (0.23 mmol) as a white solid in 18% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.94 (t, *J* = 5.9 Hz, 1H), 8.75 (s, 1H), 8.50 (s, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.96 (s, 1H), 7.57-7.54 (m, 2H), 7.39-7.32 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.26-7.20 (m, 2H), 6.35 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 4.44 (d, *J* = 5.8 Hz, 2H), 3.61 (s, 3H), 2.13 (s, 3H).
ESI-MS: 454.15 $(M+H)^+$.

N-(imidazo[1,2-*a*]pyridin-7-ylmethyl)-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**189**):



Compound **189** was synthesized from intermediate **119g** (0.15 mmol) and imidazo[1,2-*a*]pyridin-7-ylmethanamine (0.23 mmol) as a white solid in 13% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.75 (s, 1H), 8.51 (d, *J* = 6.9 Hz, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.53 (d, *J* = 1.1 Hz, 1H), 7.44 (s, 1H), 7.41-7.34 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.23 (dd, *J* = 7.3 Hz, 1.9 Hz, 1H), 6.88 (dd, *J* = 7.0 Hz, 1.6 Hz, 1H), 6.37 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 2H), 3.61 (s, 3H), 2.15 (s, 3H).
ESI-MS: 454.15 $(M+H)^+$.

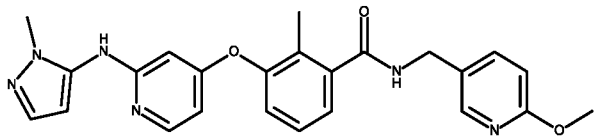
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**190**):



Compound **190** was synthesized from intermediate **119g** (0.15 mmol) and 3,5-difluorobenzylamine (0.23 mmol) as a white solid in 16% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.75 (s, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.41-7.34 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.23 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.3 Hz, 1H), 7.08-7.03 (m, 2H), 6.36 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.12 (d, *J* = 2.1 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.61 (s, 3H), 2.13 (s, 3H).

ESI-MS: 450.10 $(M+H)^+$.

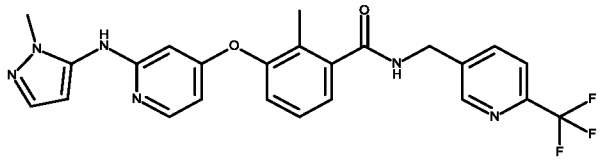
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**191**):



Compound **191** was synthesized from intermediate **119g** (0.15 mmol) and (6-methoxypyridin-3-yl)methanamine (0.23 mmol) as a white solid in 15% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (t, *J* = 6.0 Hz, 1H), 8.74 (s, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.30-7.27 (m, 2H), 7.20 (dd, *J* = 7.9 Hz, 1.1 Hz , 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.35 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 3.61 (s, 3H), 2.11 (s, 3H).

ESI-MS: 445.15 $(M+H)^+$.

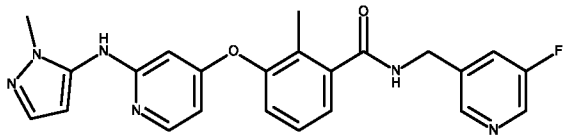
2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)-*N*-{[6-(trifluoro methyl)-3-pyridyl]methyl}benzamide (**192**):



Compound **192** was synthesized from intermediate **119g** (0.15 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.23 mmol) as a white solid in 10% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.08 (t, *J* = 5.9 Hz, 1H), 8.77 (s, 2H), 8.04 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.40-7.35 (m, 2H), 7.27 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 6.8 Hz, 2.5 Hz, 1H), 6.36 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 2.1 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 3.61 (s, 3H), 2.13 (s, 3H).

ESI-MS: 483.15 $(M+H)^+$.

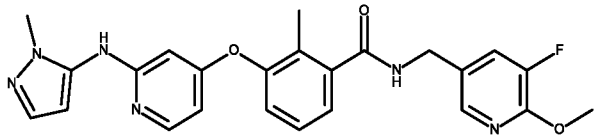
N-[(5-fluoro-3-pyridyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**193**):



Compound **193** was synthesized from intermediate **119g** (0.09 mmol) and 5-fluoro-3-pyridinemethanamine (0.14 mmol) as a white solid in 13% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 5.9 Hz, 1H), 8.75 (s, 1H), 8.49 (d, *J* = 2.8 Hz, 1H), 8.47 (s, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.69-7.65 (m, 1H), 7.40-7.34 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.22 (dd, *J* = 7.2 Hz, 2.1 Hz, 1H), 6.36 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 4.52 (d, *J* = 5.9 Hz, 2H), 3.61 (s, 3H), 2.12 (s, 3H).

ESI-MS: 433.20 $(M+H)^+$.

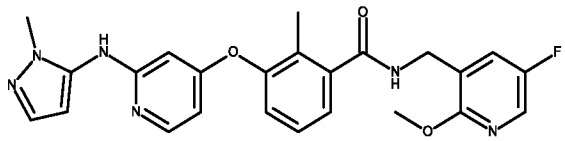
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**194**):



Compound **194** was synthesized from intermediate **119g** (0.09 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.14 mmol) as a white solid in 19% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.91 (t, *J* = 5.9 Hz, 1H), 8.75 (s, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.64 (dd, *J* = 11.4 Hz, 1.9 Hz, 1H), 7.38-7.30 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.21 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 6.35 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.93 (s, 3H), 3.61 (s, 3H), 2.11 (s, 3H).

ESI-MS: 463.25 $(M+H)^+$.

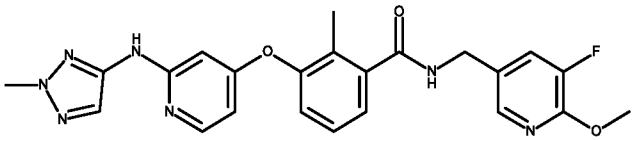
N-[(5-fluoro-2-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(2-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**195**):



Compound **195** was synthesized from intermediate **119g** (0.09 mmol) and 5-fluoro-2-methoxy-3-pyridinemethanamine (0.14 mmol) as a white solid in 14% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.85 (t, *J* = 5.7 Hz, 1H), 8.75 (s, 1H), 8.07 (d, *J* = 3.0 Hz, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.55 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 7.40-7.35 (m, 2H), 7.27 (d, *J* = 1.9 Hz, 1H), 7.25-7.20 (m, 1H), 6.36 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.16 (d, *J* = 1.9 Hz, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H), 3.61 (s, 3H), 2.14 (s, 3H).

ESI-MS: 463.25 $(M+H)^+$.

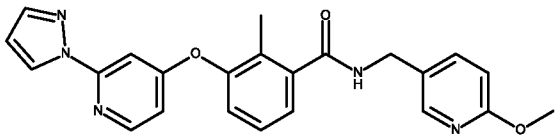
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(2-methyltriazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**350**):



Compound **350** was synthesized from intermediate **119l** (0.08 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.12 mmol) as a white solid in 56% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.59 (s, 1H), 8.90 (t, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 5.9 Hz, 1H), 7.97 (s, 1H), 7.80 (s, 1H), 7.68-7.61 (m, 1H), 7.38-7.30 (m, 2H), 7.21-7.18 (m, 1H), 6.47 (d, *J* = 2.2 Hz, 1H), 6.30 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 4.41 (d, *J* = 5.6 Hz, 2H), 4.00 (s, 3H), 3.93 (s, 3H), 2.11 (s, 3H).

ESI-MS: 464.05 $(M+H)^+$.

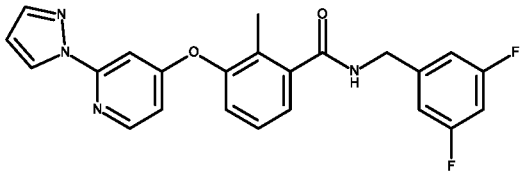
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-[(2-pyrazol-1-yl-4-pyridyl)oxy] benzamide (**196**):



Compound **196** was synthesized from intermediate **119h** (0.09 mmol) and 6-methoxypyridin-3-yl)methanamine (0.14 mmol) as a white solid in 53% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 5.9 Hz, 1H), 8.59 (d, *J* = 2.5 Hz, 1H), 8.37 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.75 (d, *J* = 1.1 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.36-7.29 (m, 2H), 7.18 (d, *J* = 2.3 Hz, 1H), 6.93 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.55-6.54 (m, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.82 (s, 3H), 2.11 (s, 3H).

ESI-MS: 416.05 $(M+H)^+$.

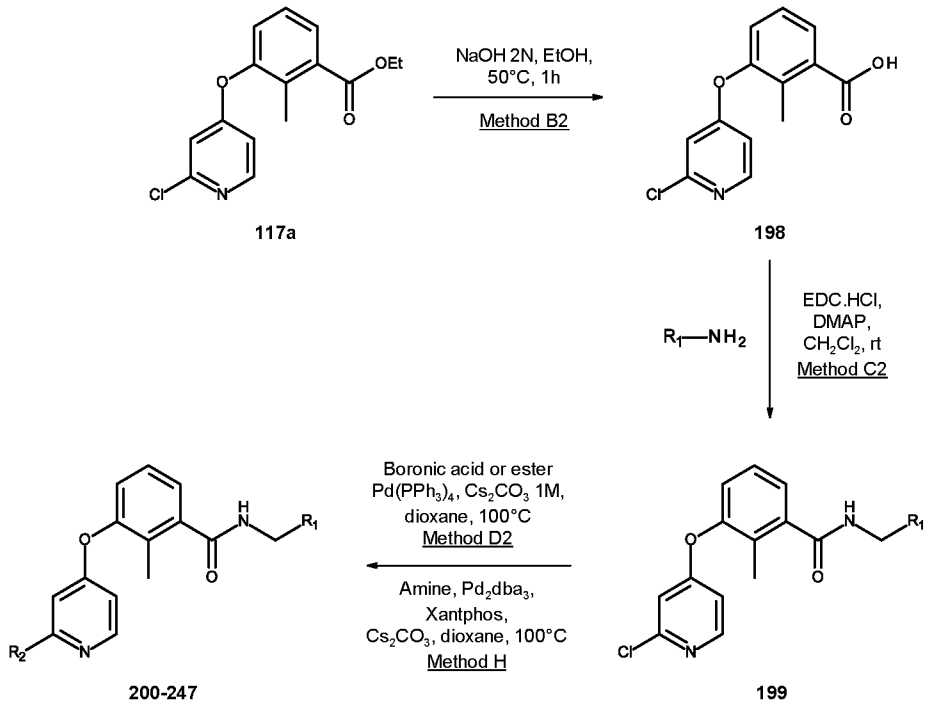
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-pyrazol-1-yl-4-pyridyl)oxy] benzamide (**197**):



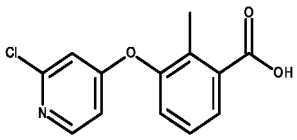
Compound **197** was synthesized from intermediate **119h** (0.09 mmol) and 3,5-difluorobenzylamine (0.14 mmol) as a white solid in 74% yield according to the general method D. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (s, 1H), 8.59 (d, J = 1.9 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.75 (s, 1H), 7.46-7.32 (m, 3H), 7.19-7.06 (m, 4H), 6.95- 6.93 (m, 1H), 6.55 (s, 1H), 4.47 (d, J = 5.8 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 421.05 $(M+H)^+$.

Example 7: General procedure for the synthesis of analogues 200 – 247

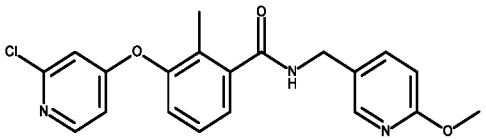
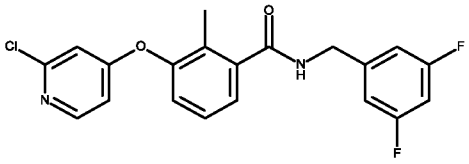


Preparation of 3-[(2-chloro-4-pyridyl)oxy]-2-methyl-benzoic acid (**198**):



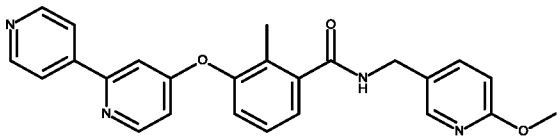
Intermediate **198** was synthesized from **117a** (1.37 mmol) as a white solid in quantitative yield according to the general method B2.

The following table illustrates intermediates **199** prepared from Method C2.

Intermediate	Structure	Synthesis procedure
Compound **199a**		Method C2
Compound **199b**		Method C2

The following compounds are examples illustrating Method D2:

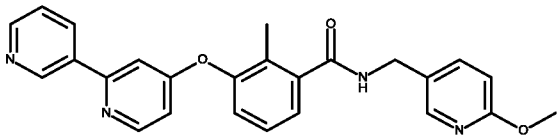
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(4-pyridyl)-4-pyridyl]oxy} benzamide (**200**):



Compound **200** was synthesized from intermediate **199a** (0.07 mmol) and pyridine-4-boronic acid hydrate (0.10 mmol) as a white solid in 61% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.89 (t, J = 5.9 Hz, 1H), 8.70-8.68 (m, 2H), 8.59 (d, J = 5.6 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 8.02-8.00 (m, 2H), 7.71-7.68 (m, 2H), 7.39 (t, J = 7.8 Hz, 1H), 7.32 (dd, J = 7.6 Hz, 1.3 Hz, 1H), 7.25 (dd, J = 7.9 Hz, 1.2 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.76 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.39 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 2.13 (s, 3H).

ESI-MS: 427.10 $(M+H)^+$.

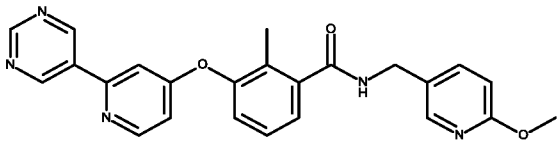
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(3-pyridyl)-4-pyridyl]oxy} benzamide (**201**):



Compound **201** was synthesized from intermediate **199a** (0.07 mmol) and pyridine-3-boronic acid (0.10 mmol) as a white solid in 61% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.21 (d, J = 1.6 Hz, 1H), 8.89 (t, J = 5.9 Hz, 1H), 8.64 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.56 (d, J = 5.7 Hz, 1H), 8.40-8.37 (m, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 8.5 Hz, 2.5 Hz , 1H), 7.63 (d, J = Hz 2.2, 1H), 7.51 (ddd, J = 8.0 Hz, 4.8 Hz, 0.7 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.32 (dd, J = 7.6 Hz , 1.3 Hz, 1H), 7.25 (dd, J = 7.9 Hz, 1.2 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.71 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 2.13 (s, 3H).

ESI-MS: 427.10 $(M+H)^+$.

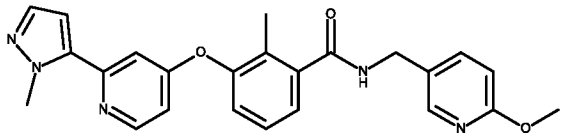
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-[(2-pyrimidin-5-yl-4-pyridyl)oxy] benzamide (**202**):



Compound **202** was synthesized from intermediate **199a** (0.07 mmol) and pyrimidine-5-boronic acid (0.10 mmol) as a white solid in 72% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.41 (s, 2H), 9.26 (s, 1H), 8.89 (t, J = 5.9 Hz, 1H), 8.59 (d, J = 5.7 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.32 (dd, J = 7.6 Hz, 1.3 Hz, 1H), 7.25 (dd, J = 7.9 Hz, 1.2 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.72 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 2.13 (s, 3H).

ESI-MS: 428.05 $(M+H)^+$.

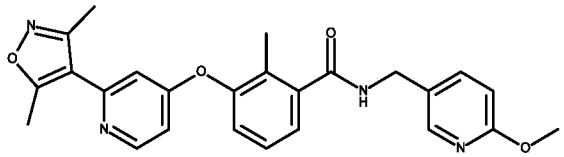
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(2-methylpyrazol-3-yl)-4-pyridyl]oxy}benzamide (**203**):



Compound **203** was synthesized from intermediate **199a** (0.07 mmol) and 1-methyl-1*H*-pyrazole-5-boronic acid pinacol ester (0.10 mmol) as a white solid in 43% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.89 (t, *J* = 5.9 Hz, 1H), 8.53 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.32-7.30 (m, 2H), 7.24 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 5.7 Hz, 2.5 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 4.11 (s, 3H), 3.83 (s, 3H), 2.12 (s, 3H).

ESI-MS: 430.10 $(M+H)^+$.

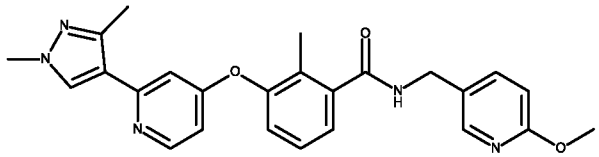
3-{[2-(3,5-dimethylisoxazol-4-yl)-4-pyridyl]oxy}-*N*-[(6-methoxy-3-pyridyl)methyl]-2-methyl-benzamide (**204**):



Compound **204** was synthesized from intermediate **199a** (0.07 mmol) and 3,5-dimethylisoxazole-4-boronic acid pinacol ester (0.10 mmol) as a white solid in 35% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (t, *J* = 5.9 Hz, 1H), 8.52 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 1.9 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.25 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H).

ESI-MS: 445.10 $(M+H)^+$.

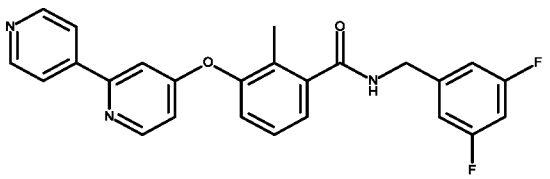
3-{[2-(1,3-dimethylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-[(6-methoxy-3-pyridyl)methyl]-2-methyl-benzamide (**205**):



Compound **205** was synthesized from intermediate **199a** (0.07 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-boronic acid pinacol ester (0.10 mmol) as a white solid in 86% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.88 (t, *J* = 5.9 Hz, 1H), 8.39 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.10 (s, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.21 (dd, *J* = 7.9 Hz, 1.2 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.54 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 2.35 (s, 3H), 2.11 (s, 3H).

ESI-MS: 444.15 $(M+H)^+$.

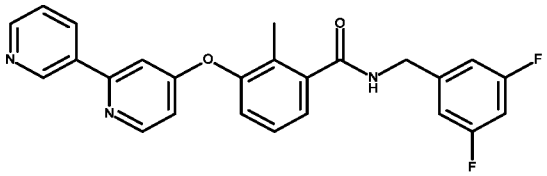
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-pyridyl)-4-pyridyl]oxy} benzamide (**206**):



Compound **206** was synthesized from intermediate **199b** (0.08 mmol) and pyridine-4-boronic acid hydrate (0.12 mmol) as a white solid in 67% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.03 (t, *J* = 6.0 Hz, 1H), 8.70-8.68 (m, 2H), 8.60 (d, *J* = 5.6 Hz, 1H), 8.03-8.01 (m, 2H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.44-7.38 (m, 2H), 7.29 (dd, *J* = 7.1 Hz, 2.2 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.77 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 432.20 $(M+H)^+$.

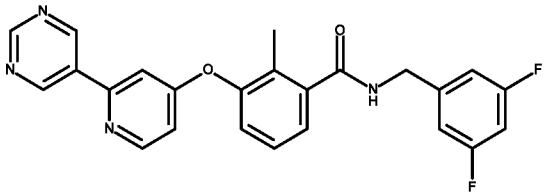
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-pyridyl)-4-pyridyl]oxy} benzamide (**207**):



Compound **207** was synthesized from intermediate **199b** (0.07 mmol) and pyridine-3-boronic acid (0.12 mmol) as a white solid in 85% yield according to the general method D2. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.22 (d, J = 1.7 Hz, 1H), 9.04 (t, J = 6.0 Hz, 1H), 8.64 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.57 (d, J = 5.7 Hz, 1H), 8.41-8.38 (m, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.51 (ddd, J = 8.0 Hz, 4.8 Hz, 0.7 Hz, 1H), 7.43-7.37 (m, 2H), 7.28 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.14 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.05 (m, 2H), 6.71 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 432.05 $(M+H)^+$.

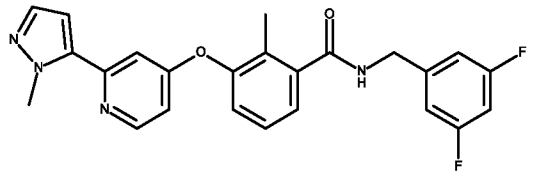
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-pyrimidin-5-yl-4-pyridyl)oxy] benzamide (**208**):



Compound **208** was synthesized from intermediate **199b** (0.08 mmol) and pyrimidine-5-boronic acid (0.12 mmol) as a white solid in 85% yield according to the general method D2. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.43 (s, 2H), 9.26 (s, 1H), 9.03 (t, J = 6.0 Hz, 1H), 8.60 (d, J = 5.7 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.43-7.38 (m, 2H), 7.28 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.11 (m, 1H), 7.09-7.05 (m, 2H), 6.73 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

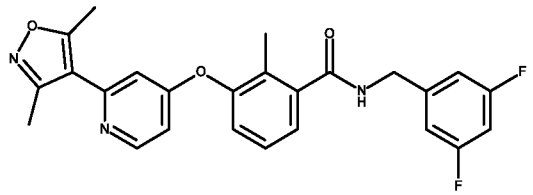
ESI-MS: 433.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-methylpyrazol-3-yl)-4-pyridyl]oxy}benzamide (**209**):



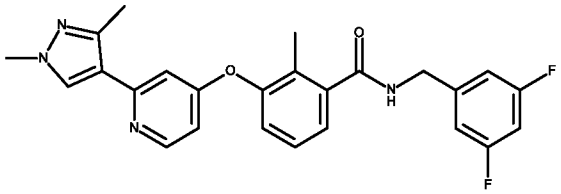
Compound **209** was synthesized from intermediate **199b** (0.08 mmol) and 1-methyl-1*H*-pyrazole-5-boronic acid pinacol ester (0.12 mmol) as a white solid in 45% yield according to the general method D2. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.04 (t, *J* = 6.1 Hz, 1H), 8.54 (d, *J* = 5.8 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.42-7.37 (m, 2H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.27 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.16-7.11 (m, 1H), 7.09-7.04 (m, 2H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 5.7 Hz, 2.5 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.12 (s, 3H), 2.14 (s, 3H).
ESI-MS: 435.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(3,5-dimethylisoxazol-4-yl)-4-pyridyl]oxy}-2-methyl-benzamide (**210**):



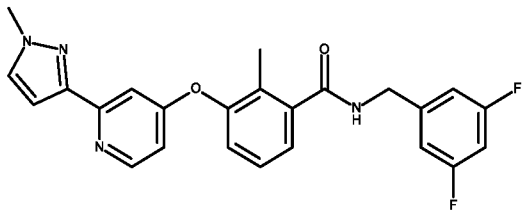
Compound **210** was synthesized from intermediate **199b** (0.08 mmol) and 3,5-dimethylisoxazole-4-boronic acid pinacol ester (0.12 mmol) as a white solid in 35% yield according to the general method D2. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.02 (t, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 5.7 Hz, 1H), 7.42-7.37 (m, 2H), 7.29 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.14-7.11 (m, 1H), 7.08-7.04 (m, 2H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.74 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.31 (s, 3H), 2.14 (s, 3H).
ESI-MS: 450.20 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(1,3-dimethylpyrazol-4-yl)-4-pyridyl]oxy}-2-methyl-benzamide (**211**):



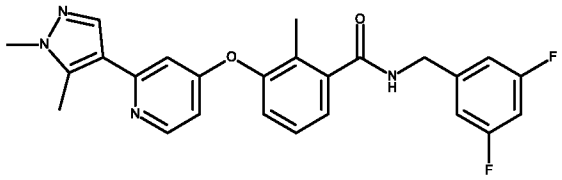
Compound **211** was synthesized from intermediate **199b** (0.08 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-boronic acid pinacol ester (0.12 mmol) as a white solid in 80% yield according to the general method D2. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.02 (t, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 5.7 Hz, 1H), 8.12 (s, 1H), 7.41-7.35 (m, 2H), 7.24 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.14 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.55 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 2.35 (s, 3H), 2.13 (s, 3H).
ESI-MS: 449.90 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-3-yl)-4-pyridyl]oxy}benzamide (**212**):



Compound **212** was synthesized from intermediate **199b** (0.06 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.10 mmol) as a white solid in 64% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, *J* = 6.0 Hz, 1H), 8.46 (d, *J* = 5.7 Hz, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.44-7.38 (m, 2H), 7.27 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz , 2.3 Hz, 1H), 7.10-7.04 (m, 2H), 6.89 (dd, *J* = 5.7 Hz, 2.5 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 2.13 (s, 3H).
ESI-MS: 435.10 $(M+H)^+$.

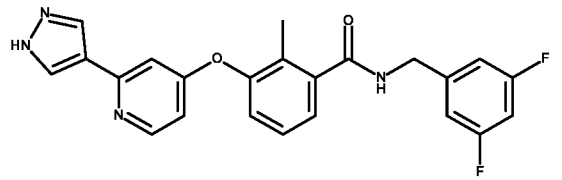
N-[(3,5-difluorophenyl)methyl]-3-{[2-(1,5-dimethylpyrazol-4-yl)-4-pyridyl]oxy}-2-methyl-benzamide (**213**):



Compound **213** was synthesized from intermediate **199b** (0.07 mmol) and 1,3-dimethyl-1*H*-pyrazole-4-boronic acid pinacol ester (0.10 mmol) as a white solid in 70% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.0 Hz, 1H), 8.40 (d, *J* = 5.8 Hz, 1H), 7.81 (s, 1H), 7.41-7.35 (m, 2H), 7.23 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.16-7.04 (m, 4H), 6.51 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.76 (s, 3H), 2.55 (s, 3H), 2.14 (s, 3H).

ESI-MS: 449.20 $(M+H)^+$.

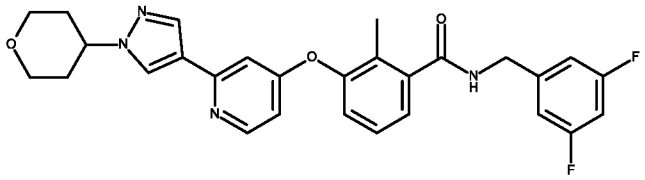
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1*H*-pyrazol-4-yl)-4-pyridyl]oxy} benzamide (**214**):



Compound **214** was synthesized from intermediate **199b** (0.07 mmol) and 1*H*-pyrazole-4-boronic acid pinacol ester (0.10 mmol) as a white solid in 41% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.06 (bs, 1H), 8.99 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.8 Hz, 1H), 8.17 (bs, 2H), 7.41-7.33 (m, 3H), 7.22 (dd, J = 7.4 Hz , 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.46 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 421.10 $(M+H)^+$.

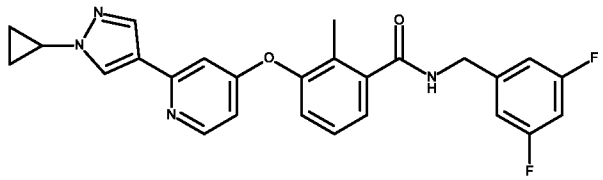
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1-tetrahydropyran-4-ylpyrazol-4-yl)-4-pyridyl]oxy}benzamide (**215**):



Compound **215** was synthesized from intermediate **199b** (0.07 mmol) and 1-(tetrahydro-2*H*-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.10 mmol) as a white solid in 42% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.37-8.35 (m, 2H), 8.00 (s, 1H), 7.42-7.34 (m, 2H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 7.3 Hz, 1.8 Hz, 1H), 7.16-7.04 (m, 3H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48-4.38 (m, 3H), 3.98-3.94 (m, 2H), 3.50-3.43 (m, 2H), 2.14 (s, 3H), 2.00-1.91 (m, 4H).

ESI-MS: 505.20 $(M+H)^+$.

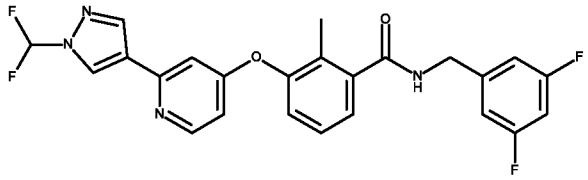
3-{[2-(1-cyclopropylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**216**):



Compound **216** was synthesized from intermediate **199b** (0.07 mmol) and 1-cyclopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole(0.10 mmol) as a white solid in 63% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.36-8.35 (m, 2H), 7.96 (d, *J* = 0.6 Hz, 1H), 7.41-7.34 (m, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 7.2 Hz, 2.1 Hz, 1H), 7.13-7.04 (m, 3H), 6.47 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.79-3.74 (m, 1H), 2.14 (s, 3H), 1.10-0.95 (m, 4H).

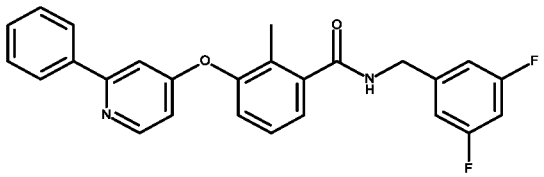
ESI-MS: 461.20 $(M+H)^+$.

3-({2-[1-(difluoromethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**217**):



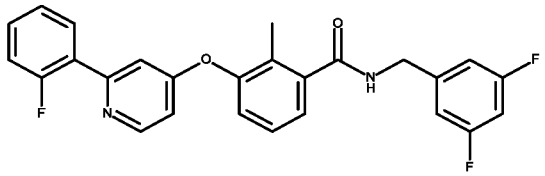
Compound **217** was synthesized from intermediate **199b** (0.06 mmol) and 1-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.10 mmol) as a white solid in 100% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.82 (s, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 8.35 (s, 1H), 7.85 (t, *J* = 59.0 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.42-7.37 (m, 2H), 7.24 (dd, *J* = 7.2 Hz, 2.2 Hz, 1H), 7.16-7.04 (m, 3H), 6.57 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).
ESI-MS: 471.20 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-phenyl-4-pyridyl)oxy]benzamide (**218**):



Compound **218** was synthesized from intermediate **199b** (0.05 mmol) and benzene boronic acid (0.08 mmol) as a white solid in 82% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.54 (d, J = 5.8 Hz, 1H), 8.03-8.01 (m, 2H), 7.50-7.36 (m, 6H), 7.27 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.16-7.09 (m, 1H), 7.08-7.04 (m, 2H), 6.71 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.16 (s, 3H).
ESI-MS: 431.05 $(M+H)^+$.

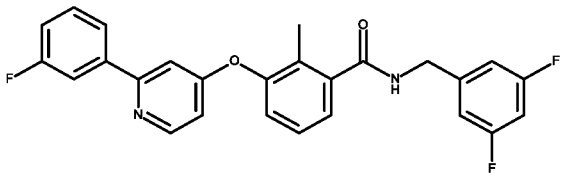
N-[(3,5-difluorophenyl)methyl]-3-{[2-(2-fluorophenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**219**):



Compound **219** was synthesized from intermediate **199b** (0.05 mmol) and 2-fluorobenzeneboronic acid (0.08 mmol) as a white solid in 74% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.1 Hz, 1H), 8.60-8.58 (m, 1H), 7.93 (td, *J* = 7.9 Hz, 1.8 Hz, 1H), 7.50-7.46 (m, 1H), 7.42-7.37 (m, 2H), 7.34-7.27 (m, 3H), 7.23-7.22 (m, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 6.86 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 449.05 $(M+H)^+$.

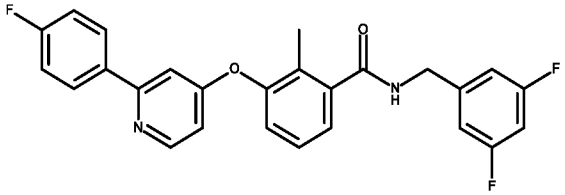
N-[(3,5-difluorophenyl)methyl]-3-{[2-(3-fluorophenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**220**):



Compound **220** was synthesized from intermediate **199b** (0.05 mmol) and 3-fluorobenzeneboronic acid (0.08 mmol) as a white solid in 83% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.1 Hz, 1H), 8.55-8.54 (m, 1H), 7.90-7.85 (m, 2H), 7.61-7.60 (m, 1H), 7.54-7.51 (m, 1H), 7.42-7.37 (m, 2H), 7.30-7.26 (m, 2H), 7.12 (tt, *J* = 9.3 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 2H), 6.71 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.16 (s, 3H).

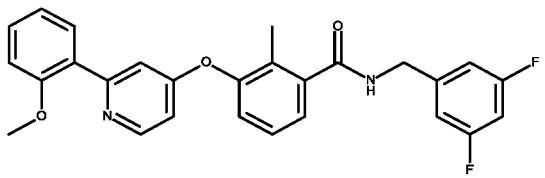
ESI-MS: 449.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(4-fluorophenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**221**):



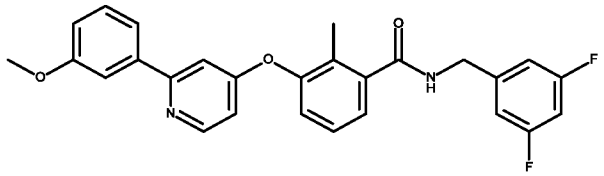
Compound **221** was synthesized from intermediate **199b** (0.05 mmol) and 4-fluorobenzeneboronic acid (0.08 mmol) as a white solid in 91% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 5.7 Hz, 1H), 8.10-8.07 (m, 2H), 7.50 (d, J = 2.3 Hz, 1H), 7.42-7.3 (m, 2H), 7.31-7.25 (m, 3H), 7.12 (tt, J = 9.3 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 2H), 6.69 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.16 (s, 3H). ESI-MS: 449.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(2-methoxyphenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**222**):



Compound **222** was synthesized from intermediate **199b** (0.05 mmol) and 2-methoxybenzeneboronic acid (0.08 mmol) as a white solid in 75% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.1 Hz, 1H), 8.53 (dd, J = 5.7 Hz, 0.4 Hz, 1H), 7.78 (dd, J = 7.7 Hz, 1.8 Hz, 1H), 7.42-7.36 (m, 3H), 7.27-7.25 (m, 2H), 7.14-7.02 (m, 5H), 6.85 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.74 (s, 3H), 2.15 (s, 3H). ESI-MS: 461.05 $(M+H)^+$.

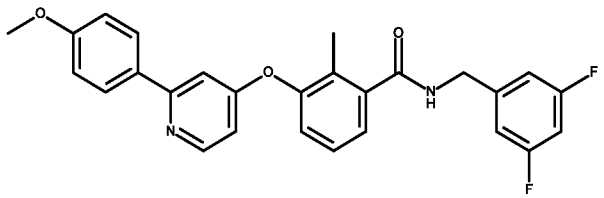
N-[(3,5-difluorophenyl)methyl]-3-{[2-(3-methoxyphenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**223**):



Compound **223** was synthesized from intermediate **199b** (0.05 mmol) and 3-methoxybenzeneboronic acid (0.08 mmol) as a white solid in 84% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.53 (d, J = 5.6 Hz, 1H), 7.60-7.59 (m, 1H), 7.57 (dd, J = 7.7 Hz, 0.9 Hz , 1H), 7.51 (d, J = 2.3 Hz, 1H), 7.42-7.37 (m, 3H), 7.26 (d, J = 7.7 Hz, 1H), 7.14-7.10 (m, 1H), 7.08-7.05 (m, 2H), 7.02-7.00 (m, 1H), 6.70-6.68 (m, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.82 (s, 3H), 2.16 (s, 3H).

ESI-MS: 461.05 $(M+H)^+$.

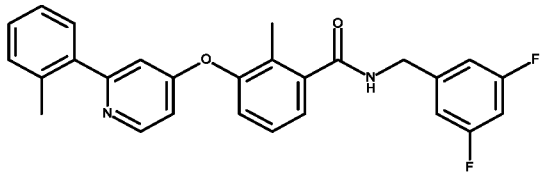
N-[(3,5-difluorophenyl)methyl]-3-{[2-(4-methoxyphenyl)-4-pyridyl]oxy}-2-methyl-benzamide (**224**):



Compound **224** was synthesized from intermediate **199b** (0.05 mmol) and 4-methoxybenzeneboronic acid (0.08 mmol) as a white solid in 92% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.1 Hz, 1H), 8.48-8.47 (m, 1H), 8.00-7.97 (m, 2H), 7.41-7.36 (m, 3H), 7.26 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 7.12 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 2H), 7.03-7.00 (m, 2H), 6.63 (dd, J = 5.6 Hz, 2.4 Hz , 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H), 2.15 (s, 3H).

ESI-MS: 461.05 $(M+H)^+$.

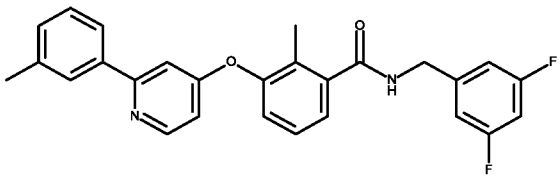
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(*o*-tolyl)-4-pyridyl]oxy}benzamide (**225**):



Compound **225** was synthesized from intermediate **199b** (0.05 mmol) and *o*-tolylboronic acid (0.08 mmol) as a white solid in 83% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.54 (dd, J = 5.7 Hz, 0.5 Hz, 1H), 7.41-7.23 (m, 7H), 7.12 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.07-7.04 (m, 2H), 6.86 (dd, J = 2.5 Hz, 0.5 Hz, 1H), 6.84 (dd, J = 5.7 Hz, 2.5 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.27 (s, 3H), 2.15 (s, 3H).

ESI-MS: 445.05 $(M+H)^+$.

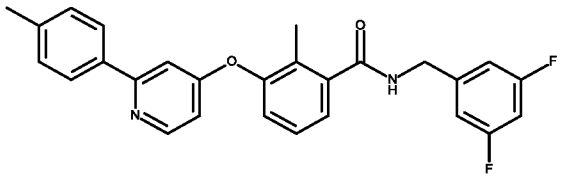
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(*m*-tolyl)-4-pyridyl]oxy}benzamide (**226**):



Compound **226** was synthesized from intermediate **199b** (0.05 mmol) and 3-tolylboronic acid (0.08 mmol) as a white solid in 83% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.1 Hz, 1H), 8.52 (dd, J = 5.7 Hz, 0.4 Hz , 1H), 7.87 (s, 1H), 7.79 (d, J = 7 Hz.8, 1H), 7.48-7.46 (m, 1H), 7.42-7.34 (m, 3H), 7.27-7.24 (m, 2H), 7.12 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 2H), 6.69 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.38 (s, 3H), 2.16 (s, 3H).

ESI-MS: 445.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(*p*-tolyl)-4-pyridyl]oxy}benzamide (**227**):

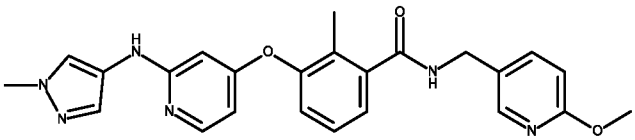


Compound **227** was synthesized from intermediate **199b** (0.05 mmol) and 4-tolylboronic acid (0.08 mmol) as a white solid in 91% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.1 Hz, 1H), 8.51-8.50 (m, 1H), 7.92-7.91 (m, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.42-7.36 (m, 2H), 7.29-7.25 (m, 3H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 2H), 6.67 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 2.15 (s, 3H).

ESI-MS: 445.05 $(M+H)^+$.

The following compounds are examples illustrating Method H:

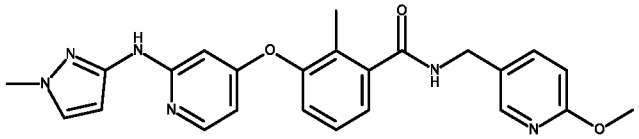
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**228**):



Compound **228** was synthesized from intermediate **199a** (0.09 mmol) and 1-methyl-1*H*-pyrazol-4-ylamine (0.18 mmol) as a white solid in 54% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.89 (t, *J* = 5.9 Hz, 1H), 8.74 (s, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.86 (s, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 7.37-7.26 (m, 3H), 7.18 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.23 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.93 (d, *J* = 2.2 Hz, 1H), 4.38 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.10 (s, 3H).

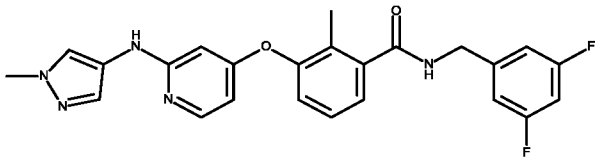
ESI-MS: 445.25 $(M+H)^+$.

N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**229**):



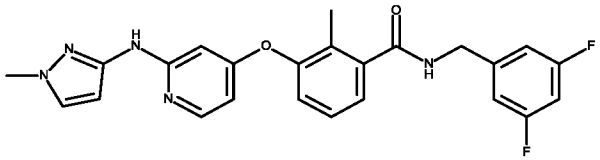
Compound **229** was synthesized from intermediate **199a** (0.09 mmol) and 1-methylpyrazol-3-amine (0.18 mmol) as a white solid in 44% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.18 (s, 1H), 8.89 (t, J = 5.9 Hz, 1H), 8.13 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 5.8 Hz, 1H), 7.69 (dd, J = 8.5 Hz, 2.4 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.27 (dd, J = 7.6 Hz, 1.1 Hz, 1H), 7.17 (dd, J = 7.9 Hz, 1.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.17 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 4.38 (d, J = 5.9 Hz, 2H), 3.83 (s, 3H), 3.67 (s, 3H), 2.11 (s, 3H).
ESI-MS: 445.90 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**230**):



Compound **230** was synthesized from intermediate **199b** (0.08 mmol) and 1-methyl-1*H*-pyrazol-4-ylamine (0.15 mmol) as a white solid in 72% yield according to the general method H. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.1 Hz, 1H), 8.76 (s, 1H), 7.99 (d, J = 5.8 Hz, 1H), 7.87 (s, 1H), 7.39-7.33 (m, 2H), 7.31 (d, J = 0.6 Hz, 1H), 7.21 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.16-7.11 (m, 1H), 7.08-7.03 (m, 2H), 6.24 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 5.93 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.76 (s, 3H), 2.12 (s, 3H).
ESI-MS: 450.25 $(M+H)^+$.

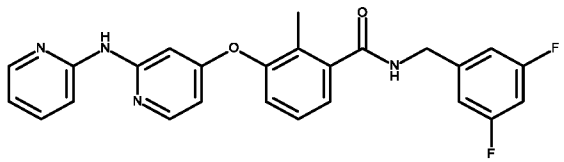
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(1-methylpyrazol-3-yl)amino]-4-pyridyl}oxy)benzamide (**231**):



Compound **231** was synthesized from intermediate **199b** (0.08 mmol) and 1-methylpyrazol-3-amine (0.15 mmol) as a white solid in 63% yield according to the general method H. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 1H), 9.01 (t, *J* = 6.1 Hz, 1H), 7.98 (d, *J* = 5.8 Hz, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.39-7.33 (m, 2H), 7.20 (dd, *J* = 7.7 Hz, 1.5 Hz, 1H), 7.15-7.11 (m, 1H), 7.08-7.04 (m, 2H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.18 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.14 (d, *J* = 2.1 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 2.13 (s, 3H).

ESI-MS: 450.25 $(M+H)^+$.

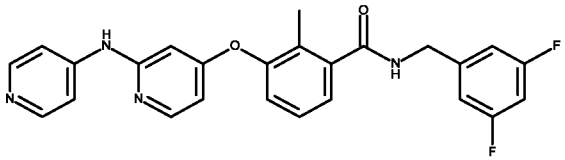
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-pyridylamino)-4-pyridyl]oxy} benzamide (**232**):



Compound **232** was synthesized from intermediate **199b** (0.10 mmol) and 2-aminopyridine (0.20 mmol) as a white solid in 33% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.70 (s, 1H), 9.01 (t, *J* = 6.1 Hz, 1H), 8.15-8.13 (m, 1H), 8.10 (d, *J* = 5.8 Hz, 1H), 7.65-7.59 (m, 2H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.41-7.34 (m, 2H), 7.22 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, *J* = 9.3 Hz, 2.3 Hz, 1H), 7.08-7.04 (m, 2H), 6.85-6.82 (m, 1H), 6.32 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 447.15 $(M+H)^+$.

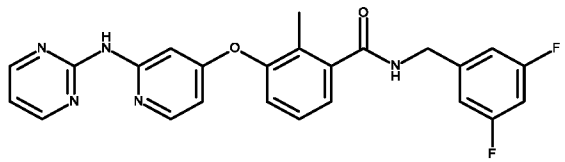
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-pyridylamino)-4-pyridyl]oxy} benzamide (**233**):



Compound **233** was synthesized from intermediate **199b** (0.10 mmol) and 4-aminopyridine (0.20 mmol) as a white solid in 44% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.48 (s, 1H), 8.98 (t, J = 6.0 Hz, 1H), 8.27 (d, J = 6.4 Hz, 2H), 8.17 (d, J = 5.8 Hz, 1H), 7.61-7.60 (m, 2H), 7.42-7.37 (m, 2H), 7.26 (dd, J = 7.5 Hz, 1.6 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.3 Hz, 1H), 7.08-7.04 (m, 2H), 6.55 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.21 (d, J = 2.2 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 447.15 $(M+H)^+$.

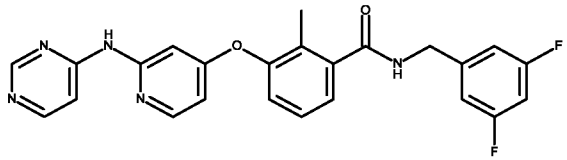
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(pyrimidin-2-ylamino)-4-pyridyl] oxy}benzamide (**234**):



Compound **234** was synthesized from intermediate **199b** (0.08 mmol) and pyrimidin-2-amine (0.17 mmol) as a white solid in 32% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.87 (s, 1H), 9.00 (t, J = 6.1 Hz, 1H), 8.51 (s, 1H), 8.50 (s, 1H), 8.14 (d, J = 5.7 Hz, 1H), 7.95 (d, J = 2.1 Hz, 1H), 7.41-7.34 (m, 2H), 7.23 (dd, J = 7.4 Hz, 1.8 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.93 (t, J = 4.8 Hz, 1H), 6.37 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 448.05 $(M+H)^+$.

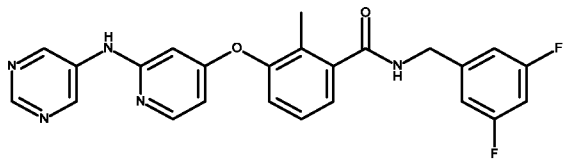
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(pyrimidin-4-ylamino)-4-pyridyl] oxy}benzamide (**235**):



Compound **235** was synthesized from intermediate **199b** (0.08 mmol) and 4-aminopyrimidine (0.17 mmol) as a white solid in 50% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.21 (s, 1H), 9.00 (t, J = 6.1 Hz, 1H), 8.65 (d, J = 0.8 Hz, 1H), 8.41-8.39 (m, 1H), 8.18 (d, J = 5.8 Hz, 1H), 7.70 (dd, J = 5.9 Hz, 1.2 Hz, 1H), 7.42-7.34 (m, 3H), 7.24 (dd, J = 7.1 Hz, 2.2 Hz, 1H), 7.12 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.03 (m, 2H), 6.47 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 448.05 $(M+H)^+$.

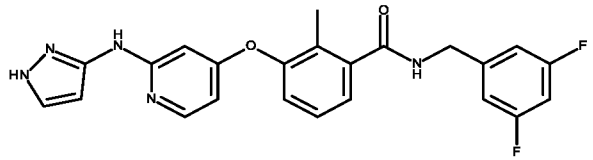
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(pyrimidin-5-ylamino)-4-pyridyl] oxy}benzamide (**236**):



Compound **236** was synthesized from intermediate **199b** (0.08 mmol) and 5-aminopyrimidine (0.17 mmol) as a white solid in 19% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.40 (s, 1H), 9.08 (s, 2H), 8.99 (t, J = 6.0 Hz, 1H), 8.69 (s, 1H), 8.13 (d, J = 5.8 Hz, 1H), 7.42-7.37 (m, 2H), 7.26 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.03 (m, 2H), 6.53 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.15 (d, J = 2.1 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 448.05 $(M+H)^+$.

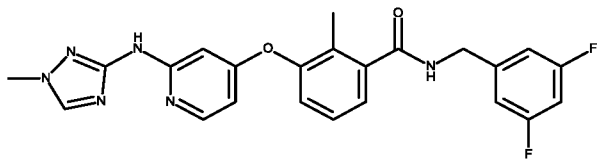
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1*H*-pyrazol-3-ylamino)-4-pyridyl] oxy}benzamide (**237**):



Compound **237** was synthesized from intermediate **199b** (0.08 mmol) and 3-aminopyrazole (0.17 mmol) as a white solid in 17% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.00 (bs, 1H), 9.22 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 8.00 (d, *J* = 5.8 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 7.39-7.31 (m, 2H), 7.21-7.03 (m, 4H), 6.83 (bs, 1H), 6.18 (dd, *J* = 5.6 Hz, 1.8 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 436.00 $(M+H)^+$.

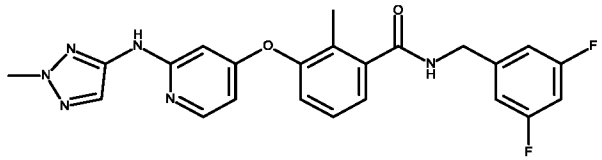
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(1-methyl-1,2,4-triazol-3-yl) amino]-4-pyridyl}oxy)benzamide (**238**):



Compound **238** was synthesized from intermediate **199b** (0.08 mmol) and 1-methyl-1*H*-1,2,4-triazol-3-amine (0.17 mmol) as a white solid in 77% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.63 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 8.20 (s, 1H), 8.04 (d, *J* = 5.7 Hz, 1H), 7.51 (d, *J* = 2.2 Hz, 1H), 7.40-7.33 (m, 2H), 7.20 (dd, *J* = 7.4 Hz , 1.8 Hz, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.10-7.03 (m, 2H), 6.21 (dd, *J* = 5.7 Hz , 2.3 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.73 (s, 3H), 2.14 (s, 3H).

ESI-MS: 451.05 $(M+H)^+$.

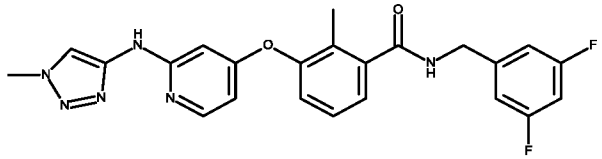
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(2-methyltriazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**239**):



Compound **239** was synthesized from intermediate **199b** (0.08 mmol) and 2-methyltriazol-4-amine (0.15 mmol) as a white solid in 57% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.61 (s, 1H), 8.99 (t, J = 6.0 Hz, 1H), 8.06 (d, J = 5.8 Hz, 1H), 7.81 (s, 1H), 7.41-7.34 (m, 2H), 7.21 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.3 Hz, 1H), 7.08-7.03 (m, 2H), 6.48 (d, J = 2.2 Hz, 1H), 6.31 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 4.00 (s, 3H), 2.14 (s, 3H).

ESI-MS: 451.10 $(M+H)^+$.

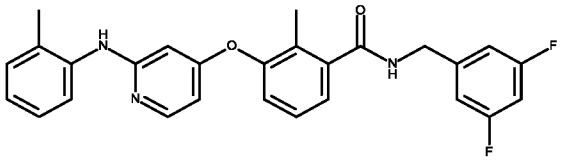
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[(1-methyltriazol-4-yl)amino]-4-pyridyl}oxy)benzamide (**240**):



Compound **240** was synthesized from intermediate **199b** (0.08 mmol) and 1-methyltriazol-4-amine (0.15 mmol) as a white solid in 30% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.63 (s, 1H), 8.98 (t, J = 6.0 Hz, 1H), 8.10 (s, 1H), 8.05 (d, J = 5.8 Hz, 1H), 7.40-7.34 (m, 2H), 7.20 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.03 (m, 2H), 6.36 (d, J = 2.2 Hz, 1H), 6.29 (dd, J = 5.8 Hz, 2.3 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 4.00 (s, 3H), 2.14 (s, 3H).

ESI-MS: 451.10 $(M+H)^+$.

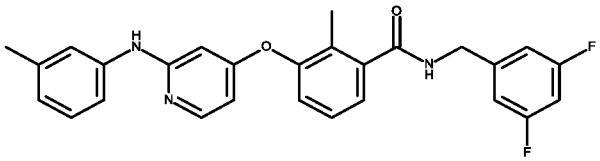
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-methylanilino)-4-pyridyl]oxy} benzamide (**241**):



Compound **241** was synthesized from intermediate **199b** (0.06 mmol) and *o*-toluidine (0.13 mmol) as a white solid in 64% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.96 (t, *J* = 6.1 Hz, 1H), 8.15 (s, 1H), 7.94 (d, *J* = 5.7 Hz, 1H), 7.51 (dd, *J* = 8.0 Hz , 0.9 Hz, 1H), 7.38-7.32 (m, 2H), 7.21 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.14-7.08 (m, 2H), 7.07-7.03 (m, 2H), 6.95 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 6.25 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.17 (s, 3H), 2.14 (s, 3H).

ESI-MS: 460.05 $(M+H)^+$.

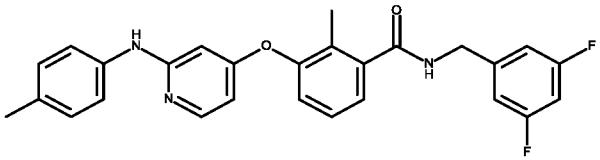
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-methylanilino)-4-pyridyl]oxy} benzamide (**242**):



Compound **242** was synthesized from intermediate **199b** (0.06 mmol) and *m*-toluidine (0.13 mmol) as a white solid in 74% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.97 (t, *J* = 6.1 Hz, 1H), 8.89 (s, 1H), 8.05 (d, *J* = 5.8 Hz, 1H), 7.41-7.35 (m, 4H), 7.23 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.14-7.04 (m, 4H), 6.69-6.67 (m, 1H), 6.37 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.24 (s, 3H), 2.15 (s, 3H).

ESI-MS: 460.10 $(M+H)^+$.

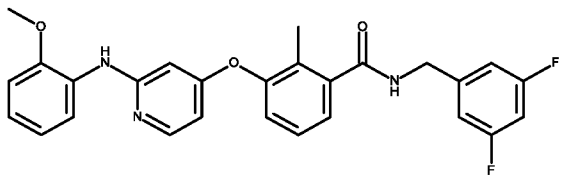
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-methylanilino)-4-pyridyl]oxy} benzamide (**243**):



Compound **243** was synthesized from intermediate **199b** (0.06 mmol) and *p*-poluidine (0.13 mmol) as a white solid in 74% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.97 (t, J = 6.1 Hz, 1H), 8.85 (s, 1H), 8.02 (d, J = 5.8 Hz, 1H), 7.49-7.46 (m, 2H), 7.40-7.34 (m, 2H), 7.22 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 7.12 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 7.02 (d, J = 8.1 Hz, 2H), 6.34 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.09 (d, J = 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.22 (s, 3H), 2.14 (s, 3H).

ESI-MS: 460.10 $(M+H)^+$.

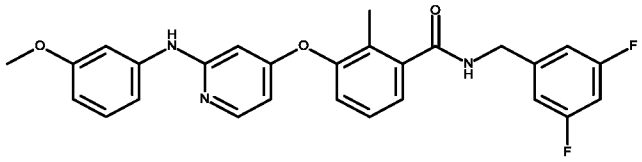
N-[(3,5-difluorophenyl)methyl]-3-{[2-(2-methoxyanilino)-4-pyridyl]oxy}-2-methyl-benzamide (**244**):



Compound **244** was synthesized from intermediate **199b** (0.06 mmol) and *o*-anisidine (0.13 mmol) as a white solid in 47% yield according to the general method H. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.96 (t, J = 6.1 Hz, 1H), 8.15 (s, 1H), 8.11 (dd, J = 7.8 Hz, 1.7 Hz, 1H), 8.00 (d, J = 5.8 Hz, 1H), 7.40-7.33 (m, 2H), 7.20 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.3 Hz, 1H), 7.09-7.03 (m, 2H), 6.98-6.83 (m, 3H), 6.39 (d, J = 2.2 Hz, 1H), 6.31 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.79 (s, 3H), 2.14 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

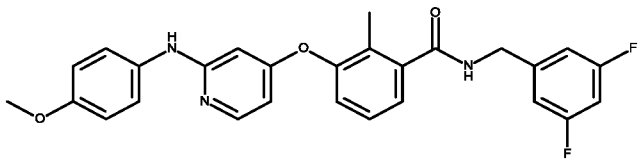
N-[(3,5-difluorophenyl)methyl]-3-{[2-(3-methoxyanilino)-4-pyridyl]oxy}-2-methyl-benzamide (**245**):



Compound **245** was synthesized from intermediate **199b** (0.06 mmol) and *m*-anisidine (0.13 mmol) as a white solid in 84% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.98-8.96 (m, 2H), 8.06 (d, *J* = 5.8 Hz, 1H), 7.41-7.35 (m, 3H), 7.23 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.14-7.09 (m, 3H), 7.08-7.04 (m, 2H), 6.45 (dt, *J* = 6.7 Hz, 2.4 Hz, 1H), 6.39 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.12 (d, *J* = 2.2 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.70 (s, 3H), 2.14 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

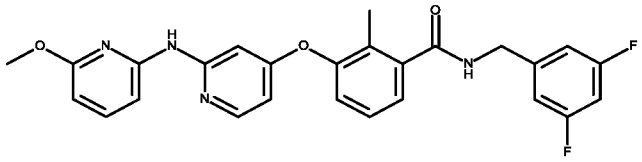
N-[(3,5-difluorophenyl)methyl]-3-{[2-(4-methoxyanilino)-4-pyridyl]oxy}-2-methyl-benzamide (**246**):



Compound **246** was synthesized from intermediate **199b** (0.06 mmol) and *p*-anisidine (0.13 mmol) as a white solid in 81% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.97 (t, *J* = 6.1 Hz, 1H), 8.75 (s, 1H), 7.99 (d, *J* = 5.8 Hz, 1H), 7.59-7.46 (m, 2H), 7.40-7.34 (m, 2H), 7.22 (dd, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 6.84-6.81 (m, 2H), 6.30 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.69 (s, 3H), 2.14 (s, 3H).

ESI-MS: 476.10 $(M+H)^+$.

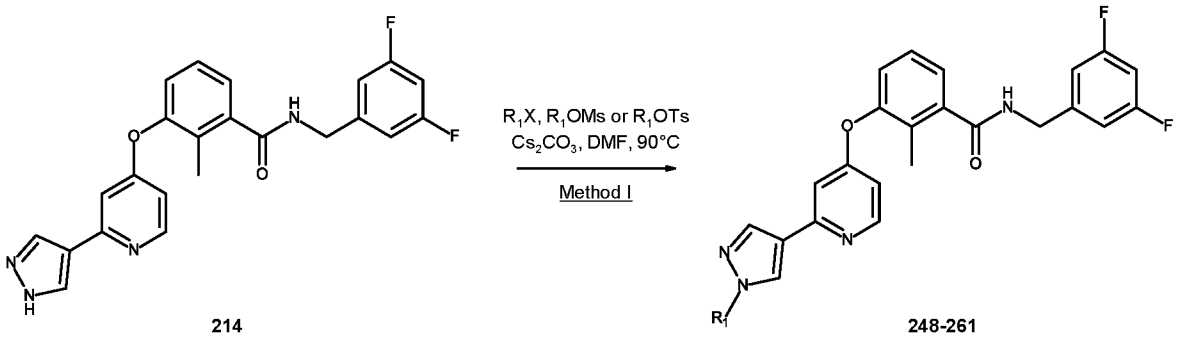
N-[(3,5-difluorophenyl)methyl]-3-({2-[(6-methoxy-2-pyridyl)amino]-4-pyridyl} oxy)-2-methyl-benzamide (**247**):



Compound **247** was synthesized from intermediate **199b** (0.06 mmol) and 2-amino-6-methoxypyridine (0.13 mmol) as a white solid in 68% yield according to the general method H. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.65 (s, 1H), 8.95 (t, *J* = 6.1 Hz, 1H), 8.13-8.12 (m, 1H), 7.50-7.47 (m, 2H), 7.37-7.35 (m, 2H), 7.25-7.22 (m, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.08-7.04 (m, 2H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.56 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 6.18 (dd, *J* = 7.9 Hz, 0.6 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 3.34 (s, 3H), 2.14 (s, 3H).

ESI-MS: 477.10 $(M+H)^+$.

Example 8: General procedure for the synthesis of analogues 248 – 261

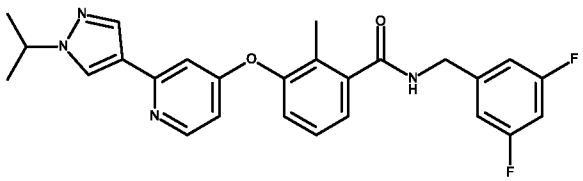


214 248-261

Method I: To a solution of **214** (1 equiv.) in DMF (10 mL/mmol) under nitrogen were added R_1-X derivative, R_1-OMs derivative or R_1-OTs derivative (1-2 equiv.) and Cs_2CO_3 (1.5 equiv.). The mixture was stirred at 90°C overnight. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 95/5) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

The following compound **248** is an example illustrating Method I:

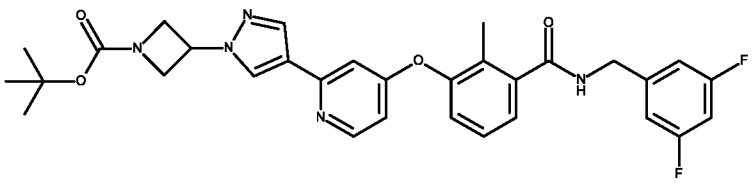
N-[(3,5-difluorophenyl)methyl]-3-{[2-(1-isopropylpyrazol-4-yl)-4-pyridyl]oxy}-2-methyl-benzamide (**248**):



Compound **248** was synthesized from intermediate **214** (0.05 mmol) and 2-iodopropane (0.05 mmol) as a white solid in 50% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.33 (s, 1H), 7.97 (s, 1H), 7.41-7.35 (m, 2H), 7.29 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 7.4 Hz, 1.8 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.55-4.47 (m, 3H), 2.14 (s, 3H), 1.44 (d, J = 6.7 Hz, 6H).

ESI-MS: 463.10 $(M+H)^+$.

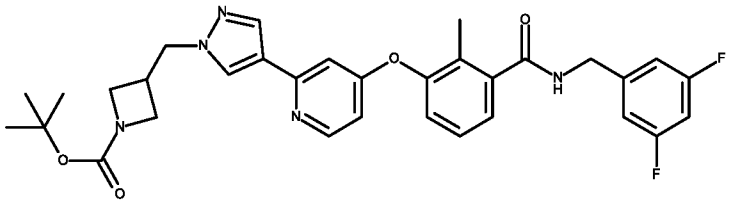
*tert-butyl 3-[4-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)pyrazol-1-yl]azetidine-1-carboxylate (**249**):*



Compound **249** was synthesized from intermediate **214** (0.10 mmol) and *tert*-butyl 3-iodoazetidine-1-carboxylate (0.11 mmol) as a white solid in 76% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.46 (s, 1H), 8.38 (d, *J* = 5.7 Hz, 1H), 8.12 (s, 1H), 7.41-7.35 (m, 2H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, *J* = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.51 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 5.27-5.20 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.30 (t, *J* = 8.2 Hz, 2H), 4.15 (bs, 2H), 2.14 (s, 3H), 1.41 (s, 9H).

ESI-MS: 576.20 $(M+H)^+$.

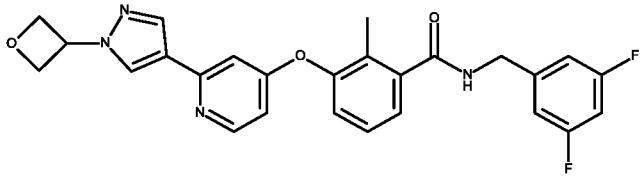
tert-butyl 3-{[4-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)pyrazol-1-yl]methyl}azetidine-1-carboxylate (**250**):



Compound **250** was synthesized from intermediate **214** (0.10 mmol) and *tert*-butyl 3-(bromomethyl)azetidine-1-carboxylate (0.11 mmol) as a white solid in 63% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.37-8.35 (m, 2H), 8.00 (s, 1H), 7.41-7.34 (m, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 7.3 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.10-7.04 (m, 2H), 6.49 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.35 (d, J = 7.2 Hz, 2H), 3.88 (t, J = 7.3 Hz, 2H), 3.68 (bs, 2H), 3.04-2.94 (m, 1H), 2.14 (s, 3H), 1.36 (s, 9H).

ESI-MS: 590.30 $(M+H)^+$.

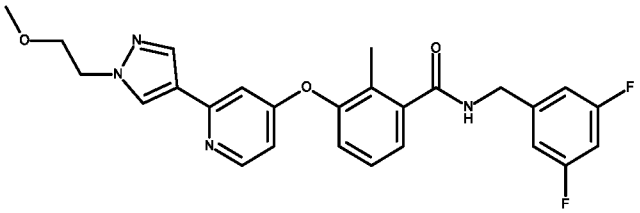
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[1-(oxetan-3-yl)pyrazol-4-yl]-4-pyridyl}oxy)benzamide (**251**):



Compound **251** was synthesized from intermediate **214** (0.05 mmol) and 3-bromooxetane (0.06 mmol) as a white solid in 35% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (bs, 1H), 8.46 (s, 1H), 8.38 (d, J = 5.3 Hz, 1H), 8.13 (s, 1H), 7.41-7.31 (m, 3H), 7.23 (d, J = 7.0 Hz, 1H), 7.15-7.06 (m, 3H), 6.51 (d, J = 3.6 Hz, 1H), 5.62-5.57 (m, 1H), 4.93-4.91 (m, 4H), 4.48 (d, J = 5.4 Hz, 2H), 2.14 (s, 3H).

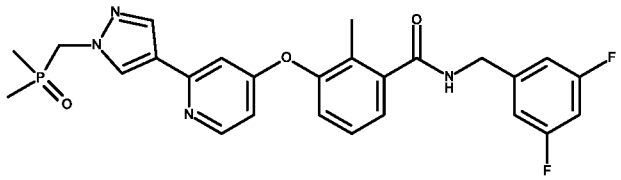
ESI-MS: 477.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-({2-[1-(2-methoxyethyl)pyrazol-4-yl]-4-pyridyl}oxy)-2-methyl-benzamide (**252**):



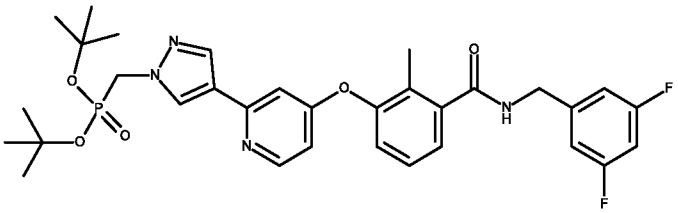
Compound **252** was synthesized from intermediate **214** (0.05 mmol) and 2-bromoethyl methyl ether (0.06 mmol) as a white solid in 78% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 5.8 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.26 (s, 1H), 7.99 (s, 1H), 7.41-7.35 (m, 2H), 7.27-7.22 (m, 2H), 7.15-7.05 (m, 3H), 6.49 (d, J = 5.0 Hz, 1H), 4.48 (d, J = 5.9 Hz, 2H), 4.28 (t, J = 5.1 Hz, 2H), 3.70 (t, J = 5.1 Hz, 2H), 3.23 (s, 3H), 2.14 (s, 3H). ESI-MS: 479.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-({2-[1-(dimethylphosphorylmethyl)pyrazol-4-yl]-4-pyridyl}oxy)-2-methyl-benzamide (**253**):



Compound **253** was synthesized from intermediate **214** (0.05 mmol) and 1-{[(dimethylphosphoryl)methoxy]sulfonyl}-4-methylbenzene (0.06 mmol) as a white solid in 75% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.38 (d, J = 5.7 Hz, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 7.41-7.35 (m, 2H), 7.28 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 7.4 Hz, 1.8 Hz, 1H), 7.13 (tt, J = 9.5 Hz , 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.52 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.69 (d, J = 7.5 Hz, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H). ^{31}P NMR (162 MHz, DMSO-d_6) δ (ppm): 38.43. ESI-MS: 511.10 $(M+H)^+$.

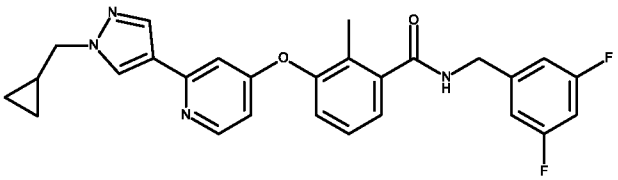
3-({2-[1-(di*tert*-butoxyphosphorylmethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**254**):



Compound **254** was synthesized from intermediate **214** (0.12 mmol) and (di-*tert*-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (0.24 mmol) as a white solid in 51% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.37 (d, J = 5.7 Hz, 1H), 8.18 (s, 1H), 8.01 (s, 1H), 7.41-7.35 (m, 2H), 7.24 (dd, J = 7.2 Hz, 2.2 Hz, 2H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.52 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.53 (d, J = 11.8 Hz, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H), 1.39 (s, 18H). ^{31}P NMR (162 MHz, DMSO-d_6) δ (ppm): 10.07.

ESI-MS: 627.15 $(M+H)^+$.

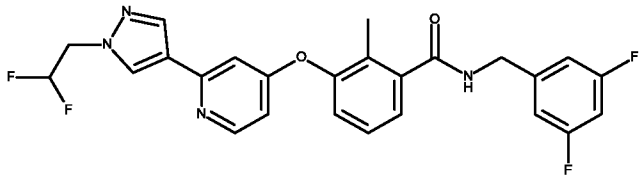
3-({2-[1-(cyclopropylmethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**255**):



Compound **255** was synthesized from intermediate **214** (0.05 mmol) and cyclopropylmethyl bromide (0.06 mmol) as a white solid in 56% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.33 (s, 1H), 7.98-7.97 (m, 1H), 7.41-7.35 (m, 2H), 7.28 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.99 (d, J = 7.1 Hz, 2H), 2.15 (s, 3H), 1.31-1.21 (m, 1H), 0.56-0.51 (m, 2H), 0.40-0.36 (m, 2H).

ESI-MS: 475.10 $(M+H)^+$.

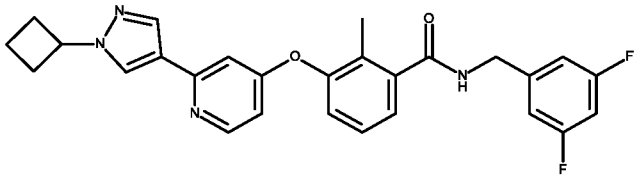
3-({2-[1-(2,2-difluoroethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl) methyl]-2-methyl-benzamide (**256**):



Compound **256** was synthesized from intermediate **214** (0.05 mmol) and 2-iodo-1,1-difluoroethane (0.06 mmol) as a white solid in 50% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.38 (d, J = 5.7 Hz, 1H), 8.35 (s, 1H), 8.09 (d, J = 0.4 Hz, 1H), 7.42-7.35 (m, 2H), 7.30 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 7.3 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.54-6.25 (m, 2H), 4.66 (td, J = 15.1 Hz, 3.7 Hz, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 485.10 $(M+H)^+$.

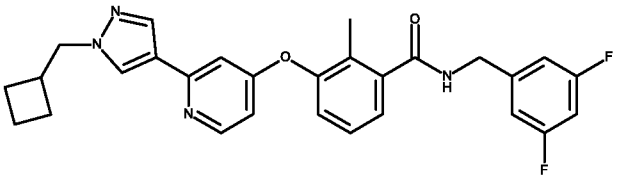
3-{[2-(1-cyclobutylpyrazol-4-yl)-4-pyridyl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**257**):



Compound **257** was synthesized from intermediate **214** (0.05 mmol) and cyclobutyl bromide (0.06 mmol) as a white solid in 39% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.39 (d, *J* = 0.5 Hz, 1H), 8.37-8.35 (m, 1H), 8.01 (d, *J* = 0.5 Hz, 1H), 7.41-7.34 (m, 2H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.48 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.85 (p, *J* = 8.5 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.50-2.35 (m, 4H), 2.14 (s, 3H), 1.82-1.73 (m, 2H).

ESI-MS: 475.10 $(M+H)^+$.

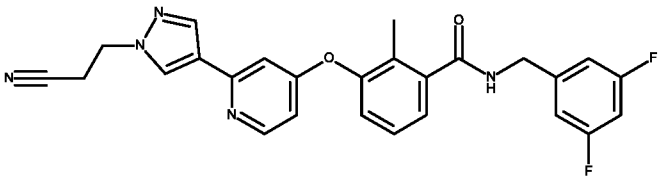
3-({2-[1-(cyclobutylmethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl) methyl]-2-methyl-benzamide (**258**):



Compound **258** was synthesized from intermediate **214** (0.05 mmol) and (bromomethyl)cyclobutane (0.06 mmol) as a white solid in 43% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.36-8.35 (m, 1H), 8.27 (d, *J* = 0.5 Hz, 1H), 7.96 (d, *J* = 0.6 Hz, 1H), 7.41-7.35 (m, 2H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.22 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.47 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.14 (d, *J* = 7.3 Hz, 2H), 2.76 (dt, *J* = 14.9 Hz, 7.5 Hz, 1H), 2.14 (s, 3H), 2.00-1.94 (m, 2H), 1.89-1.72 (m, 4H).

ESI-MS: 489.10 $(M+H)^+$.

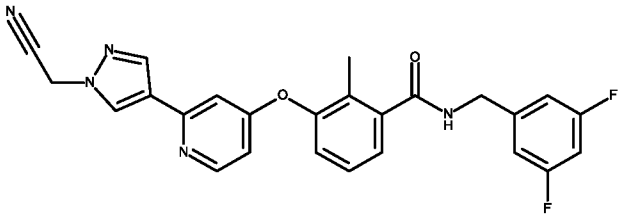
3-({2-[1-(2-cyanoethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl) methyl]-2-methyl-benzamide (**259**):



Compound **259** was synthesized from intermediate **214** (0.05 mmol) and 3-bromopropionitrile (0.06 mmol) as a white solid in 56% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.1 Hz, 1H), 8.39-8.37 (m, 2H), 8.07 (d, *J* = 0.6 Hz, 1H), 7.42-7.35 (m, 2H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.23 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.52 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.42 (t, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 474.10 $(M+H)^+$.

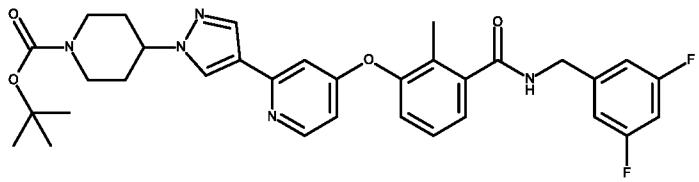
3-({2-[1-(cyanomethyl)pyrazol-4-yl]-4-pyridyl}oxy)-*N*-[(3,5-difluorophenyl) methyl]-2-methyl-benzamide (**260**):



Compound **260** was synthesized from intermediate **214** (0.05 mmol) and 2-iodoacetonitrile (0.07 mmol) as a white solid in 14% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.40-8.38 (m, 2H), 8.15 (d, J = 0.6 Hz, 1H), 7.42-7.35 (m, 2H), 7.32 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.03 (m, 2H), 6.54 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 5.53 (s, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H).

ESI-MS: 460.10 $(M+H)^+$.

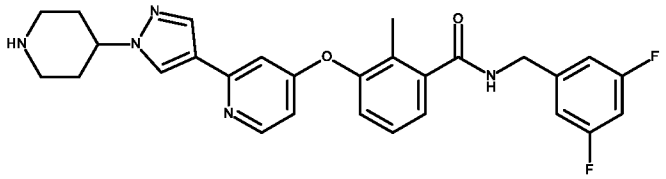
tert-butyl 4-[4-(4-{3-[(3,5-difluorophenyl)methylcarbamoyl]-2-methyl-phenoxy}-2-pyridyl)pyrazol-1-yl]piperidine-1-carboxylate (**261**):



Compound **261** was synthesized from intermediate **214** (0.10 mmol) and *tert*-butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (0.11 mmol) as a white solid in 70% yield according to the general method I. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.37-8.35 (m, 2H), 8.00 (s, 1H), 7.41-7.35 (m, 2H), 7.29 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.10-7.04 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.42-4.34 (m, 1H), 4.04 (d, J = 11.8 Hz, 2H), 2.91 (bs, 2H), 2.14 (s, 3H), 2.02 (d, J = 10.2 Hz, 2H), 1.85-1.75 (m, 2H), 1.42 (s, 9H).

ESI-MS: 604.40 $(M+H)^+$.

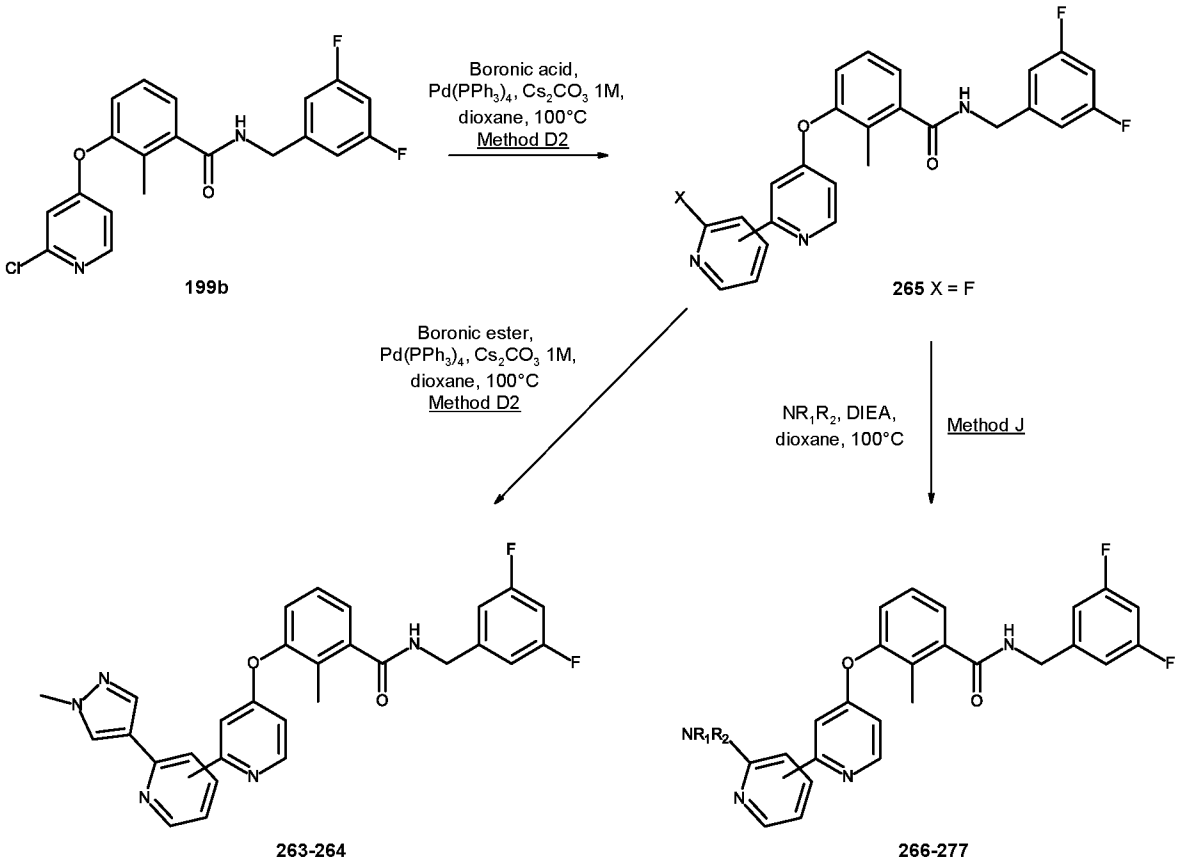
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[1-(4-piperidyl)pyrazol-4-yl]-4-pyridyl}oxy)benzamide (**262**):



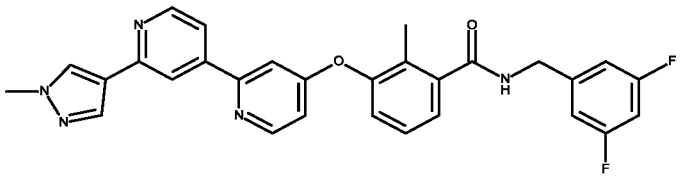
To a stirred solution of compound **261** (25 mg, 0.04 mmol) in dioxane (2 mL) was added HCl (4N in dioxane, 0.41 mL, 10 equiv.) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound as a white solid in 33% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 8.36 (d, J = 5.7 Hz, 1H), 8.32 (s, 1H), 7.99 (s, 1H), 7.41-7.34 (m, 2H), 7.29 (d, J = 2.3 Hz, 1H), 7.22 (dd, J = 7.3 Hz, 1.8 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.14 (m, 2H), 6.48 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.28-4.19 (m, 1H), 3.07 (d, J = 12.3 Hz, 2H), 2.61 (d, J = 10.8, 2H), 2.14 (s, 3H), 1.98 (d, J = 10.2, 2H), 1.87-1.78 (m, 2H).

ESI-MS: 504.10 $(M+H)^+$.

Example 9: General procedure for the synthesis of analogues 263 – 277



N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[2-(1-methylpyrazol-4-yl)-4-pyridyl]-4-pyridyl}oxy)benzamide (**263**):

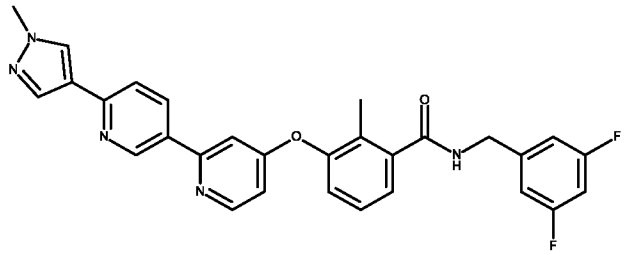


Compound **263** was synthesized in a two steps procedure from intermediate **199b** (0.08 mmol), 2-chloropyridine-4-boronic acid (0.08 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (0.15 mmol) as a white solid in 23% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.1 Hz, 1H), 8.61-8.59 (m, 2H), 8.40 (s, 1H), 8.29-8.28 (m, 1H), 8.10 (d, *J* = 0.7 Hz, 1H), 7.92 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 5.2 Hz, 1.7

Hz, 1H), 7.44-7.38 (m, 2H), 7.29 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.71 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 2.17 (s, 3H).

ESI-MS: 512.10 $(M+H)^+$.

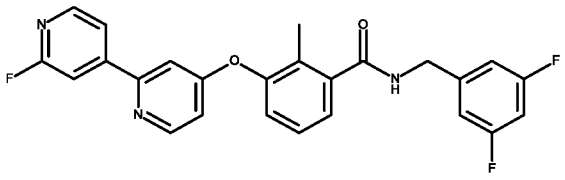
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[6-(1-methylpyrazol-4-yl)-3-pyridyl]-4-pyridyl}oxy)benzamide (**264**):



Compound **264** was synthesized in a two steps procedure from intermediate **199b** (0.08 mmol), (6-chloropyridin-3-yl)boronic acid (0.08 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (0.15 mmol)as a white solid in 15% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.16 (dd, *J* = 2.3 Hz, 0.7 Hz, 1H), 9.01 (t, *J* = 6.1 Hz, 1H), 8.55 (d, *J* = 5.7 Hz, 1H), 8.38 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.35 (s, 1H), 8.06 (d, *J* = 0.6 Hz, 1H), 7.74 (dd, *J* = 8.3 Hz, 0.6 Hz, 1H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.44-7.37 (m, 2H), 7.27 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.67 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 2.16 (s, 3H).

ESI-MS: 512.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(2-fluoro-4-pyridyl)-4-pyridyl]oxy}-2-methyl-benzamide (**265a**):

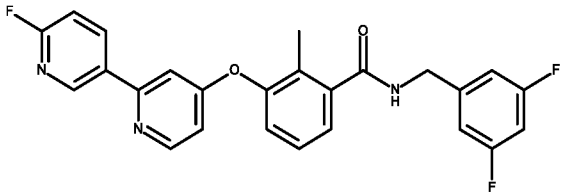


Compound **265a** was synthesized from intermediate **199b** (1.16 mmol) and 2-fluoropyridin-4-ylboronic acid (1.39 mmol) as a white solid in 100% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):

9.00 (t, *J* = 5.9 Hz, 1H), 8.61 (d, *J* = 5.6 Hz, 1H), 8.36 (d, *J* = 5.3 Hz, 1H), 8.02 (d, *J* = 5.2 Hz , 1H), 7.85 (d, *J* = 2. Hz 3, 1H), 7.82 (s, 1H), 7.44-7.38 (m, 2H), 7.28 (dd, *J* = 6.9 Hz, 2.2 Hz, 1H), 7.16-7.04 (m, 3H), 6.78 (dd, *J* = 5.6 Hz, 1.9 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.16 (s, 3H).

ESI-MS: 450.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-{[2-(6-fluoro-3-pyridyl)-4-pyridyl]oxy}-2-methyl-benzamide (**265b**):



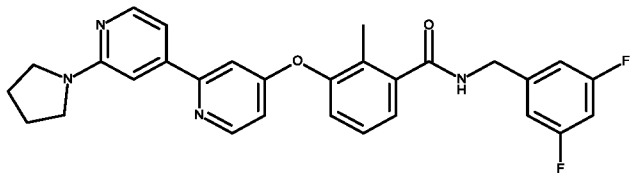
Compound **265b** was synthesized from intermediate **199b** (0.77 mmol) and 6-fluoro-3-pyridinylboronic acid (0.93 mmol) as a white solid in 100% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.0 Hz, 1H), 8.90 (d, *J* = 2.5 Hz, 1H), 8.64-8.59 (m, 1H), 8.57-8.55 (m, 1H), 7.69 (d, *J* = 2.1 Hz, 1H), 7.43-7.37 (m, 2H), 7.31 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 7.27 (dd, *J* = 7.2 Hz, 2.1 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz , 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.70 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.16 (s, 3H).

ESI-MS: 450.05 $(M+H)^+$.

Method J: To a solution of **265** (1 equiv.) in dioxane (10 mL/mmol) were added amine derivative (16 equiv.) and DIEA (6 equiv.). The mixture was stirred at 100°C until completion (from 2 h to overnight). The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

The following compound **266** is an example illustrating Method J:

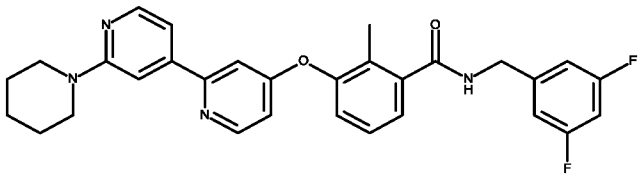
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-pyrrolidin-1-yl-4-pyridyl)-4-pyridyl]oxybenzamide (**266**):



Compound **266** was synthesized from intermediate **265a** (0.07 mmol) and pyrrolidine (0.53 mmol) as a white solid in 55% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.55 (d, J = 5.8 Hz, 1H), 8.14 (dd, J = 5.3 Hz, 0.6 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.43-7.37 (m, 2H), 7.27 (dd, J = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.04 (m, 5H), 6.71 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.46-3.43 (m, 4H), 2.15 (s, 3H), 1.98-1.94 (m, 4H).

ESI-MS: 501.10 $(M+H)^+$.

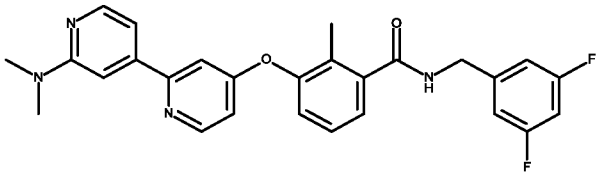
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[2-(1-piperidyl)-4-pyridyl]-4-pyridyl}oxy)benzamide (**267**):



Compound **267** was synthesized from intermediate **265a** (0.07 mmol) and piperidine (0.53 mmol) as a white solid in 50% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.55 (d, J = 5.6 Hz, 1H), 8.18 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.43-7.36 (m, 3H), 7.26 (dd, J = 7.2 Hz, 2.0 Hz, 1H), 7.17-7.04 (m, 4H), 6.69 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.60-3.58 (m, 4H), 2.16 (s, 3H), 1.62-1.55 (m, 6H).

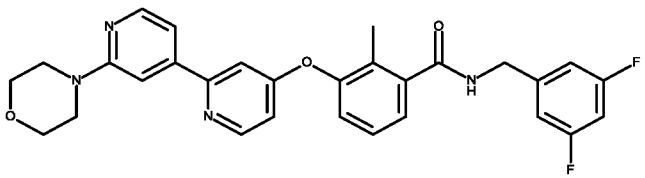
ESI-MS: 515.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-3-({2-[2-(dimethylamino)-4-pyridyl]-4-pyridyl}oxy)-2-methyl-benzamide (**268**):



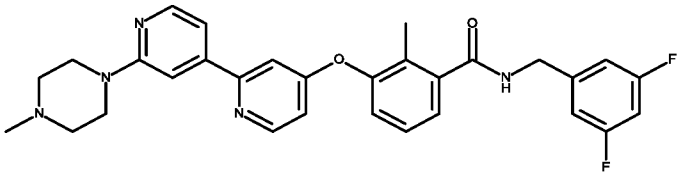
Compound **268** was synthesized from intermediate **265a** (0.07 mmol) and dimethylamine (2M THF, 0.67 mmol) as a white solid in 47% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.0 Hz, 1H), 8.56 (d, *J* = 5.6 Hz, 1H), 8.18-8.16 (m, 1H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.43-7.37 (m, 2H), 7.27 (dd, *J* = 8.1 Hz, 2.7 Hz, 2H), 7.15-7.04 (m, 4H), 6.71 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.09 (s, 6H), 2.15 (s, 3H).
ESI-MS: 475.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-morpholino-4-pyridyl)-4-pyridyl]oxy}benzamide (**269**):



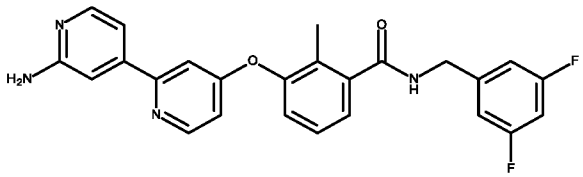
Compound **269** was synthesized from intermediate **265a** (0.07 mmol) and morpholine (1.07 mmol) as a white solid in 50% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.1 Hz, 1H), 8.55 (d, *J* = 5.7 Hz, 1H), 8.23 (d, *J* = 5.6 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.46 (s, 1H), 7.43-7.37 (m, 2H), 7.29 (dd, *J* = 5.2 Hz, 1.3 Hz, 1H), 7.26 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.69 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.73-3.71 (m, 4H), 3.54-3.51 (m, 4H), 2.16 (s, 3H).
ESI-MS: 517.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[2-(4-methylpiperazin-1-yl)-4-pyridyl]-4-pyridyl}oxy)benzamide (**270**):



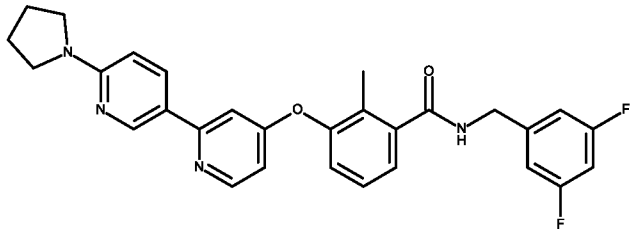
Compound **270** was synthesized from intermediate **265a** (0.07 mmol) and 1-methylpiperazine (1.07 mmol) as a white solid in 40% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.0 Hz, 1H), 8.55 (d, *J* = 5.8 Hz, 1H), 8.21-8.19 (m, 1H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.45 (s, 1H), 7.43-7.37 (m, 2H), 7.27-7.23 (m, 2H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.69 (dd, *J* = 5.6 Hz, 2.4 Hz , 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.57-3.55 (m, 4H), 2.42-2.40 (m, 4H), 2.22 (s, 3H), 2.16 (s, 3H).
ESI-MS: 530.15 $(M+H)^+$.

3-{[2-(2-amino-4-pyridyl)-4-pyridyl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**271**):



Compound **271** was synthesized from intermediate **265a** (0.07 mmol) and NH_4OH (1.5 mL) as a white solid in 34% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.1 Hz, 1H), 8.55 (d, *J* = 5.8 Hz, 1H), 7.98 (dd, *J* = 5.4 Hz, 0.6 Hz, 1H), 7.43-7.37 (m, 3H), 7.28 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.04 (m, 4H), 7.02 (dd, *J* = 5.4 Hz, 1.6 Hz, 1H), 6.78 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 6.03 (s, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).
ESI-MS: 447.05 $(M+H)^+$.

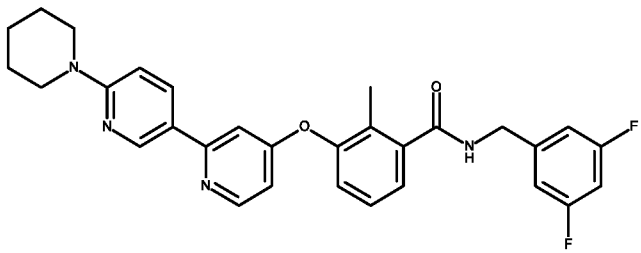
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(6-pyrrolidin-1-yl-3-pyridyl)-4-pyridyl]oxy}benzamide (**272**):



Compound **272** was synthesized from intermediate **265b** (0.07 mmol) and pyrrolidine (1.06 mmol) as a white solid in 55% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.75 (d, J = 1.9 Hz, 1H), 8.43 (d, J = 5.6 Hz , 1H), 8.13 (dd, J = 8.9 Hz , 2.5 Hz, 1H), 7.42-7.35 (m, 3H), 7.24 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.55-6.50 (m, 2H), 4.48 (d, J = 6.0 Hz, 2H), 3.45-3.42 (m, 4H), 2.15 (s, 3H), 1.97-1.94 (m, 4H).

ESI-MS: 501.10 $(M+H)^+$.

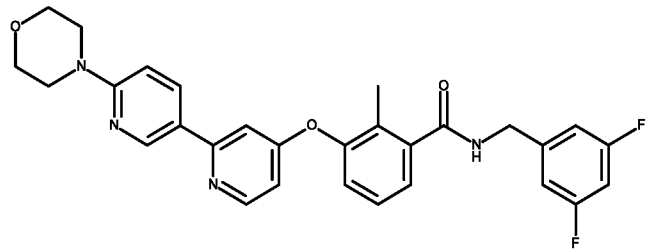
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[6-(1-piperidyl)-3-pyridyl]-4-pyridyl}oxy)benzamide (**273**):



Compound **273** was synthesized from intermediate **265b** (0.07 mmol) and piperidine (1.06 mmol) as a white solid in 65% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.75 (d, J = 2.2 Hz, 1H), 8.44 (d, J = 5.8 Hz, 1H), 8.13 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 7.42-7.35 (m, 3H), 7.24 (dd, J = 7.4 Hz, 1.8 Hz, 1H), 7.16-7.04 (m, 3H), 6.87 (d, J = 8.9 Hz, 1H), 6.56 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.61-3.58 (m, 4H), 2.15 (s, 3H), 1.63-1.54 (m, 6H).

ESI-MS: 515.20 $(M+H)^+$.

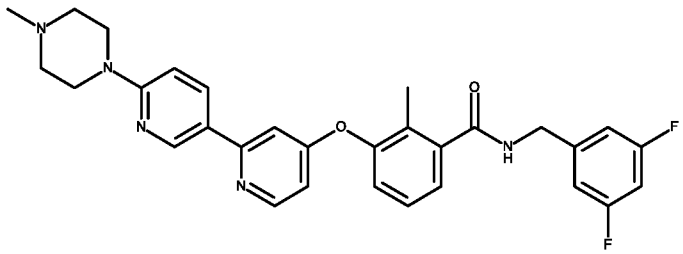
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(6-morpholino-3-pyridyl)-4-pyridyl]oxy}benzamide (**274**):



Compound **274** was synthesized from intermediate **265b** (0.07 mmol) and morpholine (1.06 mmol) as a white solid in 65% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.80 (d, J = 2.2 Hz, 1H), 8.46 (d, J = 5.7 Hz, 1H), 8.20 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 7.45 (d, J = 2.3 Hz, 1H), 7.40-7.36 (m, 2H), 7.25 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.91 (d, J = 9.0 Hz, 1H), 6.57 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.72-3.69 (m, 4H), 3.55-3.52 (m, 4H), 2.15 (s, 3H).

ESI-MS: 517.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[6-(4-methylpiperazin-1-yl)-3-pyridyl]-4-pyridyl}oxy)benzamide (**275**):

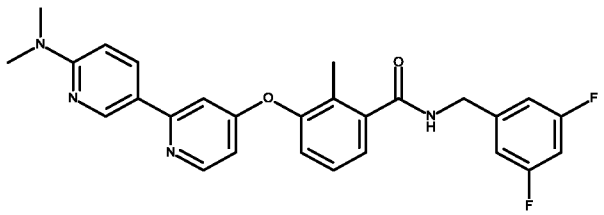


Compound **275** was synthesized from intermediate **265b** (0.07 mmol) and 1-methylpiperazine (1.06 mmol) as a white solid in 52% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.77 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 5.8 Hz, 1H), 8.16 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 7.43 (d, J = 2.2 Hz, 1H), 7.42-7.36 (m, 2H), 7.25 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H), 6.57 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.58-3.55 (m, 4H), 2.40-2.38

(m, 4H), 2.22 (s, 3H), 2.15 (s, 3H).

ESI-MS: 530.15 $(M+H)^+$.

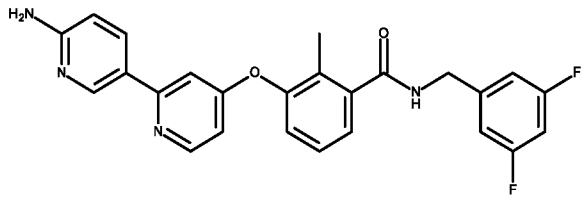
N-[(3,5-difluorophenyl)methyl]-3-({2-[6-(dimethylamino)-3-pyridyl]-4-pyridyl} oxy)-2-methyl-benzamide (**276**):



Compound **276** was synthesized from intermediate **265b** (0.07 mmol) and dimethylamine (2M THF, 1.06 mmol) as a white solid in 72% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.76 (dd, J = 2.5 Hz, 0.6 Hz, 1H), 8.44 (d, J = 5.8 Hz, 1H), 8.14 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 7.42-7.35 (m, 3H), 7.24 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.71 (dd, J = 9.0 Hz, 0.5 Hz, 1H), 6.55 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.08 (s, 6H), 2.15 (s, 3H).

ESI-MS: 475.10 $(M+H)^+$.

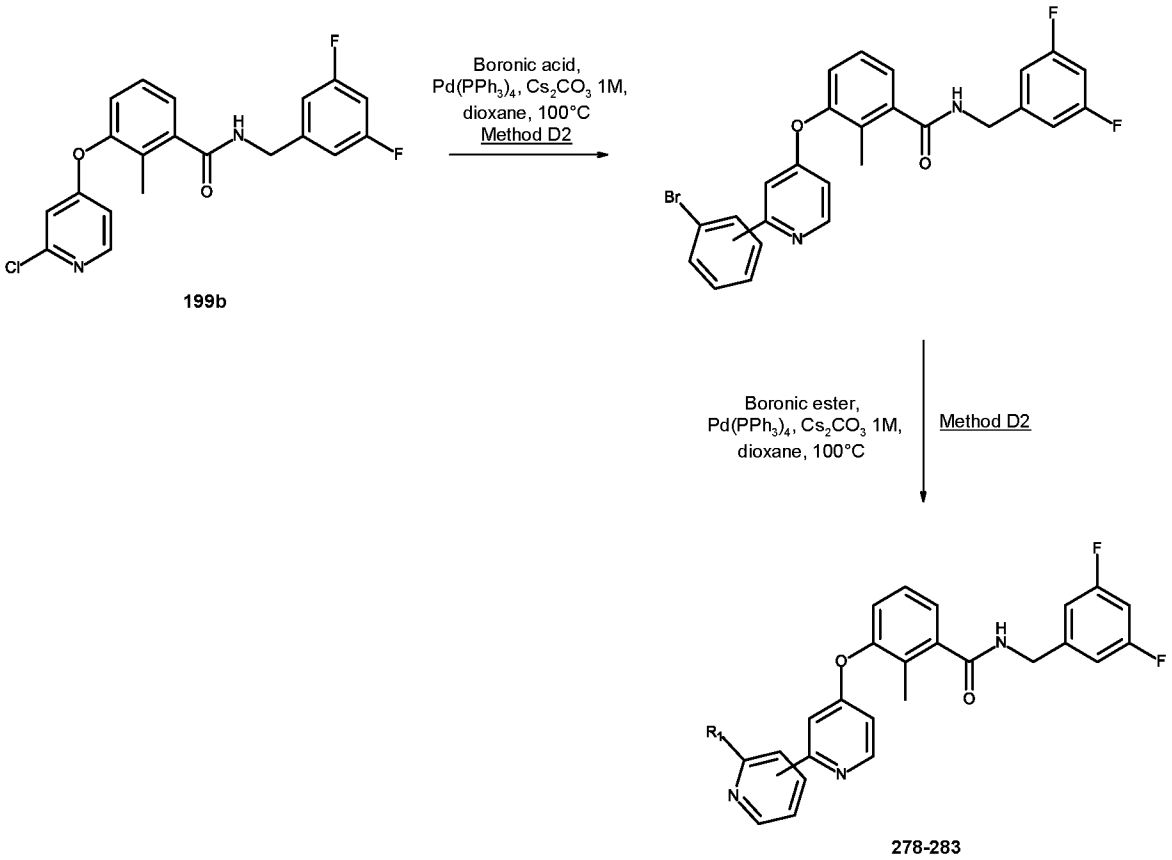
3-{[2-(6-amino-3-pyridyl)-4-pyridyl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**277**):



Compound **277** was synthesized from intermediate **265b** (0.07 mmol) and NH_4OH (1.5 mL) as a white solid in 69% yield according to the general method J. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.60-8.59 (m, 1H), 8.42 (d, J = 5.8 Hz, 1H), 8.01 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 7.42-7.35 (m, 2H), 7.34 (d, J = 2.2 Hz, 1H), 7.24 (dd, J = 7.5 Hz, 1.8 Hz , 1H), 7.13 (tt, J = 9.4 Hz , 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.55 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 6.49 (dd, J = 8.7 Hz, 0.6 Hz, 1H), 6.28 (s, 2H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 447.05 $(M+H)^+$.

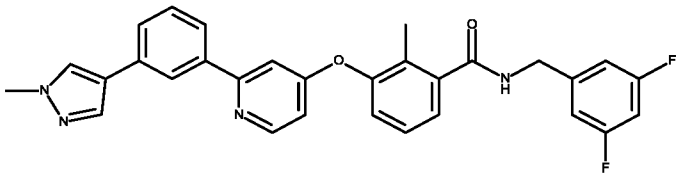
Example 10: General procedure for the synthesis of analogues 278 – 283



199b

278-283

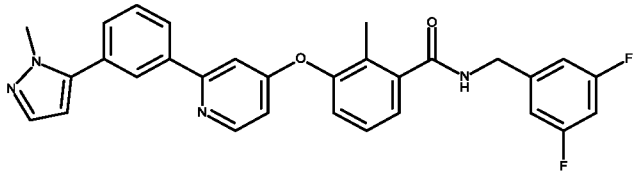
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(1-methylpyrazol-4-yl)phenyl]-4-pyridyl}oxy)benzamide (**278**):



Compound **278** was synthesized in a two steps procedure from intermediate **199b** (0.06 mmol), (3-bromophenyl)boronic acid (0.06 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (0.13 mmol) as a white solid in 10% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, J = 6.0 Hz, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.26 (s, 1H), 8.23 (t, J = 1.6 Hz, 1H), 7.95 (d, J = 0.8 Hz, 1H), 7.85-7.83 (m, 1H), 7.66 (d, J = 2.3 Hz, 1H), 7.64-7.62 (m, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.43-7.37 (m, 2H), 7.27 (dd, J = 7.8

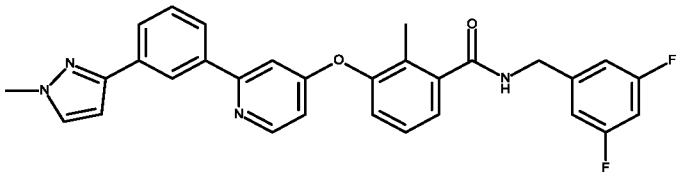
Hz, 1.4 Hz, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.05 (m, 2H), 6.66 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 2.17 (s, 3H).
ESI-MS: 511.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(2-methylpyrazol-3-yl)phenyl]-4-pyridyl}oxy)benzamide (**279**):



Compound **279** was synthesized in a two steps procedure from intermediate **199b** (0.08 mmol), (3-bromophenyl)boronic acid (0.08 mmol) and 1-methyl-1*H*-pyrazole-5-boronic acid pinacol ester (0.15 mmol) as a white solid in 6% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.56-8.55 (m, 1H), 8.15 (t, *J* = 2.0 Hz, 1H), 8.10-8.08 (m, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.62-7.60 (m, 2H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.42-7.37 (m, 2H), 7.27 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.12 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.05 (m, 2H), 6.70 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 2.16 (s, 3H).
ESI-MS: 511.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(1-methylpyrazol-3-yl)phenyl]-4-pyridyl}oxy)benzamide (**280**):

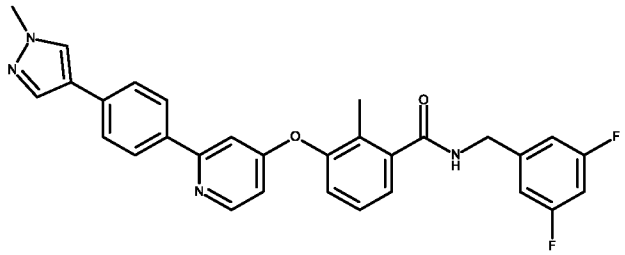


Compound **280** was synthesized in a two steps procedure from intermediate **199b** (0.08 mmol), (3-bromophenyl)boronic acid (0.08 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.15 mmol) as a white solid in 10% yield according to the general method D2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 9.00 (t, *J* = 6.0 Hz, 1H), 8.56-8.55 (m, 1H), 8.48 (t, *J* = 1.6

Hz, 1H), 7.90 (ddd, *J* = 7.8 Hz, 1.8 Hz, 1.1 Hz, 1H), 7.85 (ddd, *J* = 7.7 Hz, 1.6 Hz, 1.1 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.58 (d, *J* = 2.2 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.43-7.37 (m, 2H), 7.28 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.12 (tt, *J* = 9.3 Hz, 2.4 Hz, 1H), 7.09-7.05 (m, 2H), 6.78 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 2.17 (s, 3H).

ESI-MS: 511.10 $(M+H)^+$.

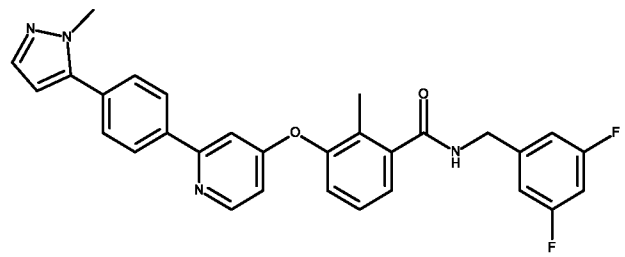
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[4-(1-methylpyrazol-4-yl)phenyl]-4-pyridyl}oxy)benzamide (**281**):



Compound **281** was synthesized in a two steps procedure from intermediate **199b** (0.10 mmol), (4-bromophenyl)boronic acid (0.15 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (0.21 mmol) as a white solid in 4% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.0 Hz, 1H), 8.52 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 0.6 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 2.3 Hz, 1H), 7.43-7.37 (m, 2H), 7.27 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.66 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 2.16 (s, 3H).

ESI-MS: 511.10 $(M+H)^+$.

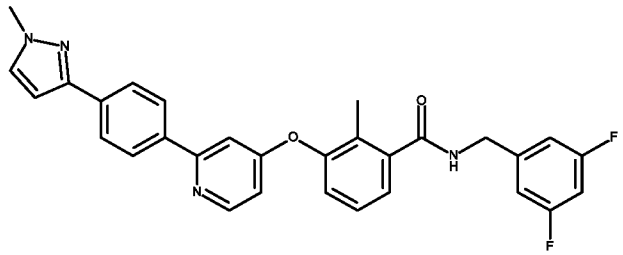
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[4-(2-methylpyrazol-3-yl)phenyl]-4-pyridyl}oxy)benzamide (**282**):



Compound **282** was synthesized in a two steps procedure from intermediate **199b** (0.10 mmol), (4-bromophenyl)boronic acid (0.15 mmol) and 1-methyl-1*H*-pyrazole-5-boronic acid pinacol ester (0.21 mmol) as a white solid in 4% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.02 (t, *J* = 6.0 Hz, 1H), 8.57 (d, *J* = 5.7 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 2.3 Hz, 1H), 7.49 (d, *J* = 1.9 Hz, 1H), 7.44-7.37 (m, 2H), 7.29 (dd, *J* = 7.3 Hz, 1.9 Hz, 1H), 7.15-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.74 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 2.17 (s, 3H).

ESI-MS: 511.10 $(M+H)^+$.

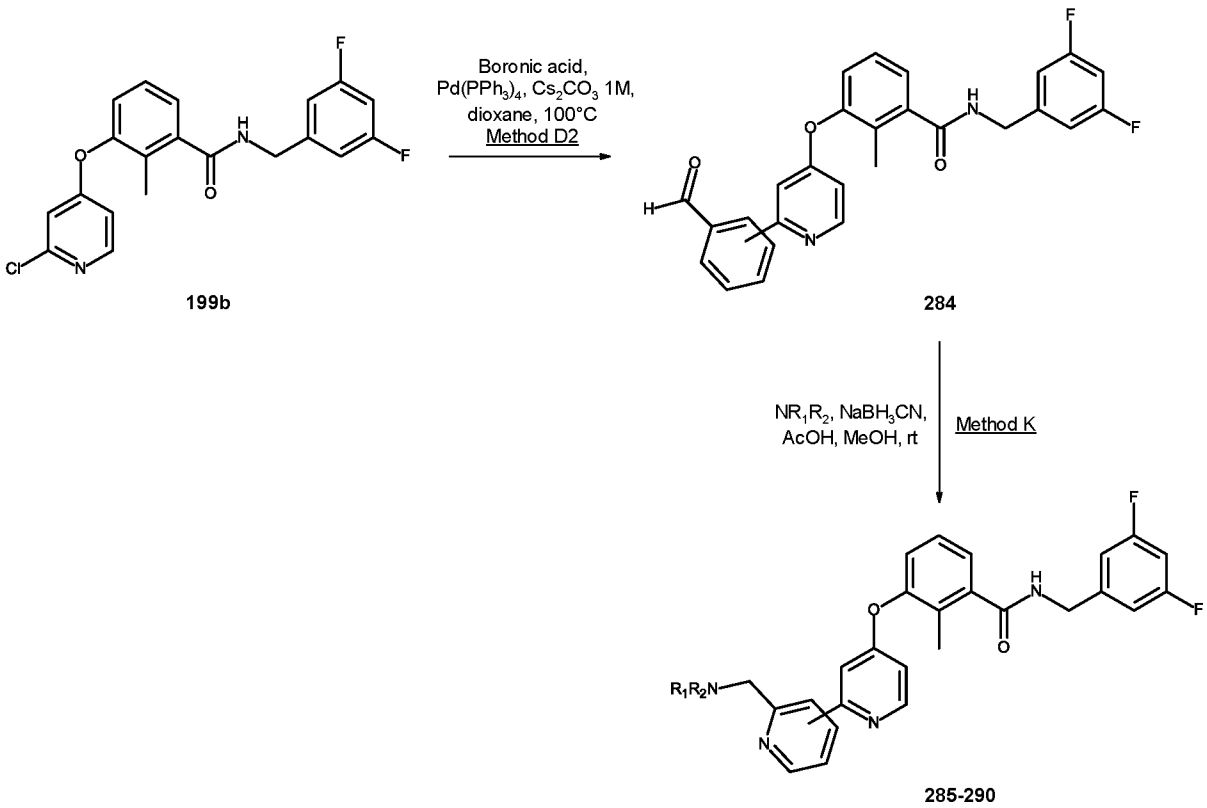
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[4-(1-methylpyrazol-3-yl)phenyl]-4-pyridyl}oxy)benzamide (**283**):



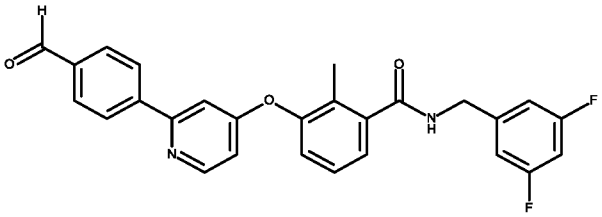
Compound **283** was synthesized in a two steps procedure from intermediate **199b** (0.10 mmol), (4-bromophenyl)boronic acid (0.15 mmol) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.21 mmol) as a white solid in 4% yield according to the general method D2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.1 Hz, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.43-7.37 (m, 2H), 7.28 (dd, *J* = 7.4 Hz, 1.8 Hz, 1H), 7.15-7.10 (m, 1H), 7.09-.704 (m, 2H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.69 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.90 (s, 3H), 2.17 (s, 3H).

ESI-MS: 511.10 $(M+H)^+$.

Example 11: General procedure for the synthesis of analogues 285 – 290



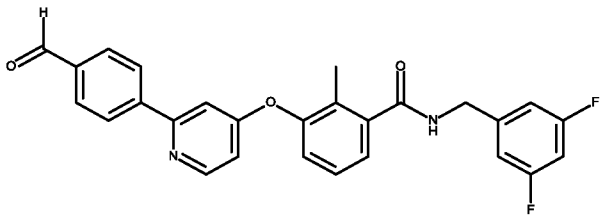
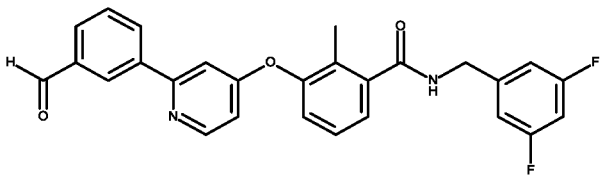
Preparation of *N*-[(3,5-difluorophenyl)methyl]-3-{[2-(4-formylphenyl)-4-pyridyl] oxy}-2-methyl-benzamide (**284a**):



Intermediate **284a** was synthesized from **199b** (0.39 mmol) as a white solid in quantitative yield according to the general method D2.

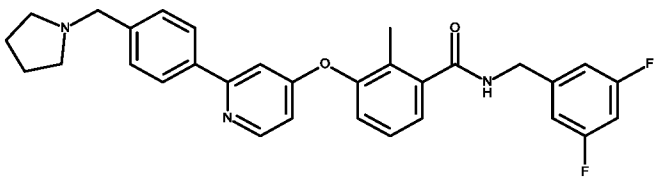
ESI-MS: 459.05 $(M+H)^+$.

The following table illustrates intermediates **284** prepared from Method D2.

Intermediate	Structure	Synthesis procedure
Compound **284a**		Method D2
Compound **284b**		Method D2

Method K: To a solution of **284** (1 equiv.) in MeOH (10 mL/mmol) were added amine derivative (1.3 equiv.), AcOH (2% v/v) and $NaBH_3CN$. The mixture was stirred at room temperature until completion (from 1 h to overnight). The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[4-(pyrrolidin-1-ylmethyl)phenyl]-4-pyridyl}oxy)benzamide (**285**):

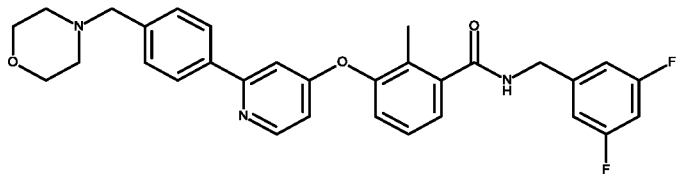


Compound **285** was synthesized from intermediate **284a** (0.05 mmol) and pyrrolidine (0.07 mmol) as a white solid in 25% yield according to the general method K. ^1H NMR (400 MHz, DMSO-d_6) δ(ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 2.2 Hz, 1H), 7.43-7.37 (m, 4H), 7.27 (dd, J = 7.3 Hz, 1.9 Hz, 1H), 7.15-7.04 (m, 3H), 6.69 (dd, J = 5.6 Hz, 2.3 Hz, 1H), 4.48 (d, J = 5.9 Hz, 2H), 3.61 (s, 2H), 2.43 (bs, 4H), 2.16 (s,

3H), 1.70 (bs, 4H).

ESI-MS: 514.15 $(M+H)^+$.

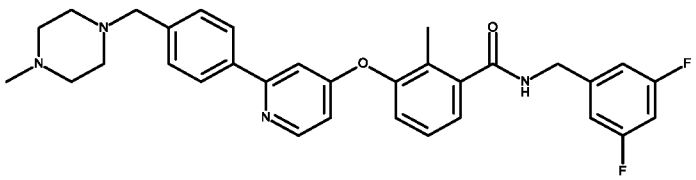
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[4-(morpholinomethyl)phenyl]-4-pyridyl}oxy)benzamide (**286**):



Compound **286** was synthesized from intermediate **284a** (0.07 mmol) and morpholine (0.09 mmol) as a white solid in 26% yield according to the general method K. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 2.3 Hz, 1H), 7.41-7.37 (m, 4H), 7.27 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.13 (tt, J = 9.5 Hz , 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.69 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.59-3.56 (m, 4H), 3.51 (s, 2H), 2.38-2.35 (m, 4H), 2.15 (s, 3H).

ESI-MS: 530.15 $(M+H)^+$.

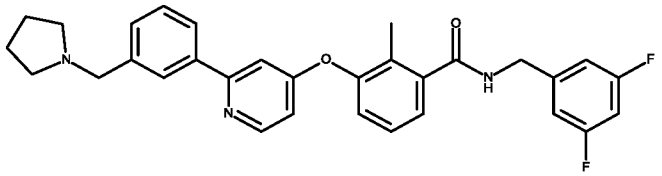
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-{4-[(4-methylpiperazin-1-yl)methyl]phenyl}-4-pyridyl)oxy]benzamide (**287**):



Compound **287** was synthesized from intermediate **284a** (0.07 mmol) and 1-methylpiperazine (0.09 mmol) as a white solid in 31% yield according to the general method K. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.1 Hz, 1H), 8.52 (d, J = 5.7 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 2.3 Hz, 1H), 7.43-7.37 (m, 4H), 7.27 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.69 (dd, J = 5.6 Hz , 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.49 (s, 2H), 2.56-2.50 (m, 4H), 2.40-2.30 (m, 4H), 2.15 (s, 3H), 2.14 (s, 3H).

ESI-MS: 543.20 $(M+H)^+$.

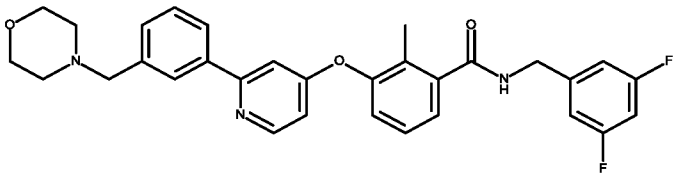
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(pyrrolidin-1-ylmethyl)phenyl]-4-pyridyl}oxy)benzamide (**288**):



Compound **288** was synthesized from intermediate **284b** (0.06 mmol) and pyrrolidine (0.09 mmol) as a white solid in 44% yield according to the general method K. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.50-7.37 (m, 5H), 7.27 (dd, J = 7.4 Hz, 1.9 Hz , 1H), 7.13 (tt, J = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.70 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.69 (s, 2H), 2.52 (bs, 4H), 2.16 (s, 3H), 1.74 (bs, 4H).

ESI-MS: 514.15 $(M+H)^+$.

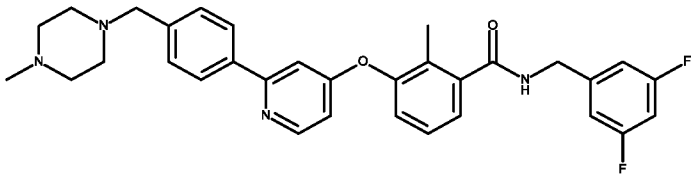
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(morpholinomethyl)phenyl]-4-pyridyl}oxy)benzamide (**289**):



Compound **289** was synthesized from intermediate **284b** (0.07 mmol) and morpholine (0.09 mmol) as a white solid in 40% yield according to the general method K. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, J = 6.0 Hz, 1H), 8.53 (d, J = 5.7 Hz, 1H), 7.99 (bs, 1H), 7.88-7.86 (m, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.45-7.37 (m, 4H), 7.27 (dd, J = 7.4 Hz, 1.9 Hz, 1H), 7.16-7.10 (m, 1H), 7.09-7.04 (m, 2H), 6.70 (dd, J = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 3.58-3.56 (m, 4H), 3.53 (s, 2H), 2.38-2.36 (s, 4H), 2.16 (s, 3H).

ESI-MS: 530.15 $(M+H)^+$.

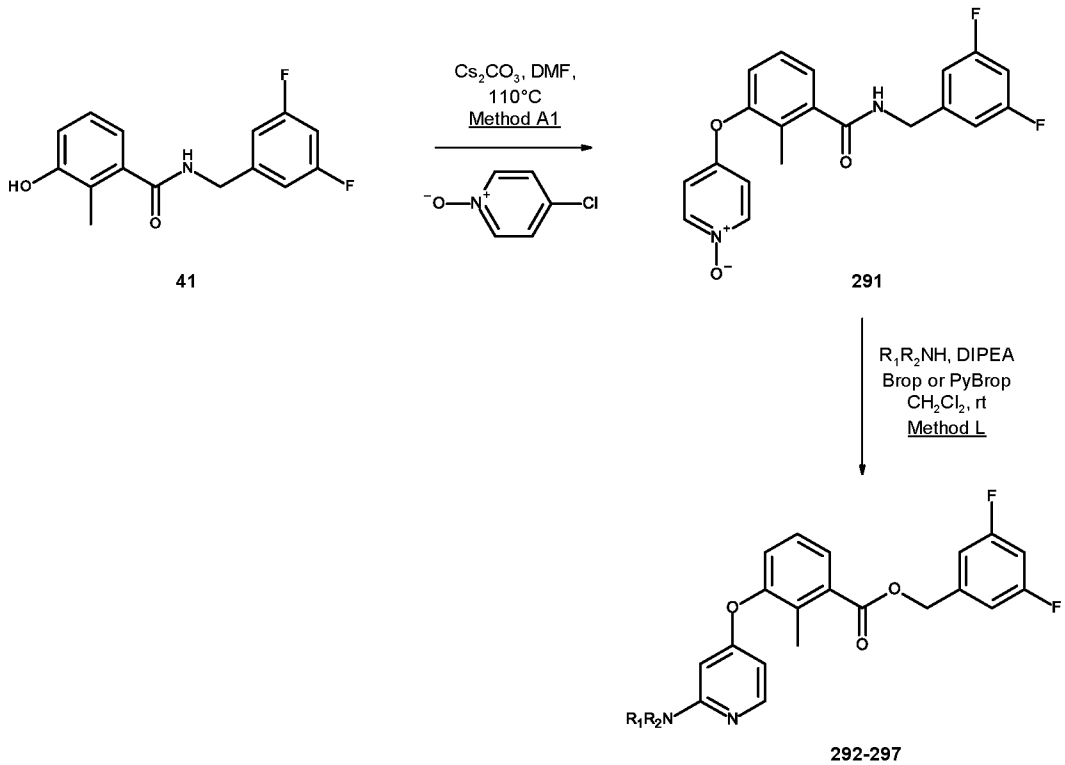
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-{3-[(4-methylpiperazin-1-yl) methyl]phenyl}-4-pyridyl)oxy]benzamide (**290**):



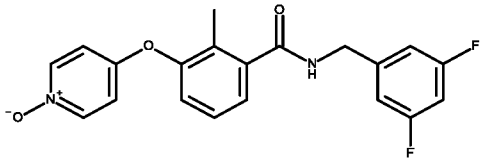
Compound **290** was synthesized from intermediate **284b** (0.07 mmol) and 1-methylpiperazine (0.09 mmol) as a white solid in 36% yield according to the general method K. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.01 (t, *J* = 6.1 Hz, 1H), 8.53 (d, *J* = 5.7 Hz, 1H), 7.97 (s, 1H), 7.88-7.84 (m, 1H), 7.46 (d, *J* = 2.2 Hz, 1H), 7.44-7.34 (m, 4H), 7.27 (dd, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz, 2.4 Hz, 1H), 7.09-7.04 (m, 2H), 6.70 (dd, *J* = 5.6 Hz, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.51 (s, 2H), 2.52-2.50 (m, 4H), 2.37-2.30 (m, 4H), 2.16 (s, 3H), 2.14 (s, 3H).

ESI-MS: 543.20 $(M+H)^+$.

Example 12: General procedure for the synthesis of analogues 292 – 297



Preparation of *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-(1-oxidopyridin-1-ium-4-yl)oxy-benzamide (**291**):



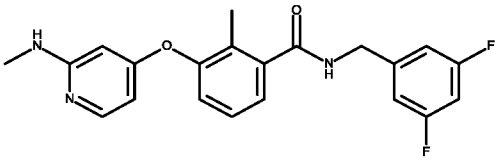
Intermediate **291** was synthesized from **41** (0.77 mmol) and 4-chloropyridine-*N*-oxide (0.77 mmol) as a white solid in 59% yield according to the general method A.

ESI-MS: 371.05 $(M+H)^+$.

Method L: To a solution of **291** (1 equiv.) in CH_2Cl_2 (10 mL/mmol) were added amine derivative (1.3 equiv.), DIPEA (3.8 equiv.) and Brop or PyBrop (1.3 equiv.). The mixture was stirred at room temperature until completion (from 1 h to overnight). The reaction mixture was diluted with DCM and washed twice with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

The following compounds are examples illustrating Method L:

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(methylamino)-4-pyridyl]oxy} benzamide (**292**):

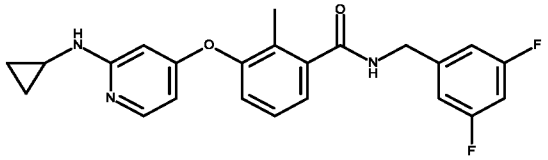


Compound **292** was synthesized from intermediate **291** (0.08 mmol) and methylamine (2M THF, 0.10 mmol) as a white solid in 32% yield according to the general method L. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, J = 6.0 Hz, 1H), 7.87 (d, J = 5.8 Hz, 1H), 7.37-7.30 (m, 2H), 7.17-7.03 (m, 4H), 6.47 (q, J =

4.7 Hz, 1H), 6.06 (dd, *J* = 5.8 Hz, 2.2 Hz, 1H), 5.75 (d, *J* = 2.2 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 2.70 (d, *J* = 4.8 Hz, 3H), 2.11 (s, 3H).

ESI-MS: 384.10 $(M+H)^+$.

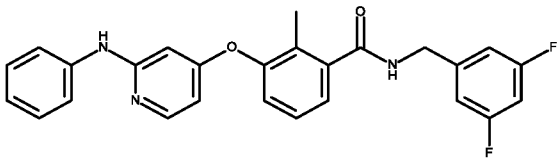
3-{[2-(cyclopropylamino)-4-pyridyl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**293**):



Compound **293** was synthesized from intermediate **291** (0.08 mmol) and cyclopropylamine (0.11 mmol) as a white solid in 30% yield according to the general method L. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 7.87 (d, *J* = 5.7 Hz, 1H), 7.38-7.31 (m, 2H), 7.18-7.10 (m, 2H), 7.09-7.03 (m, 2H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.04 (dd, *J* = 5.7 Hz, 2.1 Hz, 1H), 5.97 (d, *J* = 1.9 Hz, 1H), 4.46 (d, *J* = 5.9 Hz, 2H), 2.40-2.43 (m, 1H), 2.12 (s, 3H), 0.64-0.59 (m, 2H), 0.38-0.34 (m, 2H).

ESI-MS: 410.10 $(M+H)^+$.

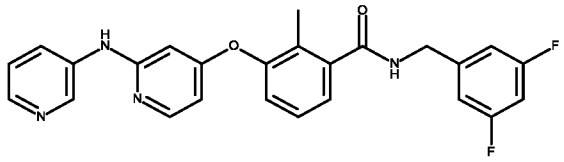
3-[(2-anilino-4-pyridyl)oxy]-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**294**):



Compound **294** was synthesized from intermediate **291** (0.05 mmol) and aniline (0.11 mmol) as a white solid in 13% yield according to the general method L. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.98 (s, 2H), 8.05 (d, *J* = 5.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.41-7.35 (m, 2H), 7.24-7.05 (m, 6H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.39-6.38 (m, 1H), 6.13 (s, 1H), 4.48 (d, *J* = 5.8 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 446.10 $(M+H)^+$.

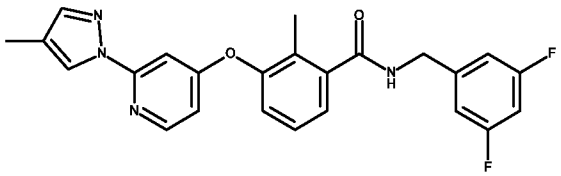
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-pyridylamino)-4-pyridyl]oxy} benzamide (**295**):



Compound **295** was synthesized from intermediate **291** (0.05 mmol) and 3-aminopyridine (0.27 mmol) as a white solid in 37% yield according to the general method L. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.20 (s, 1H), 8.99 (t, J = 5.9 Hz, 1H), 8.72 (d, J = 2.5 Hz, 1H), 8.17 (ddd, J = 8.4 Hz, 2.6 Hz, 1.5 Hz, 1H), 8.10-8.06 (m, 2H), 7.43-7.36 (m, 2H), 7.26-7.23 (m, 2H), 7.13 (tt, J = 9.4 Hz, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.46 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 6.13 (d, J = 2.2 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 447.10 $(M+H)^+$.

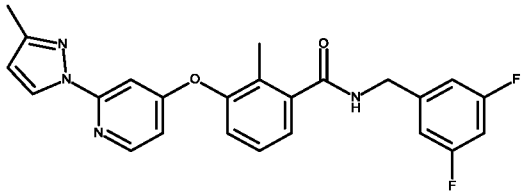
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-methylpyrazol-1-yl)-4-pyridyl] oxy}benzamide (**296**):



Compound **296** was synthesized from intermediate **291** (0.07 mmol) and 4-methylpyrazole (0.34 mmol) as a white solid in 38% yield according to the general method L. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.08 (t, J = 6.0 Hz, 1H), 8.37 (s, 1H), 8.34 (d, J = 5.7 Hz, 1H), 7.57 (s, 1H), 7.45-7.40 (m, 2H), 7.31 (dd, J = 7.0 Hz, 2.3 Hz, 1H), 7.16-7.09 (m, 2H), 7.09-7.04 (m, 2H), 6.90 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.47 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H), 2.08 (s, 3H).

ESI-MS: 435.10 $(M+H)^+$.

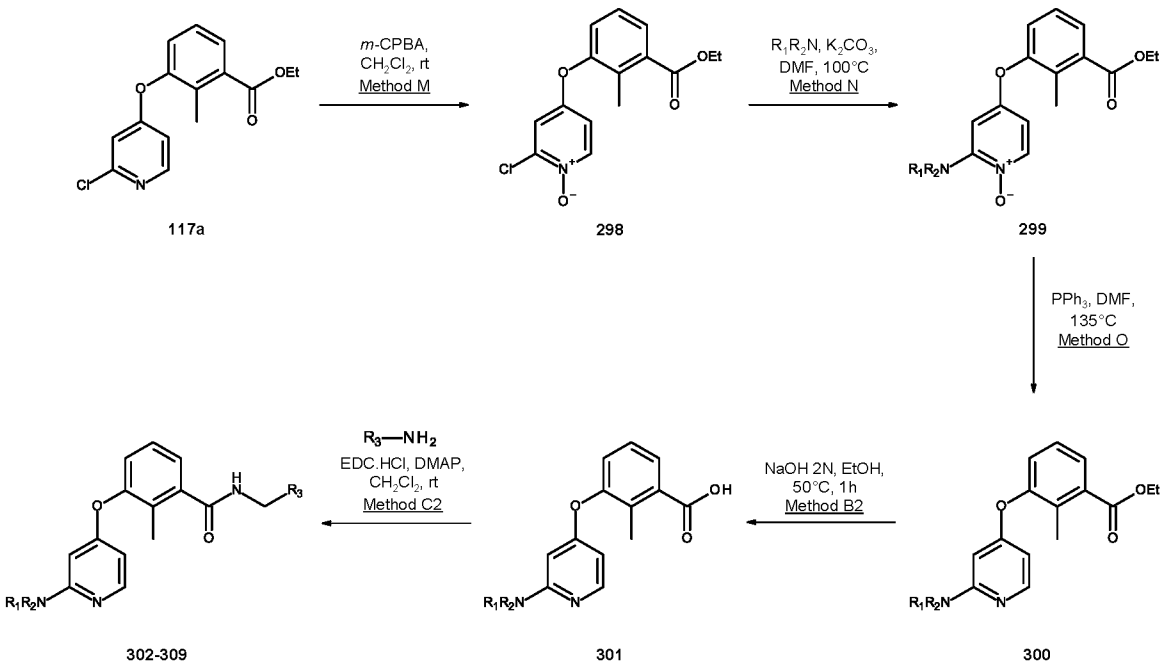
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-methylpyrazol-1-yl)-4-pyridyl]oxy}benzamide (**297**):



Compound **297** was synthesized from intermediate **291** (0.16 mmol) and 3-methylpyrazole (0.78 mmol) as a white solid in 15% yield according to the general method L. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.06 (t, *J* = 6.0 Hz, 1H), 8.47 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 5.7 Hz, 1H), 7.46-7.40 (m, 2H), 7.31 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.16-7.09 (m, 2H), 7.08-7.04 (m, 2H), 6.88 (dd, *J* = 5.7 Hz, 2.4 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.22 (s, 3H), 2.15 (s, 3H).

ESI-MS: 435.20 $(M+H)^+$.

Example 13: General procedure for the synthesis of analogues 302 – 309

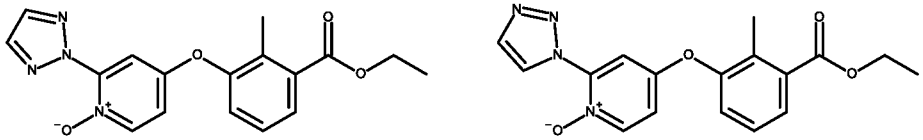


Method M: To a stirred solution of **117a** (400 mg, 1.37 mmol) in CH_2Cl_2 (6 mL/ mmol) was added *m*-CPBA (77%, 922 mg, 4.11 mmol) and the reaction mixture was stirred at room temperature for 24h. The reaction mixture was diluted with DCM and washed twice with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH from 100/0 to 93/7) to give 356 mg of ethyl 3-(2-chloro-1-oxido-pyridin-1-ium-4-yl)oxy-2-methyl-benzoate **298** in 85% yield as yellow oil. ESI-MS: 308.00 $(M+H)^+$.

Method N: To a stirred solution of **298** (1 equiv.) in DMF (10 mL/ mmol) were added amine derivative (1 to 3 equiv.) and K_2CO_3 (1.2 equiv.). The reaction mixture was stirred at 100°C overnight. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 94/6) to give the expected compounds.

The following compound **299** is an example illustrating Method N:

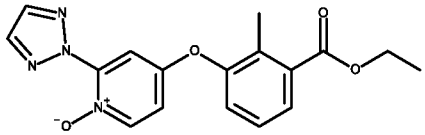
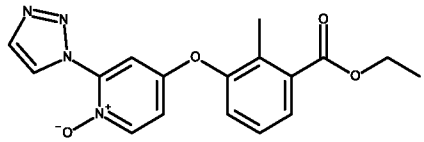
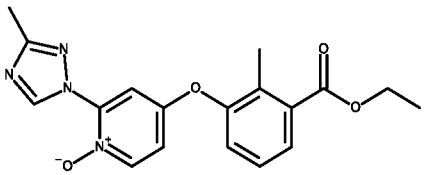
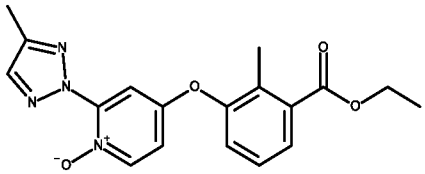
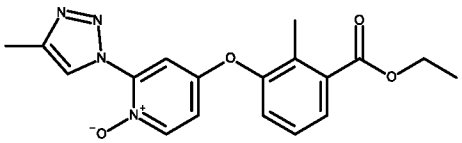
Preparation of ethyl 2-methyl-3-[1-oxido-2-(triazol-2-yl)pyridin-1-ium-4-yl]oxy-benzoate (**299a**) and ethyl 2-methyl-3-[1-oxido-2-(triazol-1-yl)pyridin-1-ium-4-yl]oxy-benzoate (**299b**):



Intermediate **299a** and **299b** were synthesized from **298** (1.02 mmol) and 1*H*-1,2,3-triazole (6.02 mmol) as a white solid in 33% and 23% yield respectively according to the general method N.

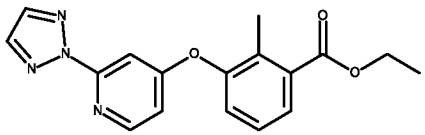
ESI-MS: 341.00 $(M+H)^+$.

The following table illustrates intermediates **299** prepared from method N:

Intermediate	Structure	Synthesis procedure
Compound **299a**		Method N
Compound **299b**		Method N
Compound **299c**		Method N
Compound **299d**		Method N
Compound **299e**		Method N

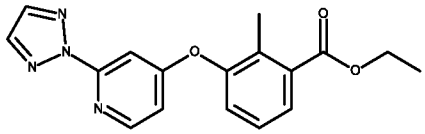
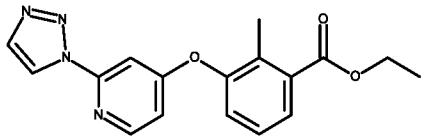
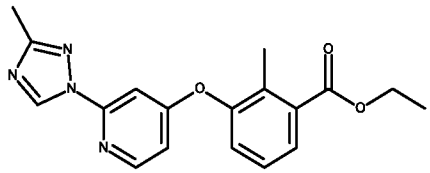
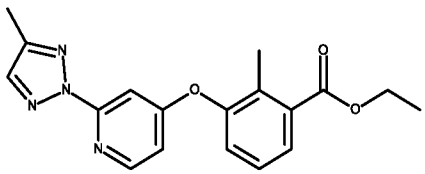
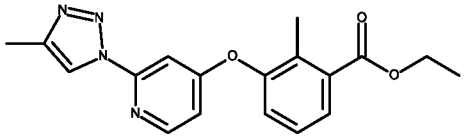
Method O: To a stirred solution of **299** (1 equiv.) in DMF (10 mL/ mmol) was added PPh_3 (2 equiv.) and the reaction mixture was stirred at 135°C overnight. The reaction mixture was concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 96/4) to give the expected compound.

Preparation of ethyl 2-methyl-3-{[2-(triazol-2-yl)-4-pyridyl]oxy}benzoate (**300a**):

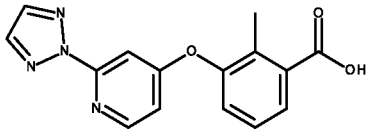
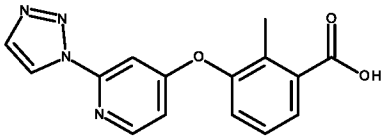
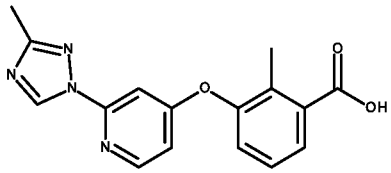
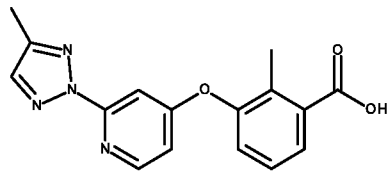
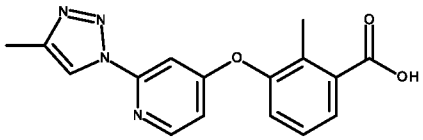


Intermediate **300a** was synthesized from **299a** (0.32 mmol) and PPh_3 (0.64 mmol) as a white solid in 70% yield according to the general method O. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.47 (d, J = 5.7 Hz, 1H), 8.14 (s, 2H), 7.81-7.76 (m, 1H), 7.50-7.45 (m, 2H), 7.30 (d, J = 2.2 Hz, 1H), 7.03 (dd, J = 5.7 Hz, 2.3 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).
ESI-MS: 325.05 $(M+H)^+$.

The following table illustrates intermediates **300** prepared from method O:

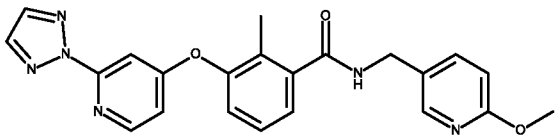
Intermediate	**Structure**	**Synthesis procedure**
Compound **300a**		Method O
Compound **300b**		Method O
Compound **300c**		Method O
Compound **300d**		Method O
Compound **300e**		Method O

The following table illustrates intermediates **301** prepared from method B2:

Intermediate	Structure	Synthesis procedure
Compound **301a**		Method B2
Compound **301b**		Method B2
Compound **301c**		Method B2
Compound **301d**		Method B2
Compound **301e**		Method B2

The following compounds are examples illustrating Method C2:

N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(triazol-2-yl)-4-pyridyl]oxy} benzamide (**302**):

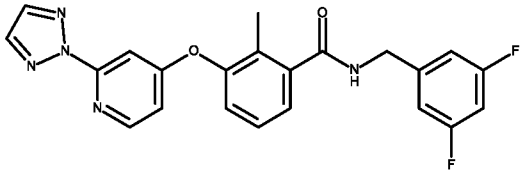


Compound **302** was synthesized from intermediate **301a** (0.07 mmol) and 6-methoxypyridin-3-yl)methanamine (0.10 mmol) as a white solid in 79% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.95 (t, J = 5.9 Hz, 1H), 8.47 (d, J = 5.7 Hz, 1H), 8.14 (s, 3H), 7.69 (dd, J = 8.5

Hz, 2.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.36-7.30 (m, 3H), 7.03 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.12 (s, 3H).

ESI-MS: 417.05 $(M+H)^+$.

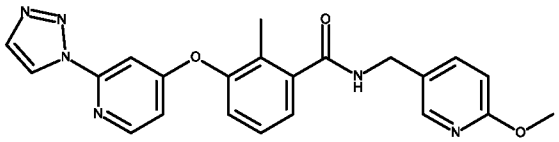
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(triazol-2-yl)-4-pyridyl]oxy} benzamide (**303**):



Compound **303** was synthesized from intermediate **301a** (0.07 mmol) and 3,5-difluorobenzylamine (0.10 mmol) as a white solid in 82% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.05 (t, *J* = 6.1 Hz, 1H), 8.47 (d, *J* = 5.7 Hz, 1H), 8.14 (s, 2H), 7.46-7.41 (m, 2H), 7.34 (dd, *J* = 7.0 Hz, 2.4 Hz, 1H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.15-7.09 (m, 1H), 7.09-7.03 (m, 3H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).

ESI-MS: 422.05 $(M+H)^+$.

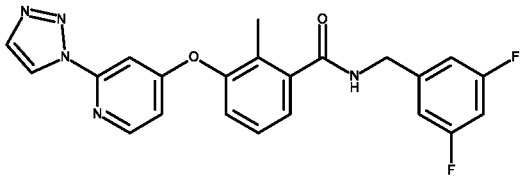
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(triazol-1-yl)-4-pyridyl]oxy} benzamide (**304**):



Compound **304** was synthesized from intermediate **301b** (0.07 mmol) and 6-methoxypyridin-3-yl)methanamine (0.10 mmol) as a white solid in 68% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.97 (t, *J* = 5.9 Hz, 1H), 8.84 (d, *J* = 1.2 Hz, 1H), 8.49 (d, *J* = 5.8 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 1.2 Hz, 1H), 7.70 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.45-7.40 (m, 2H), 7.37-7.32 (m, 2H), 7.07 (dd, *J* = 5.8 Hz, 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.13 (s, 3H).

ESI-MS: 417.05 $(M+H)^+$.

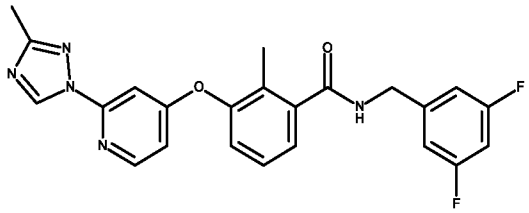
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(triazol-1-yl)-4-pyridyl]oxy} benzamide (**305**):



Compound **305** was synthesized from intermediate **301b** (0.07 mmol) and 3,5-difluorobenzylamine (0.10 mmol) as a white solid in 64% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, J = 6.1 Hz, 1H), 8.85 (d, J = 1.2 Hz, 1H), 8.50 (d, J = 5.8 Hz, 1H), 7.98 (d, J = 1.2 Hz, 1H), 7.48-7.42 (m, 3H), 7.36 (dd, J = 7.1 Hz, 2.3 Hz, 1H), 7.15-7.04 (m, 4H), 4.48 (d, J = 6.0 Hz, 2H), 2.16 (s, 3H).

ESI-MS: 422.10 $(M+H)^+$.

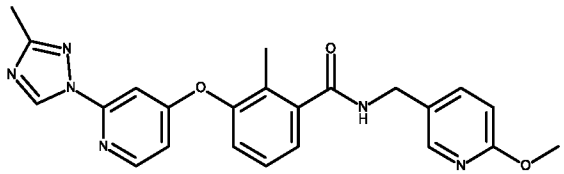
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-methyl-1,2,4-triazol-1-yl)-4-pyridyl]oxy}benzamide (**306**):



Compound **306** was synthesized from intermediate **301c** (0.06 mmol) and 3,5-difluorobenzylamine (0.10 mmol) as a white solid in 65% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 1H), 9.07 (t, J = 6.0 Hz, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.47-7.42 (m, 2H), 7.33 (dd, J = 6.9 Hz, 2.4 Hz, 1H), 7.13 (tt, J = 9.4 Hz, 2.3 Hz, 1H), 7.09-7.05 (m, 3H), 7.01 (dd, J = 5.7 Hz, 2.3 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.32 (s, 3H), 2.14 (s, 3H).

ESI-MS: 436.15 $(M+H)^+$.

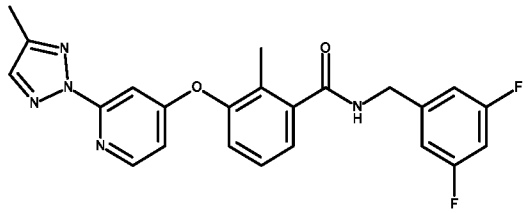
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(3-methyl-1,2,4-triazol-1-yl)-4-pyridyl]oxy}benzamide (**307**):



Compound **307** was synthesized from intermediate **301c** (0.06 mmol) and 6-methoxypyridin-3-yl)methanamine (0.10 mmol) as a white solid in 54% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.21 (s, 1H), 8.97 (t, *J* = 5.9 Hz, 1H), 8.41 (d, *J* = 5.7 Hz, 1H), 8.14 (d, *J* = 2.2 Hz, 1H), 7.69 (dd, *J* = 8.5 Hz, 2.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.36-7.34 (m, 1H), 7.32-7.29 (m, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.00 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 4.39 (d, *J* = 5.9 Hz, 2H), 3.83 (s, 3H), 2.32 (s, 3H), 2.11 (s, 3H).

ESI-MS: 431.15 $(M+H)^+$.

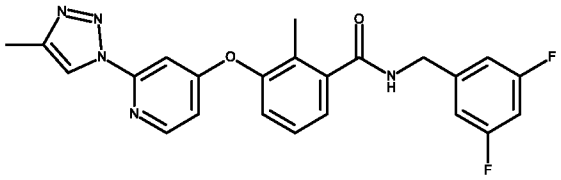
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-methyltriazol-2-yl)-4-pyridyl]oxy}benzamide (**308**):



Compound **308** was synthesized from intermediate **301d** (0.11 mmol) and 3,5-difluorobenzylamine (0.16 mmol) as a white solid in 81% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.07 (t, *J* = 6.1 Hz, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 7.91 (s, 1H), 7.47-7.40 (m, 2H), 7.34 (dd, *J* = 7.0 Hz, 2.3 Hz, 1H), 7.23 (d, *J* = 2.2 Hz, 1H), 7.13 (tt, *J* = 9.4 Hz , 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 7.01 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.33 (s, 3H), 2.14 (s, 3H).

ESI-MS: 436.10 $(M+H)^+$.

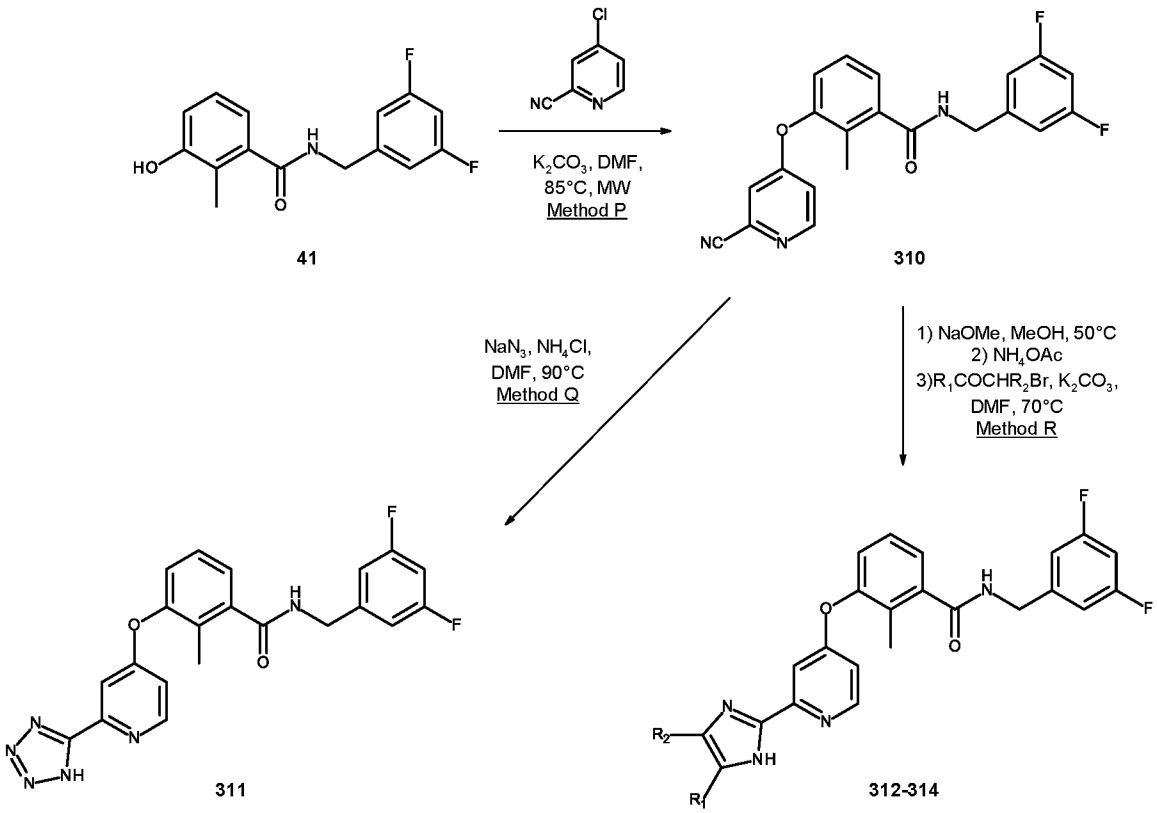
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-methyltriazol-1-yl)-4-pyridyl] oxy}benzamide (**309**):



Compound **309** was synthesized from intermediate **301e** (0.11 mmol) and 3,5-difluorobenzylamine (0.16 mmol) as a white solid in 59% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, J = 6.0 Hz, 1H), 8.58 (d, J = 0.8 Hz, 1H), 8.47 (d, J = 5.8 Hz, 1H), 7.47-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.13 (tt, J = 9.5 Hz, 2.3 Hz, 1H), 7.09-7.04 (m, 3H), 4.48 (d, J = 6.0 Hz, 2H), 2.32 (s, 3H), 2.15 (s, 3H).

ESI-MS: 436.15 $(M+H)^+$.

Example 14: General procedure for the synthesis of analogues 310 – 314



Method P: Compound **41** (515 mg, 1.86 mmol) and 4-chloropyridine-2-carbonitrile (198 mg, 1.43 mmol) were dissolved in DMF (10 mL / mmol) in an oven-dried screw-cap test tube. K_2CO_3 (395 mg, 2.90 mmol) was added and the reaction mixture was stirred and heated under microwave irradiation at 85°C for 8h. The reaction mixture was diluted with EtOAc and washed twice with a saturated solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH from 100/0 to 95/5) to give 321 mg of 3-[(2-cyano-4-pyridyl)oxy]-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide **310** in 59% yield as white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.99 (t, *J* = 6.0 Hz, 1H), 8.60 (dd, *J* = 5.8 Hz, 0.4 Hz, 1H), 7.62 (dd, *J* = 2.5 Hz, 0.4 Hz, 1H), 7.45-7.40 (m, 2H), 7.30-7.26 (m, 1H), 7.16-7.04 (m, 4H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.11 (s, 3H).

ESI-MS: 436.15 $(M+H)^+$.

Method Q: To a stirred solution of **310** (20 mg, 0.05 mmol) in DMF (1 mL) were added NH_4Cl (6 mg, 0.11 mmol) and sodium azide (7 mg, 0.11 mmol). The reaction mixture was stirred at 90°C overnight. The reaction mixture was diluted with DCM and washed twice with a saturated solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH from 100/0 to 80/20) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give 3 mg of *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1*H*-tetrazol-5-yl)-4-pyridyl]oxy} benzamide **311** in 14% yield as beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.09 (t, *J* = 6.0 Hz, 1H), 8.63 (d, *J* = 5.7 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.47-7.40 (m, 2H), 7.32 (dd, *J* = 7.3 Hz, 2.0 Hz, 1H), 7.15-7.03 (m, 4H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.15 (s, 3H).

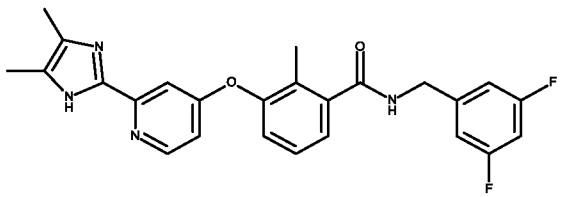
ESI-MS: 423.00 $(M+H)^+$.

Method R: To a stirred solution of **310** (1 equiv.) in *n*-propanol (10 mL / mmol) was added NaOMe (25% in MeOH, 1.2 equiv.) and the reaction mixture was stirred at 50°C for 1h30. Then, NH_4OAc was added and the reaction mixture was stirred at 70°C for 1h.The reaction mixture was diluted with EtOAc and washed

twice with water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the amidine derivative with was used directly in the next step. Compound was dissolved in DMF (10 mL / mmol) and K_2CO_3 (2 equiv.) and bromo derivative (1.2 to 2 equiv.) were added. The reaction mixture was stirred at 90°C for 3h. The reaction mixture was diluted with EtOAc and washed twice with a saturated solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (CH_2Cl_2/MeOH from 100/0 to 90/10) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give the expected compound.

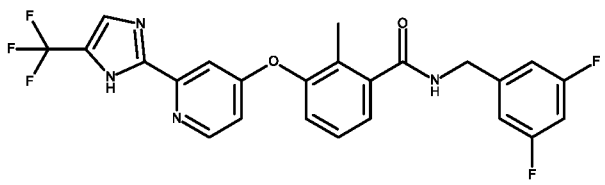
The following compounds are examples illustrating Method R:

N-[(3,5-difluorophenyl)methyl]-3-{[2-(4,5-dimethyl-1*H*-imidazol-2-yl)-4-pyridyl]oxy}-2-methyl-benzamide (**312**):



Compound **312** was synthesized from intermediate **310** (0.07 mmol) and 3-bromo-2-butanone (0.13 mmol) as a white solid in 23% yield according to the general method R. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.33 (bs, 1H), 9.07 (t, *J* = 6.0 Hz, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 7.45-7.38 (m, 2H), 7.28 (dd, *J* = 7.6 Hz, 1.7 Hz, 1H), 7.16-7.04 (m, 4H), 6.91 (dd, *J* = 5.7 Hz, 2.6 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H).
ESI-MS: 449.10 $(M+H)^+$.

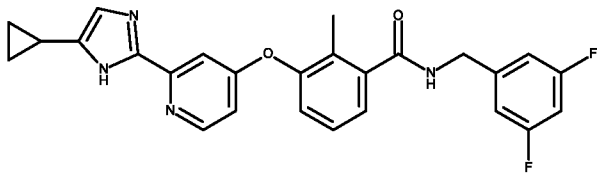
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridyl}oxy)benzamide (**313**):



Compound **313** was synthesized from intermediate **310** (0.05 mmol) and 3-bromo-1,1,1-trifluoroacetone (0.06 mmol) as a white solid in 23% yield according to the general method R. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.47 (bs, 1H), 9.07 (t, J = 6.0 Hz, 1H), 8.55 (d, J = 5.7 Hz, 1H), 7.84 (s, 1H), 7.46-7.39 (m, 2H), 7.35 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 7.1-7.09 (m, 1H), 7.09-7.03 (m, 3H), 4.47 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).

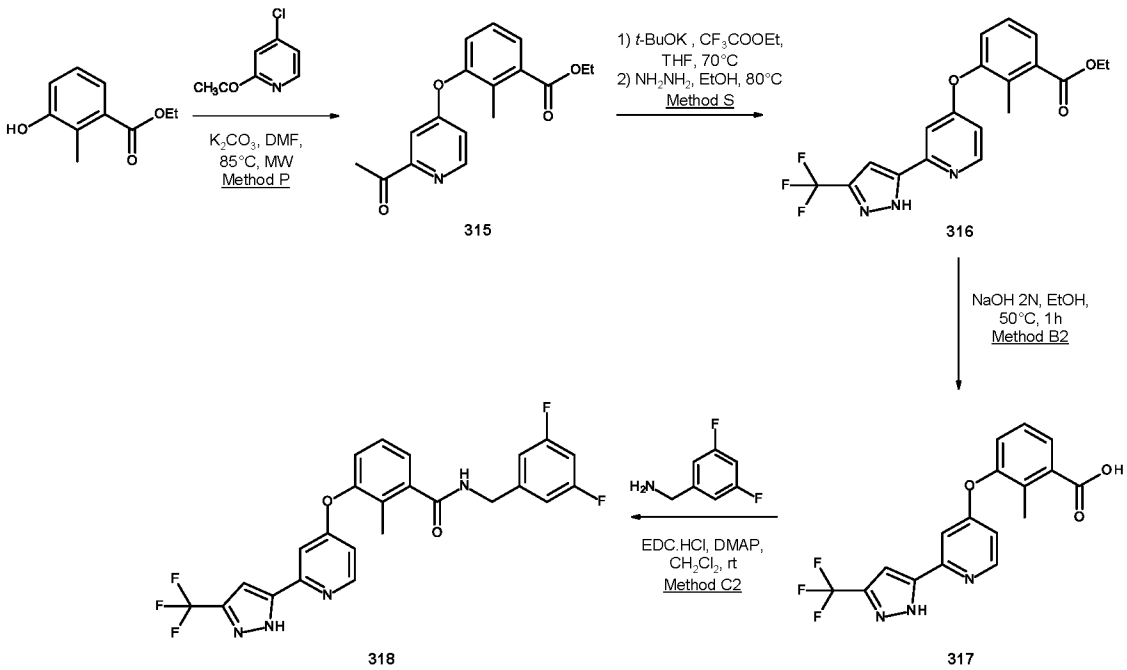
ESI-MS: 489.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[5-(trifluoromethyl)-1*H*-imidazol-2-yl]-4-pyridyl}oxy)benzamide (**314**):

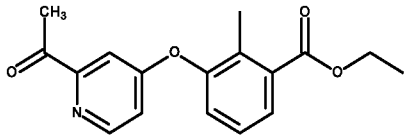


Compound **314** was synthesized from intermediate **310** (0.07 mmol) and 2-bromo-1-cyclopropylethanone (0.13 mmol) as a white solid in 26% yield according to the general method R. ESI-MS: 461.10 $(M+H)^+$.

Example 15: General procedure for the synthesis of analogues 318



Preparation of ethyl 3-[(2-acetyl-4-pyridyl)oxy]-2-methyl-benzoate (**315**):



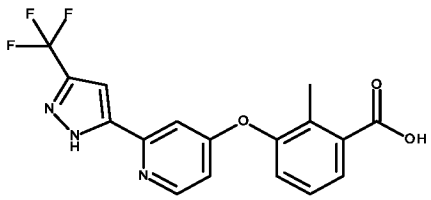
Intermediate **315** was synthesized from ethyl 3-hydroxy-2-methyl-benzoate (0.96 mmol) and 1-(4-chloro-2-pyridyl)ethanone (0.64 mmol) as an orange oil in 40% yield according to the general method P.

ESI-MS: 299.95 $(M+H)^+$.

Method S: To a stirred solution of **315** (20 mg, 0.07 mmol) in THF (1mL) was added at 0°C *t*-BuOK (1M THF, 0.134 mL, 0.13 mmol). After 5 min, ethyl trifluoroacetate (16 µL, 0.13 mmol) was added and the reaction mixture was stirred at 70°C for 4h. After cooling to room temperature, *t*-BuOK (1M THF, 0.134 mL, 0.13 mmol) and ethyl trifluoroacetate (16 µL, 0.13 mmol) were added and the reaction mixture was stirred at 70°C overnight. The reaction mixture was diluted with EtOAc and washed twice with a saturated solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The intermediate was dissolved in EtOH (1 mL) and hydrazine hydrate was added (9 µL, 0.18 mmol). The reaction mixture was stirred at 80°C overnight. The reaction mixture was concentrated under reduce pressure and ethyl 2-methyl-3-({2-[3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-4-pyridyl}oxy)benzoate **316** was directly used in the next step without purification.

ESI-MS: 392.00 $(M+H)^+$.

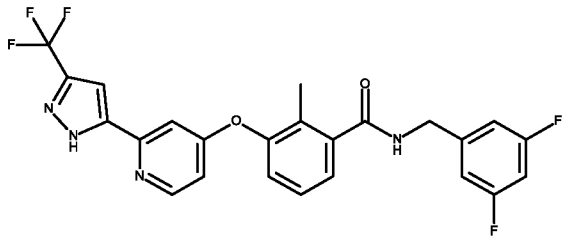
Preparation of 2-methyl-3-({2-[3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-4-pyridyl}oxy) benzoic acid (**317**):



Intermediate **317** was synthesized from **316** according to the general method B2.

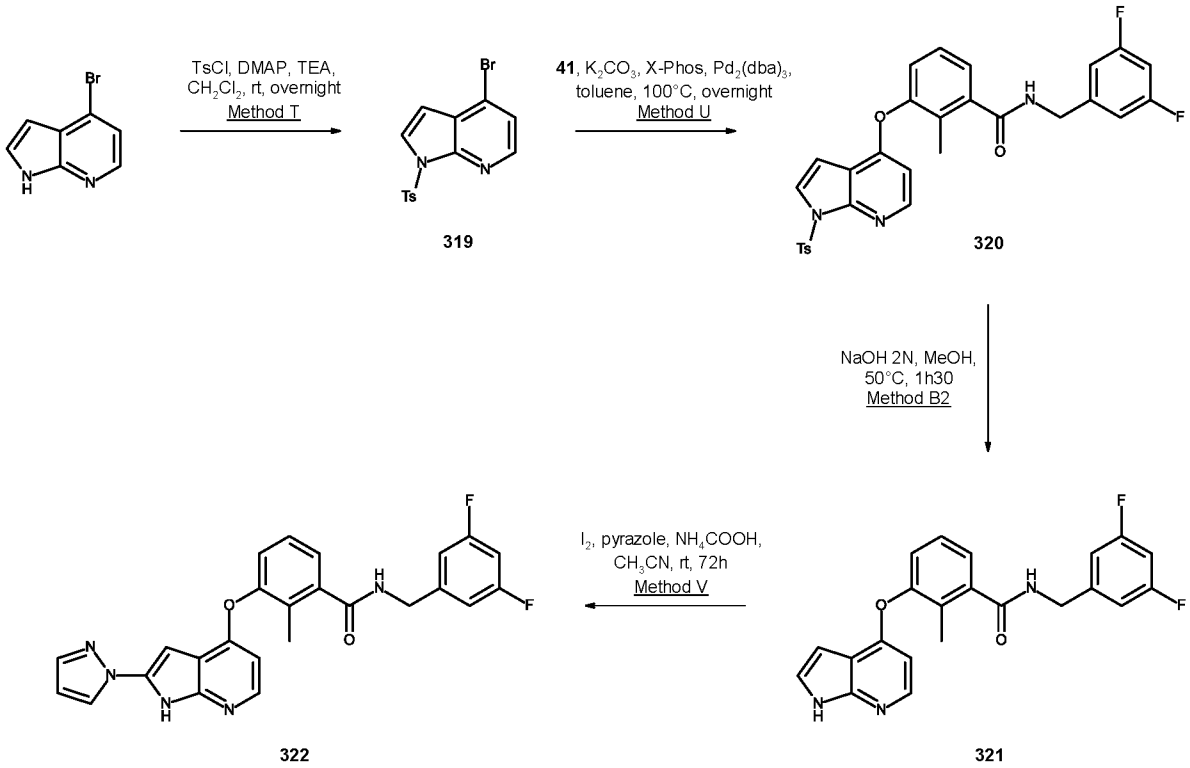
ESI-MS: 363.95 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-({2-[3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-4-pyridyl}oxy)benzamide (**318**):



Compound **318** was synthesized from intermediate **317** and 3,5-difluorobenzylamine as a white solid in 9% yield according to the general method C2. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 14.34 (bs, 1H), 9.00 (t, J = 5.9 Hz, 1H), 8.50 (d, J = 5.7 Hz, 1H), 7.60 (s, 1H), 7.42-7.38 (m, 2H), 7.31 (s, 1H), 7.27 (dd, J = 7.5 Hz, 1.8 Hz, 1H), 7.12 (tt, J = 9.3 Hz, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.73 (dd, J = 5.7 Hz, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 2.15 (s, 3H).
ESI-MS: 489.10 $(M+H)^+$.

Example 16: General procedure for the synthesis of analogues 321 and 322



Method T: To a stirred solution of 4-bromo-7-azaindole (2.5 g, 12.69 mmol) in dichloromethane (40 mL) were added DMAP (155 mg, 1.27 mmol), triethylamine (2.1 mL, 15.23 mmol) and tosyl chloride (2.66 g, 13.96 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the crude was purified by flash column chromatography (Cyclohexane/EtOAc from 100/0 to 60/40) to give 3.914 g of 4-bromo-1-(*p*-tolylsulfonyl)pyrrolo[2,3-*b*]pyridine **319** as a yellow powder in 88% yield.

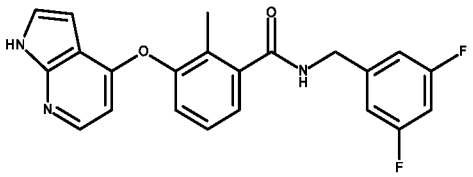
ESI-MS: 350.85-352.80 $(M+H)^+$.

Method U: To a stirred solution of intermediate **319** (200 mg, 0.57 mmol) in toluene (10 mL) were added under nitrogen intermediate **41** (237 mg, 0.85 mmol), K_2CO_3 (197 mg, 1.42 mmol), X-Phos (54 mg, 0.11 mmol), and $Pd_2(dba)_3$ (52 mg, 0.06 mmol). The reaction mixture was stirred at 100°C overnight. The reaction mixture was diluted with EtOAc and washed twice with a saturated

solution of NH_4Cl. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Cyclohexane/EtOAc from 100/0 to 50/50) to give 200 mg of *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-[1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridin-4-yl] oxy-benzamide **320** as a white powder in 93% yield.

ESI-MS: 548.10 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yloxy) benzamide (**321**):



Compound **321** was synthesized from intermediate **320** (0.49 mmol) and NaOH (2.46 mmol) as a white solid in 87% yield according to the general method B2.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.74 (bs, 1H), 9.02 (t, *J* = 6.0, 1H), 8.06 (d, *J* = 5.4, 1H), 7.39-7.32 (m, 3H), 7.20 (dd, *J* = 6.7, 2.6, 1H), 7.15-7.02 (m, 3H), 6.26 (d, *J* = 5.4, 1H), 6.23 (d, *J* = 3.4, 1H), 4.47 (d, *J* = 6.0, 2H), 2.15 (s, 3H).

ESI-MS: 394.05 $(M+H)^+$.

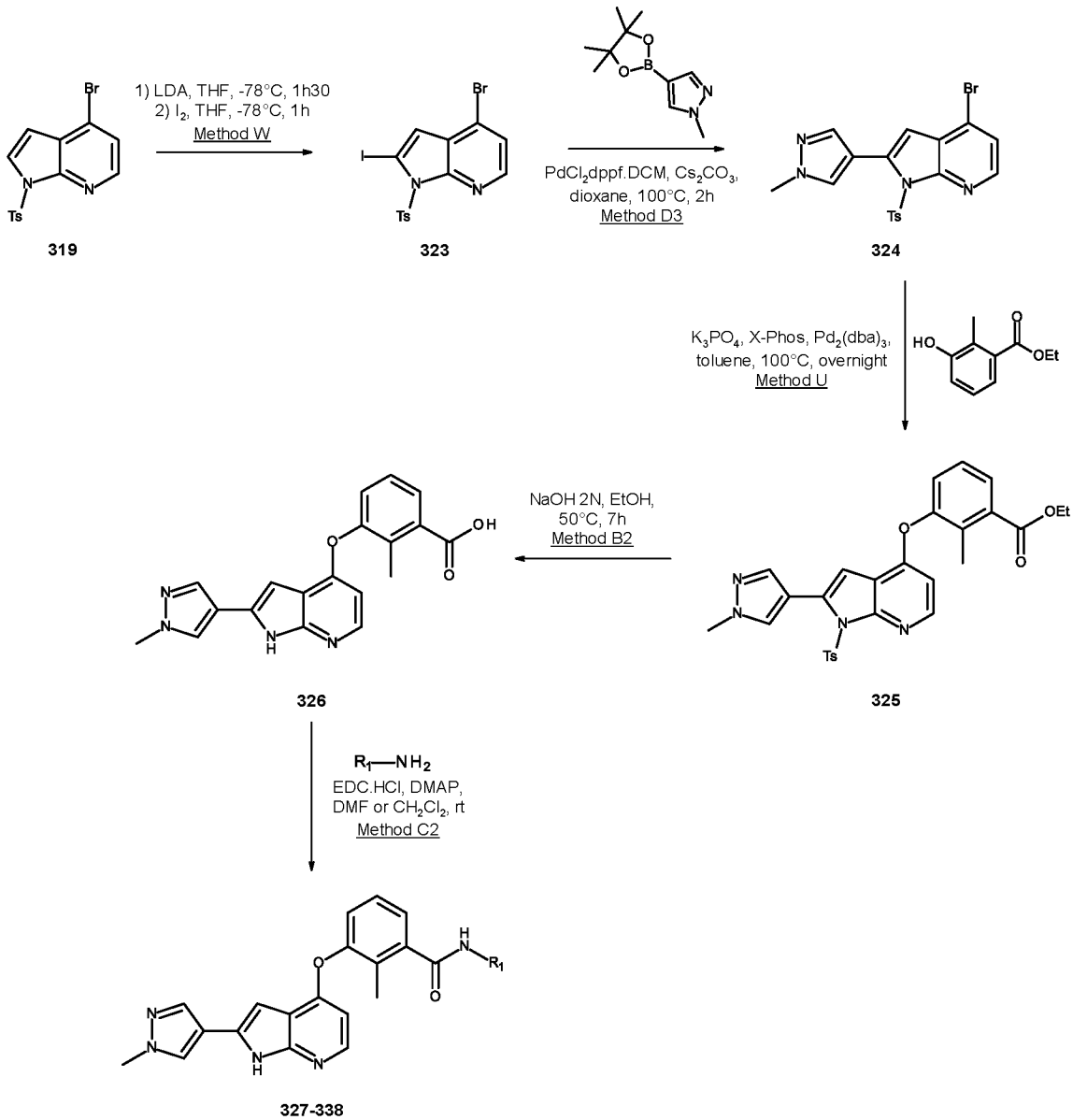
Method V: To a stirred solution of intermediate **321** (30 mg, 0.08 mmol) in acetonitrile (0.15 mL) were added pyrazole (18 mg, 0.27 mmol), I_2 (48 mg, 0.19 mmol), and a saturated aqueous solution of ammonium formate (0.15 mL). The reaction mixture was stirred at room temperature for 72h. The reaction mixture was diluted with EtOAc and washed a saturated solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 94/6) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-[(2-pyrazol-1-yl-1*H*-pyrrolo[2,3-*b*] pyridin-4-yl)oxy]benzamide **322** as a white powder in 11% yield.

^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.68 (bs, 1H), 9.02 (t, *J* = 6.1, 1H), 8.47 (d, *J* = 2.4, 1H), 8.06 (d, *J* = 5.5, 1H), 7.81 (d, *J* = 1.5, 1H), 7.40-7.34 (m, 2H),

7.22 (dd, *J* = 6.9, 2.4, 1H), 7.16-7.05 (m, 3H), 6.59-6.58 (m, 1H), 6.49 (s, 1H), 6.31 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.0, 2H), 2.18 (s, 3H).

ESI-MS: 460.00 $(M+H)^+$.

Example 17: General procedure for the synthesis of analogues 327-338

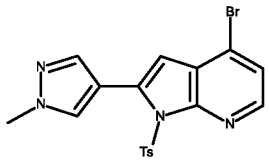


Method W: To a stirred solution of intermediate **319** (2 g, 5.70 mmol) in dry THF (45 mL) under nitrogen was added LDA (1M in hexane, 6.8 mL, 6.83 mmol) at -

78°C. The reaction mixture was stirred at -78°C for 2h. Then iodine (2.02 g, 7.97 mmol) in THF (10 mL) was added and the reaction mixture was stirred at -78°C for 1h. Reaction was quenched with saturated aqueous solution of of NH_4Cl and product was extracted with ethyl acetate. Organic layers were washed with saturated solution of $Na_2S_2O_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Cyclohexane/EtOAc from 100/0 to 85/15) and recrystallized from acetonitrile to give 4-bromo-2-iodo-1*H*-pyrrolo[2,3-*b*]pyridine **323** as a white powder in 56% yield.

ESI-MS: 476.85-478.85 $(M+H)^+$.

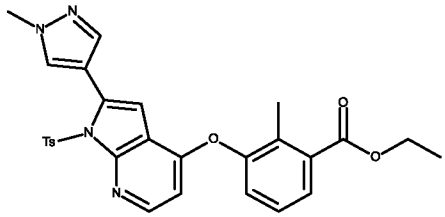
Preparation of 4-bromo-2-(1-methylpyrazol-4-yl)-1-(*p*-tolylsulfonyl)pyrrolo[2,3-*b*]pyridine (**324**):



Intermediate **324** was synthesized from **323** (1.05 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-1*H*-pyrazole (1.05 mmol) as a yellow oil in 55% yield according to the general method D3.

ESI-MS: 430.90-432.90 $(M+H)^+$.

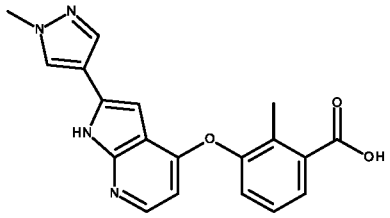
Preparation of ethyl 2-methyl-3-[2-(1-methylpyrazol-4-yl)-1-(*p*-tolylsulfonyl) pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzoate (**325**):



Intermediate **325** was synthesized from **324** (0.50 mmol), ethyl 3-hydroxy-2-methyl-benzoate (0.75 mmol) and K_3PO_4 (1.24 mmol) as a yellow oil in 57% yield according to the general method U.

ESI-MS: 531.10 $(M+H)^+$.

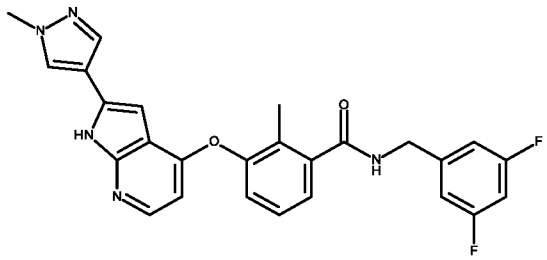
Preparation of 2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzoic acid (**326**):



Intermediate **326** was synthesized from **325** (0.42 mmol) and NaOH 2N (1.27 mmol) as a yellow solid in 92% yield according to the general method B2.
ESI-MS: 349.05 $(M+H)^+$.

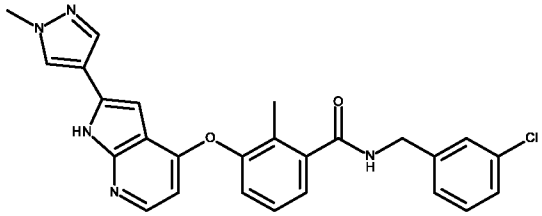
The following compounds are examples illustrating Method C2:

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**327**):



Compound **327** was synthesized from intermediate **326** (0.05 mmol) and 3,5-difluorobenzylamine (0.08 mmol) as a white solid in 68% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 9.00 (t, *J* = 5.6, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (d, *J* = 0.6, 1H), 7.39-7.33 (m, 2H), 7.20-7.05 (m, 4H), 6.49 (s, 1H), 6.21 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.1, 2H), 3.88 (s, 3H), 2.18 (s, 3H).
ESI-MS: 474.10 $(M+H)^+$.

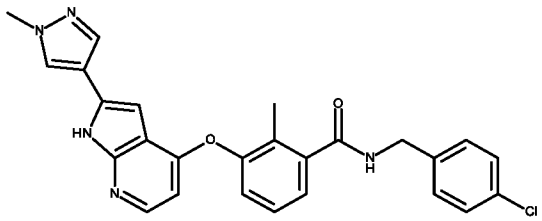
N-[(3-chlorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**328**):



Compound **328** was synthesized from intermediate **326** (0.05 mmol) and 3-chlorobenzylamine (0.08 mmol) as a white solid in 29% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (bs, 1H), 8.99 (t, *J* = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.96 (s, 1H), 7.41-7.30 (m, 6H), 7.19 (dd, *J* = 7.7, 1.2, 1H), 6.50 (d, *J* = 2.0, 1H), 6.20 (d, *J* = 5.5, 1H), 4.47 (d, *J* = 6.0, 2H), 3.88 (s, 3H), 2.17 (s, 3H).

ESI-MS: 472.10 $(M+H)^+$.

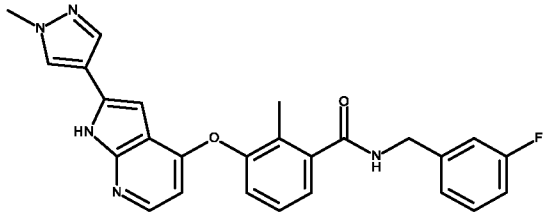
N-[(4-chlorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**329**):



Compound **329** was synthesized from intermediate **326** (0.05 mmol) and 4-chlorobenzylamine (0.08 mmol) as a white solid in 16% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 8.97 (t, *J* = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (s, 1H), 7.43-7.30 (m, 6H), 7.18 (dd, *J* = 7.7, 1.3, 1H), 6.49 (d, *J* = 2.0, 1H), 6.19 (d, *J* = 5.5, 1H), 4.44 (d, *J* = 6.0, 2H), 3.88 (s, 3H), 2.16 (s, 3H).

ESI-MS: 472.10 $(M+H)^+$.

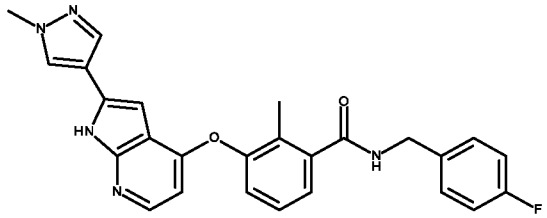
N-[(3-fluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**330**):



Compound **330** was synthesized from intermediate **326** (0.05 mmol) and 3-fluorobenzylamine (0.08 mmol) as a white solid in 25% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 8.99 (t, *J* = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (s, 1H), 7.43-7.31 (m, 3H), 7.21-7.15 (m, 3H), 7.09 (td, *J* = 8.5, 2.2, 1H), 6.49 (d, *J* = 2.0, 1H), 6.20 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.0, 2H), 3.88 (s, 3H), 2.17 (s, 3H).

ESI-MS: 456.10 $(M+H)^+$.

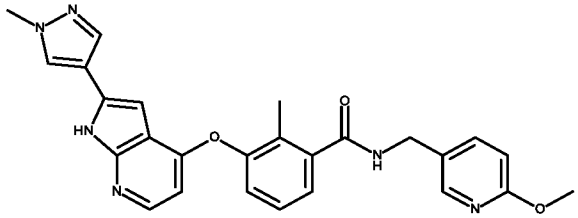
N-[(4-fluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**331**):



Compound **331** was synthesized from intermediate **326** (0.05 mmol) and 4-fluorobenzylamine (0.08 mmol) as a white solid in 17% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 8.95 (t, *J* = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (s, 1H), 7.42-7.28 (m, 4H), 7.20-7.15 (m, 3H), 6.49 (d, *J* = 1.9, 1H), 6.19 (d, *J* = 5.5, 1H), 4.44 (d, *J* = 6.0, 2H), 3.88 (s, 3H), 2.16 (s, 3H).

ESI-MS: 456.15 $(M+H)^+$.

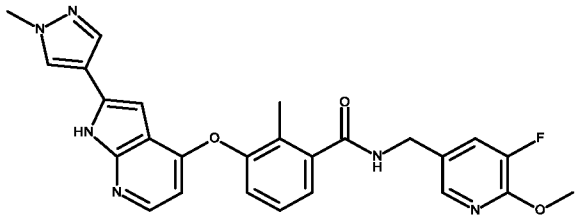
N-[(6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**332**):



Compound **332** was synthesized from intermediate **326** (0.06 mmol) and (6-methoxypyridin-3-yl)methanamine (0.09 mmol) as a white solid in 55% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 8.91 (t, *J* = 5.9, 1H), 8.15-8.14 (m, 2H), 7.97 (d, *J* = 5.5, 1H), 7.95 (d, *J* = 0.7, 1H), 7.70 (dd, *J* = 8.5, 2.5, 1H), 7.34 (t, *J* = 7.7, 1H), 7.28 (dd, *J* = 7.6, 1.3, 1H), 7.17 (dd, *J* = 7.9, 1.2, 1H), 6.81 (dd, *J* = 8.5, 0.6, 1H), 6.48 (d, *J* = 2.1, 1H), 6.19 (d, *J* = 5.5, 1H), 4.39 (d, *J* = 5.9, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 2.15 (s, 3H).

ESI-MS: 469.10 $(M+H)^+$.

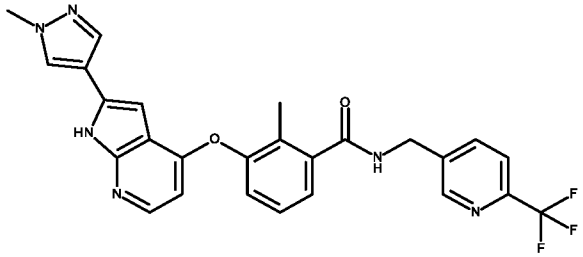
N-[(5-fluoro-6-methoxy-3-pyridyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**333**):



Compound **333** was synthesized from intermediate **326** (0.06 mmol) and (5-fluoro-6-methoxy-3-pyridyl)methanamine (0.09 mmol) as a white solid in 46% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 8.94 (t, *J* = 5.9, 1H), 8.15 (s, 1H), 7.99-7.95 (m, 3H), 7.65 (dd, *J* = 11.4, 1.9, 1H), 7.36-7.29 (m, 2H), 7.18 (dd, *J* = 7.7, 1.5, 1H), 6.48 (s, 1H), 6.19 (d, *J* = 5.5, 1H), 4.42 (d, *J* = 5.9, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 2.15 (s, 3H).

ESI-MS: 487.15 $(M+H)^+$.

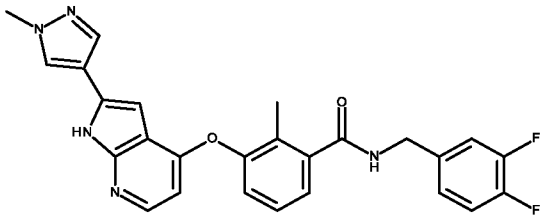
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}-*N*-{[6-(trifluoromethyl)-3-pyridyl]methyl}benzamide (**334**):



Compound **334** was synthesized from intermediate **326** (0.06 mmol) and [6-(trifluoromethyl)-3-pyridyl]methanamine (0.09 mmol) as a white solid in 55% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (bs, 1H), 9.09 (t, *J* = 5.9, 1H), 8.77 (d, *J* = 1.6, 1H), 8.15 (s, 1H), 8.05 (dd, *J* = 8.1, 1.5, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (d, *J* = 0.7, 1H), 7.91 (d, *J* = 8.1, 1H), 7.38-7.34 (m, 2H), 7.21-7.18 (m, 1H), 6.49 (s, 1H), 6.19 (d, *J* = 5.5, 1H), 4.59 (d, *J* = 5.9, 2H), 3.88 (s, 3H), 2.17 (s, 3H).

ESI-MS: 507.10 $(M+H)^+$.

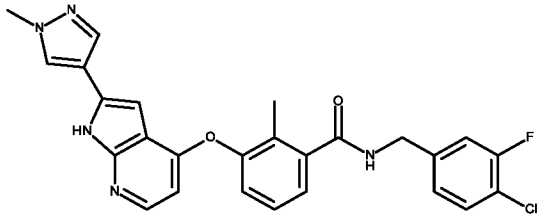
N-[(3,4-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide(**335**):



Compound **335** was synthesized from intermediate **326** (0.06 mmol) and 3,4-difluorobenzylamine (0.09 mmol) as a white solid in 44% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (bs, 1H), 8.98 (t, *J* = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (d, *J* = 0.6, 1H), 7.45-7.31 (m, 4H), 7.23-7.17 (m, 2H), 6.49 (s, 1H), 6.19 (d, *J* = 5.5, 1H), 4.44 (d, *J* = 6.0, 2H), 3.88 (s, 3H), 2.16 (s, 3H).

ESI-MS: 474.05 $(M+H)^+$.

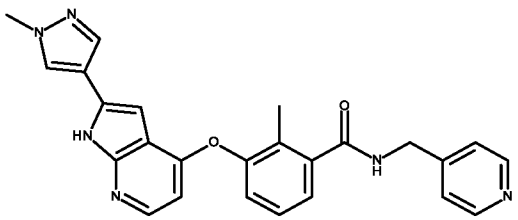
N-[(4-chloro-3-fluoro-phenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**336**):



Compound **336** was synthesized from intermediate **326** (0.06 mmol) and 4-chloro-3-fluorobenzylamine (0.09 mmol) as a white solid in 50% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (bs, 1H), 9.00 (t, J = 6.0, 1H), 8.15 (s, 1H), 7.98 (d, J = 5.5, 1H), 7.96 (s, 1H), 7.57 (t, J = 8.0, 1H), 7.39-7.32 (m, 3H), 7.24 (dd, J = 8.3, 1.2, 1H), 7.19 (dd, J = 7.3, 1.9, 1H), 6.49 (s, 1H), 6.20 (d, J = 5.5, 1H), 4.46 (d, J = 6.0, 2H), 3.88 (s, 3H), 2.17 (s, 3H).

ESI-MS: 490.10 $(M+H)^+$.

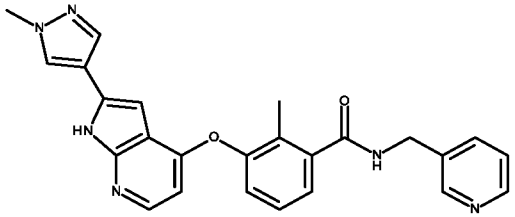
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}-*N*-(4-pyridylmethyl)benzamide (**337**):



Compound **337** was synthesized from intermediate **326** (0.06 mmol) and 4-(aminomethyl)pyridine (0.08 mmol) as a white solid in 63% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.03 (bs, 1H), 9.04 (t, J = 6.0, 1H), 8.54-8.52 (m, 2H), 8.15 (s, 1H), 7.98 (d, J = 5.5, 1H), 7.96 (s, 1H), 7.38-7.34 (m, 4H), 7.20 (p, J = 3.6, 1H), 6.50 (s, 1H), 6.20 (d, J = 5.5, 1H), 4.49 (d, J = 6.0, 2H), 3.88 (s, 3H), 2.19 (s, 3H).

ESI-MS: 439.15 $(M+H)^+$.

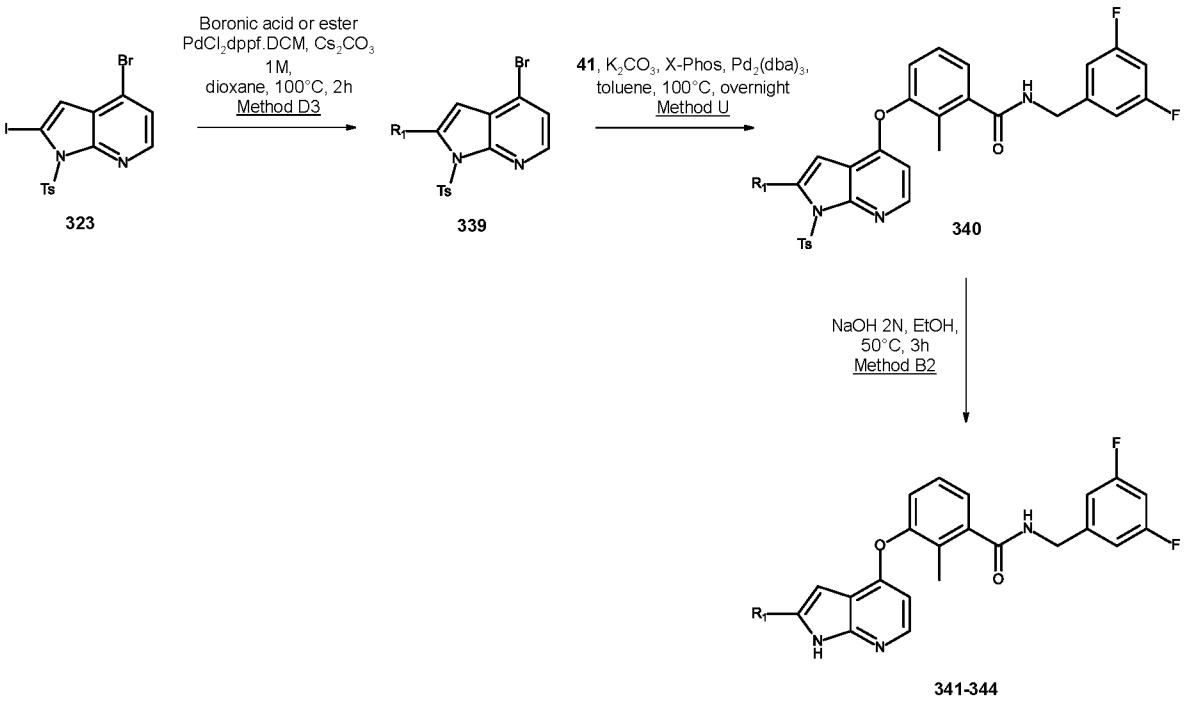
2-methyl-3-{[2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}-*N*-(3-pyridylmethyl)benzamide (**338**):



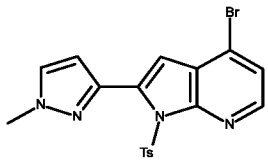
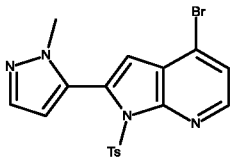
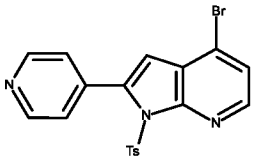
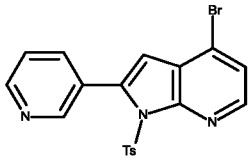
Compound **338** was synthesized from intermediate **326** (0.06 mmol) and 3-(aminomethyl)pyridine (0.08 mmol) as a white solid in 70% yield according to the general method C2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.02 (bs, 1H), 9.00 (t, *J* = 6.0, 1H), 8.58 (d, *J* = 1.8, 1H), 8.48 (dd, *J* = 4.8, 1.6, 1H), 8.15 (s, 1H), 7.98 (d, *J* = 5.5, 1H), 7.95 (d, *J* = 0.5, 1H), 7.77 (dt, *J* = 7.8, 1.9, 1H), 7.40-7.30 (m, 3H), 7.18 (dd, *J* = 7.6, 1.6, 1H), 6.49 (s, 1H), 6.19 (d, *J* = 5.5, 1H), 4.49 (d, *J* = 5.9, 2H), 3.88 (s, 3H), 2.16 (s, 3H).

ESI-MS: 439.10 $(M+H)^+$.

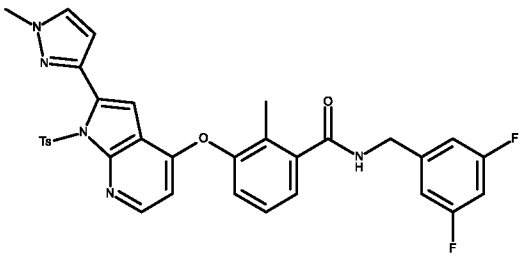
Example 18: General procedure for the synthesis of analogues 341-344

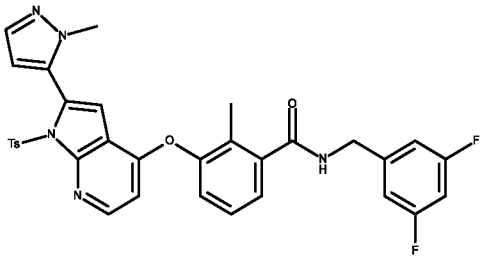


The following table illustrates intermediates **339** prepared from method D3:

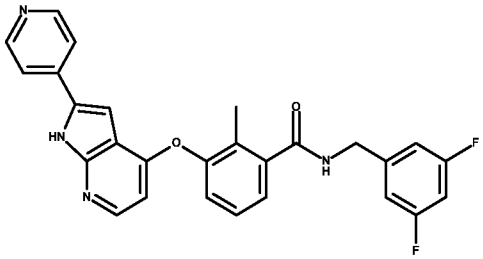
Intermediate	Structure	Synthesis procedure
Compound **339a**		Method D3
Compound **339b**		Method D3
Compound **339c**		Method D3
Compound **339d**		Method D3

The following table illustrates intermediates **340** prepared from method U:

Intermediate	Structure	Synthesis procedure
Compound **340a**		Method U

Compound **340b**		Method U

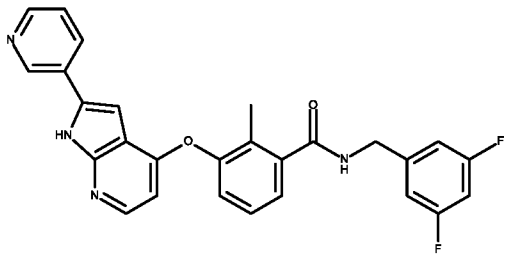
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(4-pyridyl)-1*H*-pyrrolo[2,3-*b*] pyridin-4-yl]oxy}benzamide (**341**):



Compound **341** was synthesized from intermediate **339c** (0.13 mmol) and **41** (0.18 mmol) as a white solid in 10% yield according to the general method U. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.55 (bs, 1H), 9.03 (t, *J* = 6.1, 1H), 8.63-8.61 (m, 2H), 8.14 (d, *J* = 5.5, 1H), 7.93-7.91 (m, 2H), 7.43-7.37 (m, 2H), 7.31-7.26 (m, 1H), 7.24 (s, 1H), 7.16-7.04 (m, 3H), 6.21 (d, *J* = 5.5, 1H), 4.49 (d, *J* = 6.0, 2H), 2.17 (s, 3H).

ESI-MS: 471.05 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(3-pyridyl)-1*H*-pyrrolo[2,3-*b*] pyridin-4-yl]oxy}benzamide (**342**):

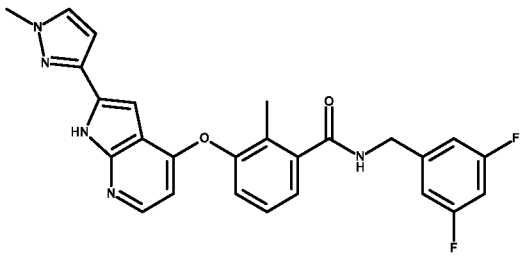


Compound **342** was synthesized from intermediate **339d** (0.12 mmol) and **41** (0.17 mmol) as a white solid in 4% yield according to the general method U. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.43 (bs, 1H), 9.16 (d, *J* = 1.7, 1H), 9.03

(t, *J* = 6.0, 1H), 8.53 (dd, *J* = 4.8, 1.5, 1H), 8.32-8.28 (m, 1H), 8.10 (d, *J* = 5.5, 1H), 7.48 (ddd, *J* = 8.0, 4.8, 0.7, 1H), 7.42-7.37 (m, 2H), 7.26 (dd, *J* = 6.9, 2.4, 1H), 7.16-7.05 (m, 4H), 6.21 (d, *J* = 5.5, 1H), 4.49 (d, *J* = 6.0, 2H), 2.17 (s, 3H).
ESI-MS: 471.05 $(M+H)^+$.

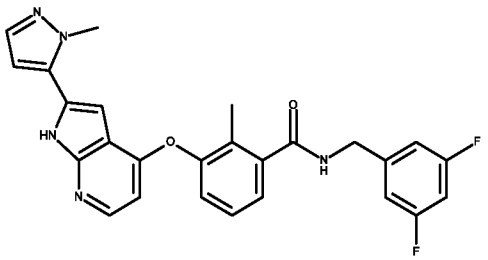
The following compounds are examples illustrating Method B2:

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(1-methylpyrazol-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**343**):



Compound **343** was synthesized from intermediate **340a** (0.11 mmol) and NaOH (0.32 mmol) as a white solid in 60% yield according to the general method B2.
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.12 (bs, 1H), 9.02 (t, *J* = 6.0, 1H), 8.04 (d, *J* = 5.4, 1H), 7.76 (d, *J* = 2.2, 1H), 7.39-7.33 (m, 2H), 7.20 (dd, *J* = 6.9, 2.4, 1H), 7.16-7.05 (m, 3H), 6.79 (d, *J* = 2.3, 1H), 6.55 (d, *J* = 2.1, 1H), 6.28 (d, *J* = 5.4, 1H), 4.48 (d, *J* = 6.0, 2H), 3.89 (s, 3H), 2.19 (s, 3H).
ESI-MS: 474.15 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[2-(2-methylpyrazol-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide (**344**):

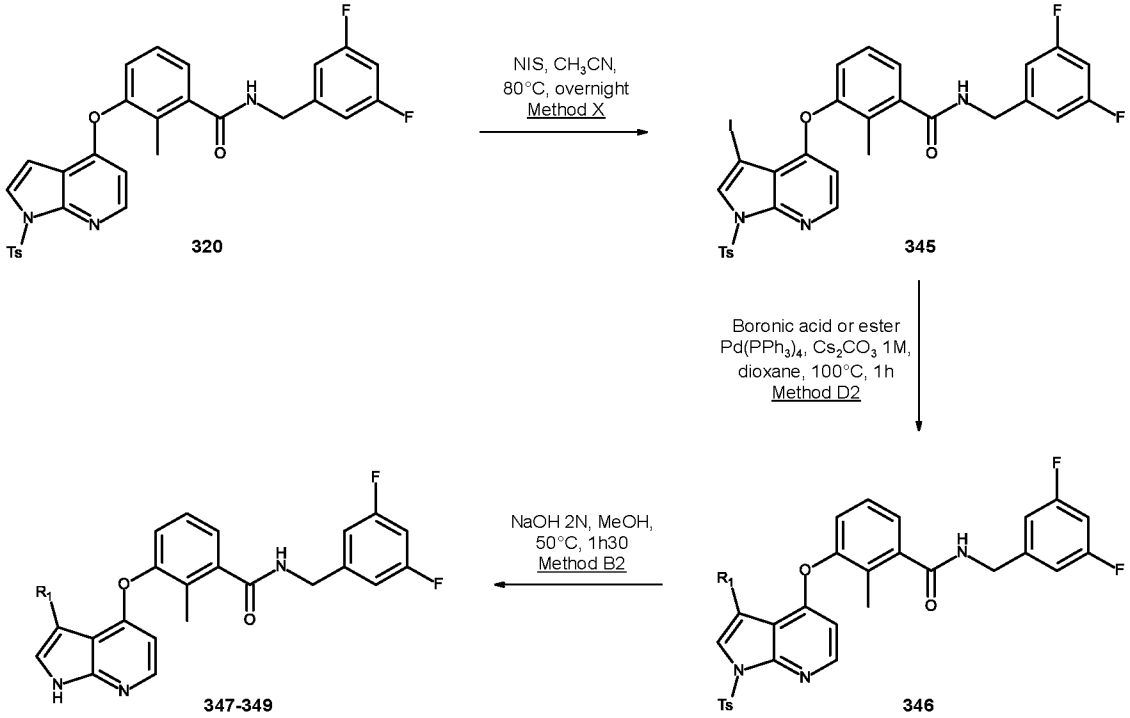


Compound **344** was synthesized from intermediate **340b** (0.09 mmol) and NaOH (0.46 mmol) as a white solid in 18% yield according to the general method B2.
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.24 (bs, 1H), 9.03 (t, *J* = 6.0, 1H), 8.12

(d, *J* = 5.5, 1H), 7.49 (d, *J* = 1.9, 1H), 7.42-7.37 (m, 2H), 7.28 (dd, *J* = 6.5, 2.8, 1H), 7.16-7.04 (m, 3H), 6.78 (d, *J* = 1.9, 1H), 6.61 (d, *J* = 2.0, 1H), 6.26 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.0, 2H), 4.01 (s, 3H), 2.17 (s, 3H).

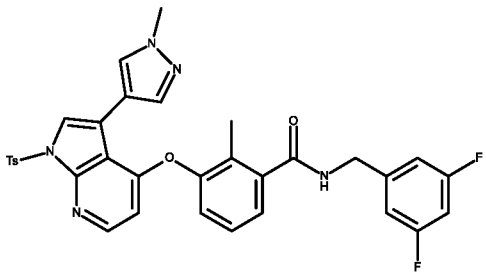
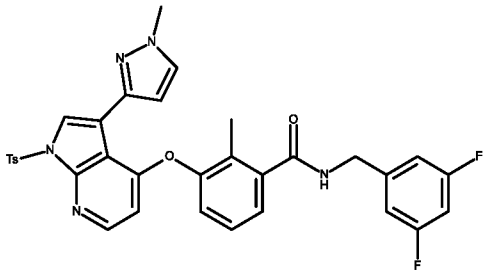
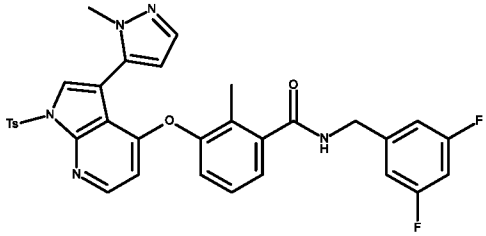
ESI-MS: 474.15 $(M+H)^+$.

Example 19: General procedure for the synthesis of analogues 347-349



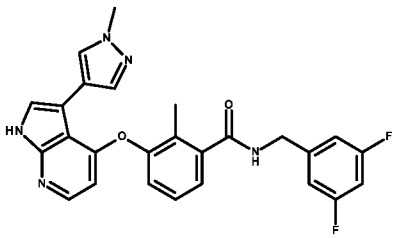
Method X: To a stirred solution of intermediate **320** (100 mg, 0.18 mmol) in acetonitrile (2 mL) was added NIS (82 mg, 0.37 mmol). The reaction mixture was stirred at 80°C overnight. The reaction mixture was diluted with EtOAc and washed a saturated solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/EtOAc from 100/0 to 90/10) to give *N*-[(3,5-difluorophenyl)methyl]-3-[3-iodo-1-(*p*-tolylsulfonyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-2-methyl-benzamide **345** as a beige powder in 39% yield.

The following table illustrates intermediates **346** prepared from method D2:

Intermediate	Structure	Synthesis procedure
Compound **346a**		Method D2
Compound **346b**		Method D2
Compound **346c**		Method D2

The following compounds are examples illustrating Method B2:

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[3-(1-methylpyrazol-4-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**347**):

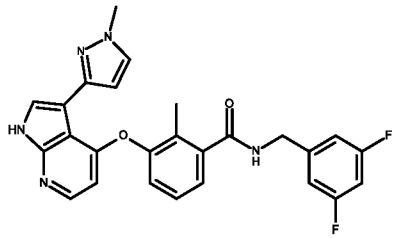


Compound **347** was synthesized from intermediate **346a** (0.02 mmol) and NaOH (0.11 mmol) as a white solid in 90% yield according to the general method B2.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.82 (bs, 1H), 9.01 (t, J = 6.0, 1H), 8.02 (d, J = 5.4, 1H), 7.86 (s, 1H), 7.73 (d, J = 0.5, 1H), 7.56 (d, J = 1.7, 1H), 7.40-7.33 (m, 2H), 7.24 (dd, J = 7.5, 1.8, 1H), 7.15-7.04 (m, 3H), 6.08 (d, J = 5.4, 1H), 4.48 (d, J = 6.0, 2H), 3.80 (s, 3H), 2.14 (s, 3H).

ESI-MS: 474.00 $(M+H)^+$.

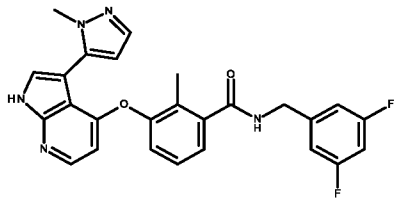
N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[3-(1-methylpyrazol-3-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**348**):



Compound **348** was synthesized from intermediate **346b** (0.02 mmol) and NaOH (0.12 mmol) as a white solid in 72% yield according to the general method B2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.91 (bs, 1H), 9.00 (t, J = 6.1, 1H), 8.05 (d, J = 5.4, 1H), 7.63 (d, J = 2.2, 1H), 7.59 (d, J = 2.1, 1H), 7.39-7.31 (m, 2H), 7.21 (dd, J = 7.6, 1.7, 1H), 7.15-7.03 (m, 3H), 6.59 (d, J = 2.2, 1H), 6.13 (d, J = 5.4, 1H), 4.47 (d, J = 6.0, 2H), 3.82 (s, 3H), 2.15 (s, 3H).

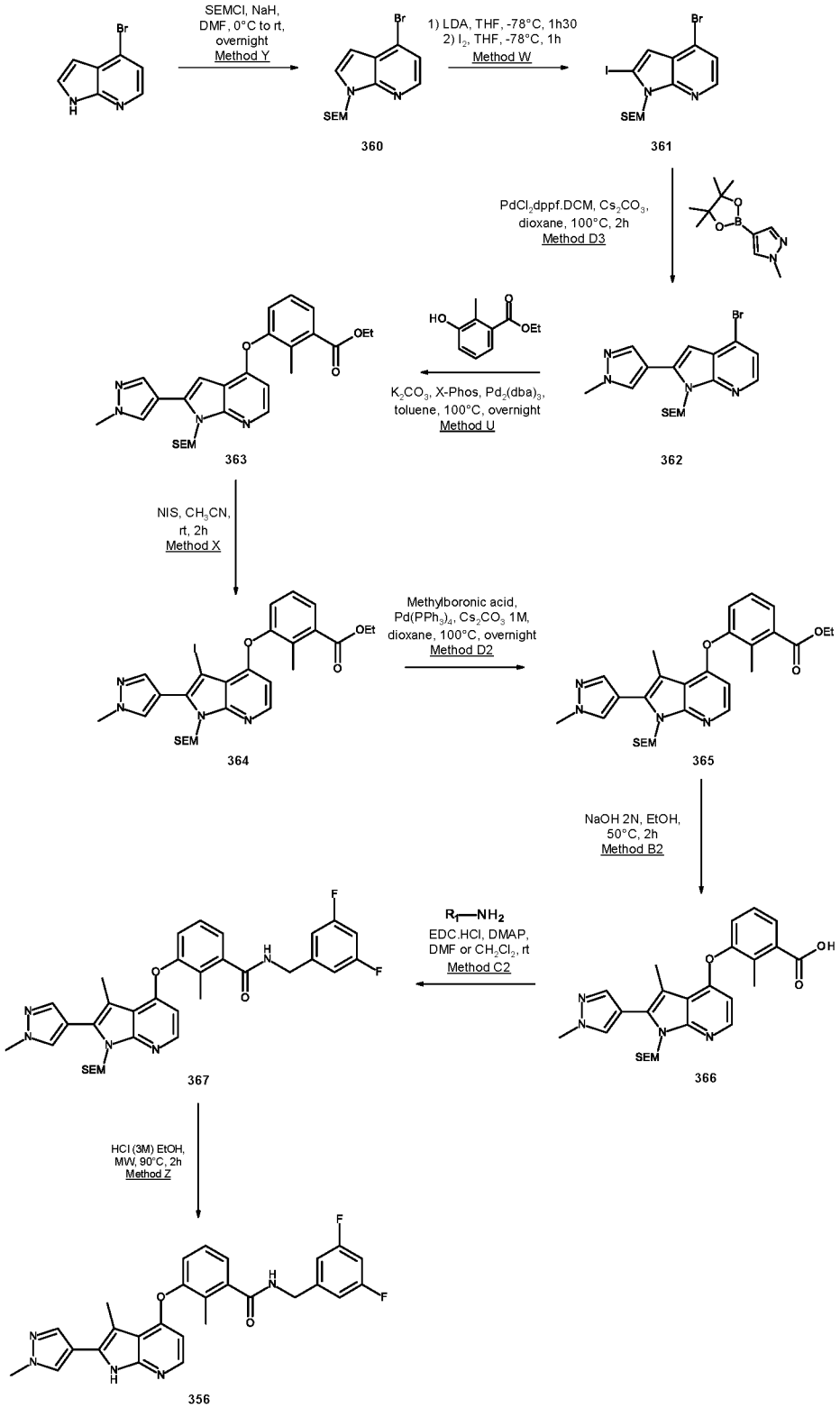
ESI-MS: 474.00 $(M+H)^+$.

N-[(3,5-difluorophenyl)methyl]-2-methyl-3-{[3-(2-methylpyrazol-3-yl)-1*H*-pyrrolo [2,3-*b*]pyridin-4-yl]oxy}benzamide (**349**):



Compound **349** was synthesized from intermediate **346c** (0.02 mmol) and NaOH (0.08 mmol) as a white solid in 50% yield according to the general method B2. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.20 (bs, 1H), 8.95 (t, J = 6.1, 1H), 8.11 (d, J = 5.5, 1H), 7.62 (d, J = 2.3, 1H), 7.38 (d, J = 1.8, 1H), 7.36-7.28 (m, 2H), 7.18 (dd, J = 7.7, 1.5, 1H), 7.15-7.02 (m, 3H), 6.32 (d, J = 1.8, 1H), 6.17 (d, J = 5.5, 1H), 4.45 (d, J = 6.0, 2H), 3.78 (s, 3H), 2.01 (s, 3H). ESI-MS: 473.95 $(M+H)^+$.

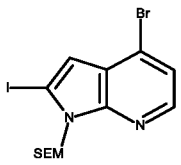
Example 20: General procedure for the synthesis of analogue 356



Method Y: To a stirred solution of 4-bromo-7-azaindole (500 mg, 2.54 mmol) in DMF (6 mL) was added under nitrogen at 0°C NaH (60%) (155 mg, 3.88 mmol). The reaction mixture was stirred at room temperature for 30 minutes and SEM-Cl was added (0.538 mL, 3.07 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (Cyclohexane/EtOAc from 100/0 to 90/10) to give 683 mg of 2-[(4-bromopyrrolo[2,3-*b*]pyridin-1-yl)methoxy]ethyl-trimethylsilane **360** as a colorless oil in 82% yield.

ESI-MS: 326.85-328.85 $(M+H)^+$.

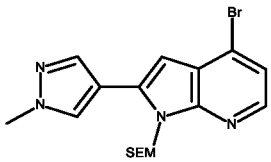
Preparation of 2-[(4-bromo-2-iodo-pyrrolo[2,3-*b*]pyridin-1-yl)methoxy]ethyl-trimethylsilane (**361**):



Intermediate **361** was synthesized from **360** (3.94 mmol) as a colorless oil in 73% yield according to the general method W.

ESI-MS: 452.80-454.80 $(M+H)^+$.

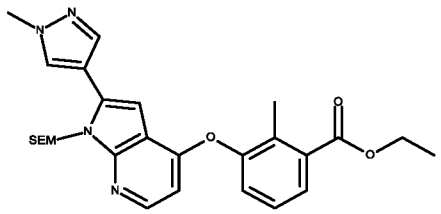
Preparation of 2-{[4-bromo-2-(1-methylpyrazol-4-yl)pyrrolo[2,3-*b*]pyridin-1-yl]methoxy}ethyl-trimethylsilane (**362**):



Intermediate **362** was synthesized from **361** (4.23 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-1*H*-pyrazole (4.23 mmol) as a yellow oil in 59% yield according to the general method D3.

ESI-MS: 406.95-408.95 $(M+H)^+$.

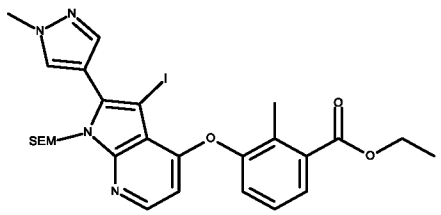
Preparation of ethyl 2-methyl-3-[2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilyl ethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzoate (**363**):



Intermediate **363** was synthesized from **362** (1.60 mmol), ethyl 3-hydroxy-2-methyl-benzoate (2.40 mmol) and K_2CO_3 (4.01 mmol) as a yellow oil in 99% yield according to the general method U.

ESI-MS: 507.15 $(M+H)^+$.

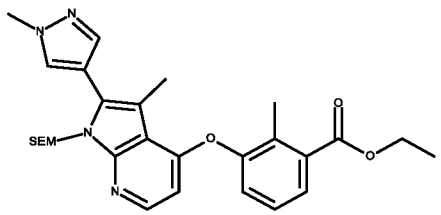
Preparation of ethyl 3-[3-iodo-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxy methyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-2-methyl-benzoate (**364**):



Intermediate **364** was synthesized from **363** (0.49 mmol) and NIS (0.99 mmol) as a white gum in 82% yield according to the general method X.

ESI-MS: 633.00 $(M+H)^+$.

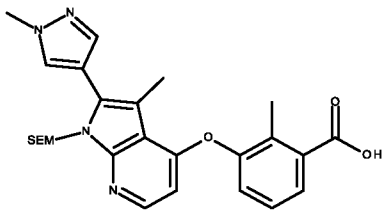
Preparation of ethyl 2-methyl-3-[3-methyl-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzoate (**365**):



Intermediate **365** was synthesized from **364** (0.08 mmol) and methylboronic acid (0.80 mmol) as a yellow oil in 90% yield according to the general method D2.

ESI-MS: 521.15 $(M+H)^+$.

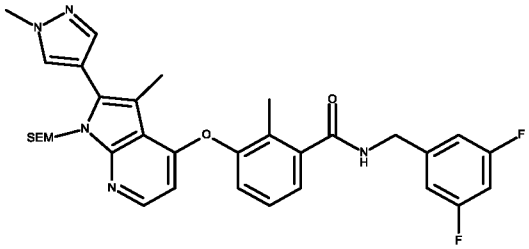
Preparation of 2-methyl-3-[3-methyl-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilyl ethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzoic acid (**366**):



Intermediate **366** was synthesized from **365** (0.14 mmol) and 2N sodium hydroxide (0.43 mmol) as a yellow oil in 100% yield according to the general method B2.

ESI-MS: 493.10 $(M+H)^+$.

Preparation of *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-[3-methyl-2-(1-methyl pyrazol-4-yl)-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzamide (**367**):



Intermediate **367** was synthesized from **366** (0.14 mmol) and 3,5-difluorobenzylamine (0.22 mmol) as a white solid in 67% yield according to the general method C2.

ESI-MS: 618.20 $(M+H)^+$.

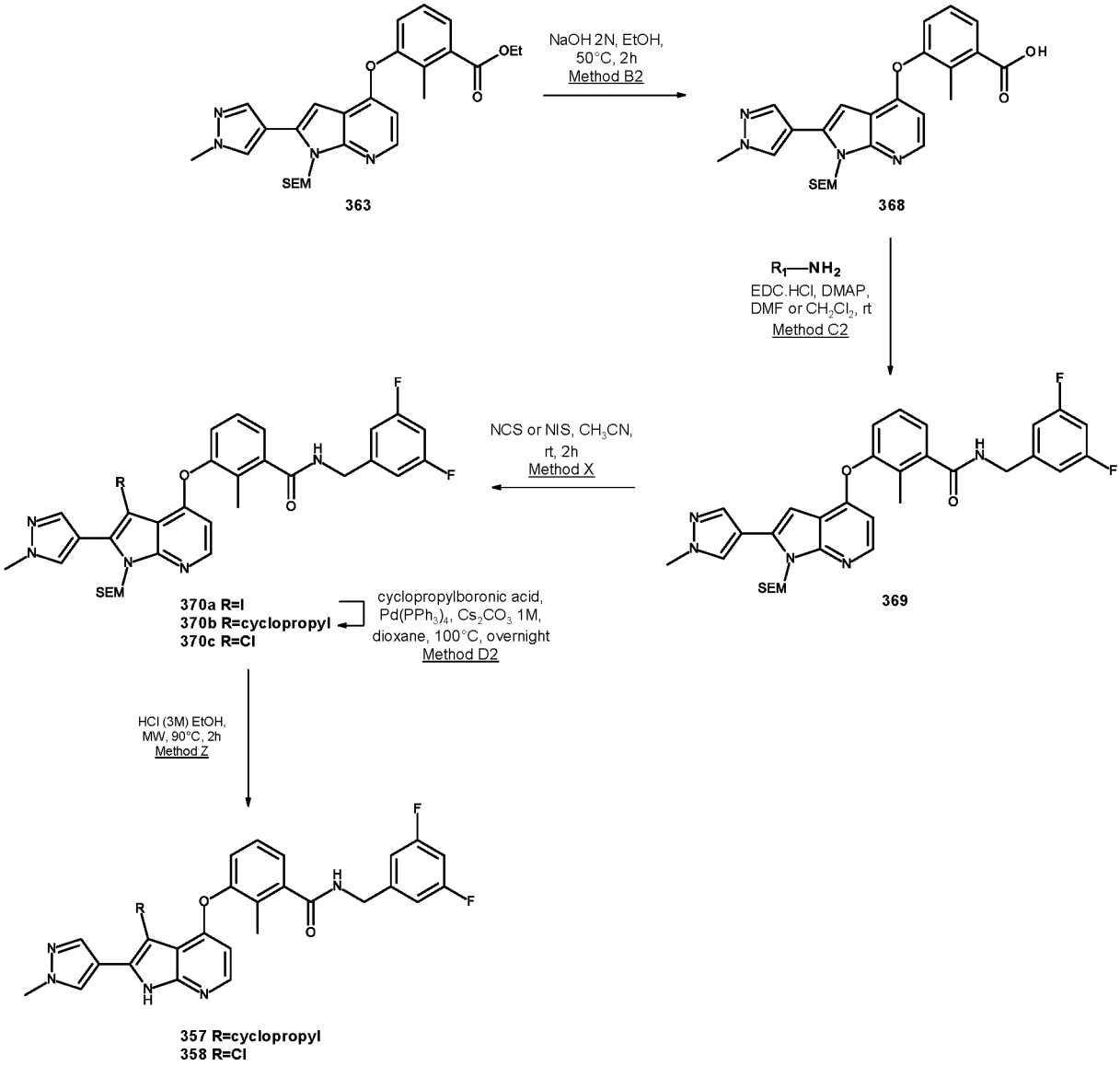
Method Z: Intermediate **367** (60 mg, 0.10 mmol) was dissolved in ethanol (1 mL) in an oven-dried screw-cap test tube. HCl 3M (1.2 mL, 3.59f mmol) was added. The reaction mixture was stirred and heated under microwave irradiation at 90°C for 2h. The reaction mixture was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (DCM/MeOH from 100/0 to 95/5) and reverse phase chromatography (H_2O/MeOH from 100/0 to 0/100) to give *N*-[(3,5-

difluorophenyl)methyl]-2-methyl-3-{[3-methyl-2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}benzamide **356** as a white powder in 51% yield.

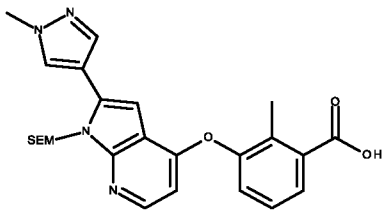
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.71 (bs, 1H), 9.00 (t, *J* = 6.0, 1H), 8.14 (s, 1H), 7.95-7.91 (m, 2H), 7.42-7.29 (m, 2H), 7.23-7.02 (m, 4H), 6.09 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.0, 2H), 3.92 (s, 3H), 2.52 (s, 3H), 2.18 (s, 3H).

ESI-MS: 488.10 $(M+H)^+$.

Example 21: General procedure for the synthesis of analogues 357-358



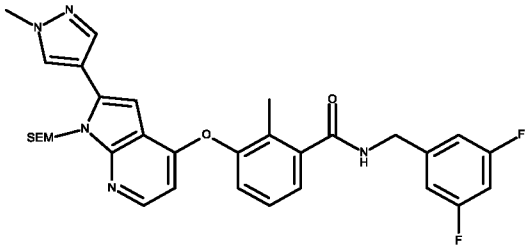
Preparation of 2-methyl-3-[2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzoic acid (**368**):



Intermediate **368** was synthesized from **363** (0.72 mmol) and 2N sodium hydroxide (2.16 mmol) as a yellow solid in 83% yield according to the general method B2.

ESI-MS: 479.10 $(M+H)^+$.

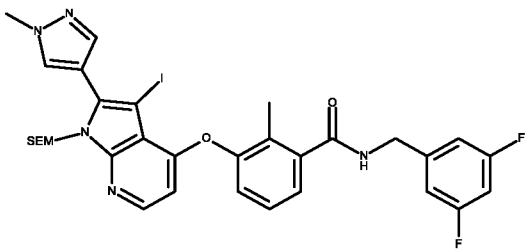
Preparation of *N*-[(3,5-difluorophenyl)methyl]-2-methyl-3-[2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-benzamide (**369**):



Intermediate **369** was synthesized from **368** (0.60 mmol) and 3,5-difluorobenzylamine (0.89 mmol) as a yellow solid in 78% yield according to the general method C2.

ESI-MS: 604.20 $(M+H)^+$.

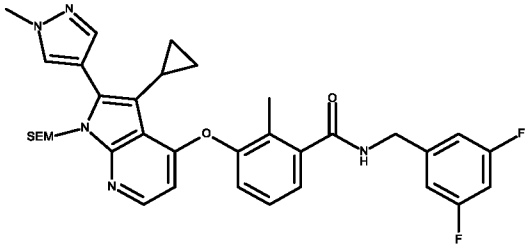
Preparation of *N*-[(3,5-difluorophenyl)methyl]-3-[3-iodo-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-2-methyl-benzamide (**370a**):



Intermediate **370a** was synthesized from **369** (0.08 mmol) and NIS (0.16 mmol) as a yellow oil in 93% yield according to the general method X.

ESI-MS: 730.05 $(M+H)^+$.

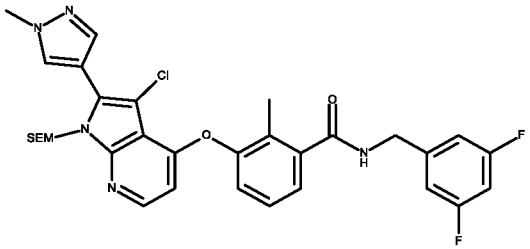
Preparation of 3-[3-cyclopropyl-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilyl ethoxymethyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**370b**):



Intermediate **370b** was synthesized from **370a** (0.08 mmol) and cyclopropylboronic acid (0.15 mmol) as a colorless oil in 63% yield according to the general method D2.

ESI-MS: 644.20 $(M+H)^+$.

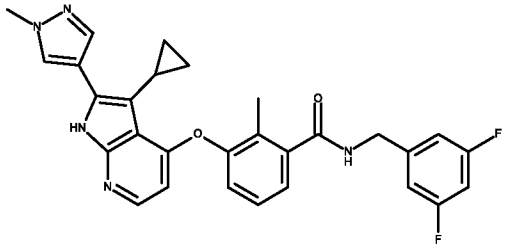
Preparation of 3-[3-chloro-2-(1-methylpyrazol-4-yl)-1-(2-trimethylsilylethoxy methyl)pyrrolo[2,3-*b*]pyridin-4-yl]oxy-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**370c**):



Intermediate **370c** was synthesized from **369** (0.08 mmol) and NCS (0.16 mmol) as a yellow oil in 100% yield according to the general method X.

ESI-MS: 638.10 $(M+H)^+$.

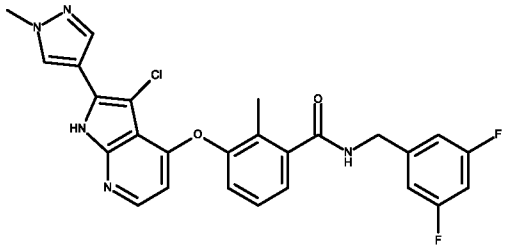
3-{[3-cyclopropyl-2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**357**):



Compound **357** was synthesized from intermediate **370b** (0.05 mmol) and HCl 3M (1.40 mmol) as a white solid in 29% yield according to the general method Z. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.72 (bs, 1H), 9.00 (t, *J* = 6.1, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 0.6, 1H), 7.94 (d, *J* = 5.5, 1H), 7.40-7.27 (m, 2H), 7.19-7.02 (m, 4H), 6.10 (d, *J* = 5.5, 1H), 4.49 (d, *J* = 6.1, 2H), 3.93 (s, 3H), 2.23 (s, 3H), 1.92-1.85 (m, 1H), 0.97-0.91 (m, 2H), 0.56-0.52 (m, 2H).

ESI-MS: 514.10 $(M+H)^+$.

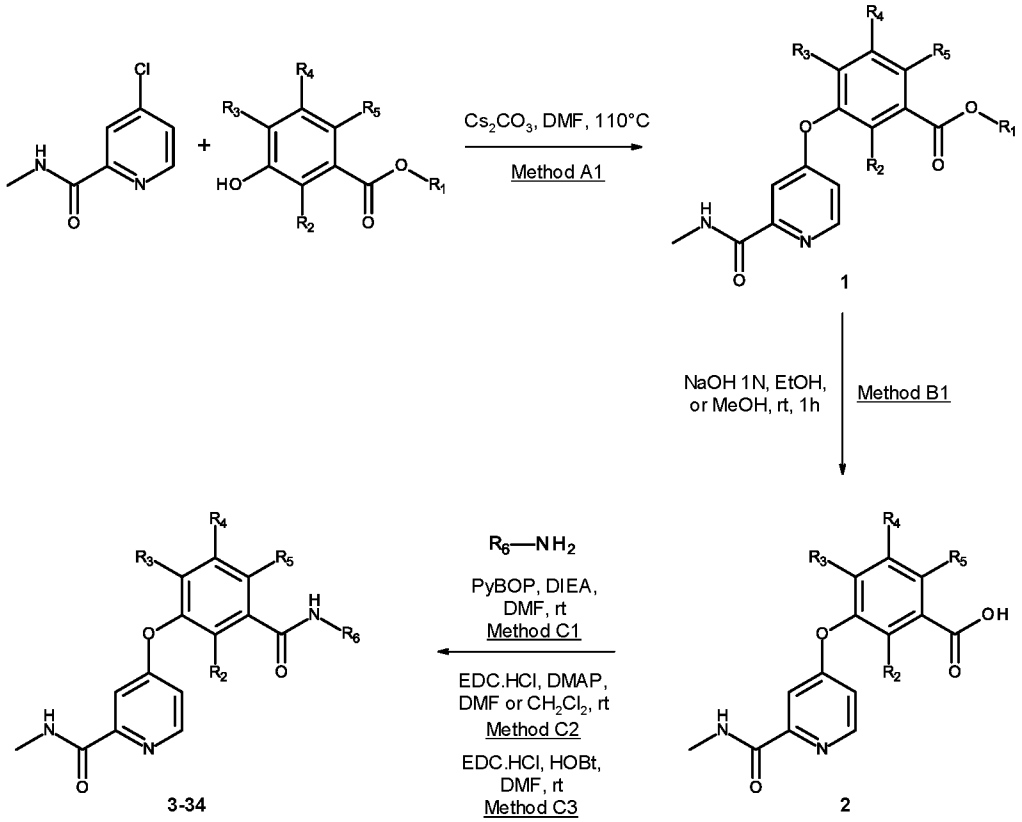
3-{[3-chloro-2-(1-methylpyrazol-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]oxy}-*N*-[(3,5-difluorophenyl)methyl]-2-methyl-benzamide (**358**):



Compound **358** was synthesized from intermediate **370c** (0.08 mmol) and HCl 3M (1.25 mmol) as a white solid in 43% yield according to the general method Z. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.34 (bs, 1H), 9.00 (t, *J* = 6.0, 1H), 8.37 (s, 1H), 8.11 (d, *J* = 0.6, 1H), 8.05 (d, *J* = 5.5, 1H), 7.41-7.32 (m, 2H), 7.23 (dd, *J* = 7.7, 1.6, 1H), 7.16-7.05 (m, 3H), 6.21 (d, *J* = 5.5, 1H), 4.48 (d, *J* = 6.0, 2H), 3.94 (s, 3H), 2.19 (s, 3H).

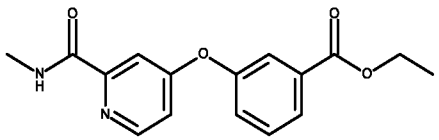
ESI-MS: 508.05 $(M+H)^+$.

Example 22: General procedure for the synthesis of analogues CC11, CC20, CC24, and CC25



The following compound **1a** is an example illustrating Method A1:

Preparation of ethyl 3-{[2-(methylcarbamoyl)-4-pyridyl]oxy}benzoate (**1a**):



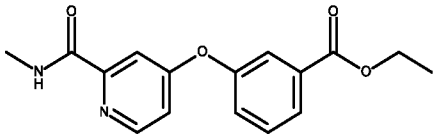
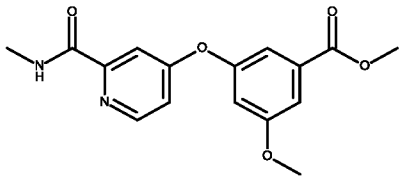
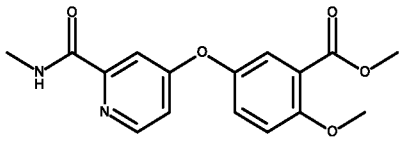
Intermediate **1a** was synthesized from ethyl-3-hydroxybenzoate (6.02 mmol) and 4-chloro-N-methylpyridine-2-carboxamide (6.02 mmol) as a colorless oil in 73% yield according to the general method A1.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41 (d, *J* = 5.6 Hz, 1H), 8.06 (bs, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 6.99 (dd, *J* = 5.6 Hz, 2.5 Hz, 1H), 4.38 (q, *J* =

7.1 Hz, 2H), 3.01 (d, *J* = 5.1 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H).

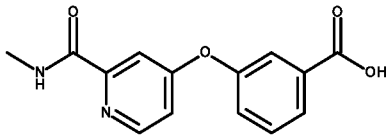
ESI-MS: 301.50 $(M+H)^+$.

The following table illustrates intermediates **1** prepared from method A1:

Intermediate	Structure	Synthesis procedure
Compound **1a**		Method A1
Compound **1b**		Method A1
Compound **1c**		Method A1

The following compound **2a** is an example illustrating Method B1:

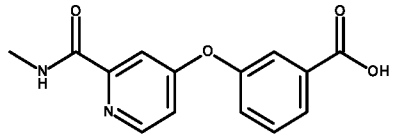
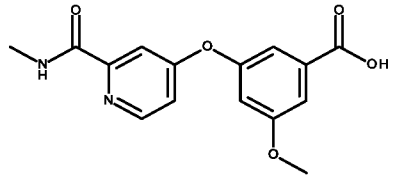
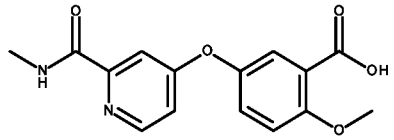
Preparation of 3-{[2-(methylcarbamoyl)-4-pyridyl]oxy}benzoic acid (**2a**):



Intermediate **2a** was synthesized from intermediate **1a** (4.37 mmol) as a white powder in 97% yield according to the general method B1.

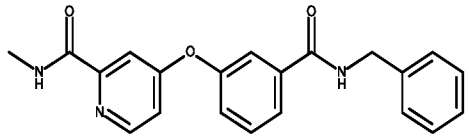
1H NMR (400 MHz, DMSO) δ (ppm): 13.26 (bs, 1H), 8.78 (q, *J* = 4.5 Hz, 1H), 8.61-8.48 (m, 1H), 7.98-7.84 (m, 1H), 7.68-7.63 (m, 2H), 7.52 (ddd, *J* = 8.1 Hz, 2.5 Hz, 1.0 Hz, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.20 (dd, *J* = 5.6 Hz, 2.6 Hz, 1H), 2.79 (d, *J* = 4.9 Hz, 3H).

The following table illustrates intermediates **2** prepared from method B:

Intermediate	Structure	Synthesis procedure
Compound **2a**		Method B1
Compound **2b**		Method B1
Compound **2c**		Method B1

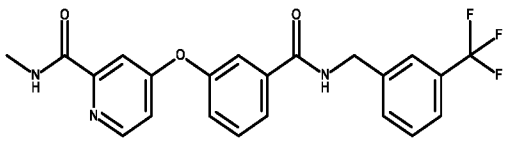
The following compounds are examples illustrating Method C:

4-[3-(benzylcarbamoyl)phenoxy]-*N*-methyl-pyridine-2-carboxamide (**11**):



Compound **11** was synthesized from intermediate **2a** (0.25 mmol) and benzylamine (0.30 mmol) as a white solid in 84% yield according to the general method C2. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.14 (t, *J* = 5.8 Hz, 1H), 8.80-8.77 (m, 1H), 8.54 (d, *J* = 5.6 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.72 (s, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.44-7.41 (m, 2H), 7.32-7.31 (m, 4H), 7.28-7.17 (m, 2H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.79 (d, *J* = 4.8 Hz, 3H).

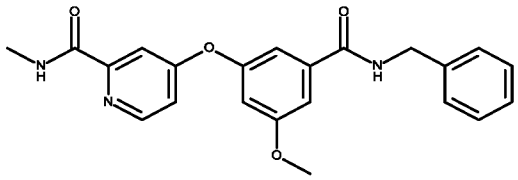
N-methyl-4-(3-{[3-(trifluoromethyl)phenyl]methylcarbamoyl}phenoxy)pyridine-2-carboxamide (**20**):



Compound **20** was synthesized from intermediate **2a** (0.34 mmol) and 3-(trifluoromethyl)benzylamine (0.44 mmol) as a white solid in 79% yield according to the general method C3. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.08 (bs, 1H), 7.70-7.65 (m, 2H), 7.60-7.45 (m, 6H), 7.26- 7.24 (m, 1H), 7.01 (dd, *J* = 5.6 Hz, 2.6 Hz, 1H), 6.67 (t, *J* = 5.3 Hz, 1H), 4.69 (d, *J* = 5.9 Hz, 2H), 2.99 (d, *J* = 5.1 Hz, 3H).

ESI-MS: 430.40 $(M+H)^+$.

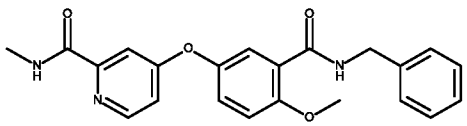
4-[3-(benzylcarbamoyl)-5-methoxy-phenoxy]-*N*-methyl-pyridine-2-carboxamide (**24**):



Compound **24** was synthesized from intermediate **2b** (0.25 mmol) and benzylamine (0.32 mmol) as a white solid in 82% yield according to the general method C3. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 8.40 (d, *J* = 5.2 Hz, 1H), 7.99 (bs, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.38-7.28 (m, 5H), 7.25 (dd, *J* = 2.3 Hz, 1.5 Hz, 1H), 7.04 (dd, *J* = 2.0 Hz, 1.5 Hz, 1H), 6.97 (dd, *J* = 5.6 Hz, 2.6 Hz, 1H), 6.76 (t, *J* = 2.2 Hz, 1H), 6.35 (t, *J* = 5.0 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.84 (s, 3H), 3.01 (d, *J* = 5.1 Hz, 3H).

ESI-MS: 392.30 $(M+H)^+$.

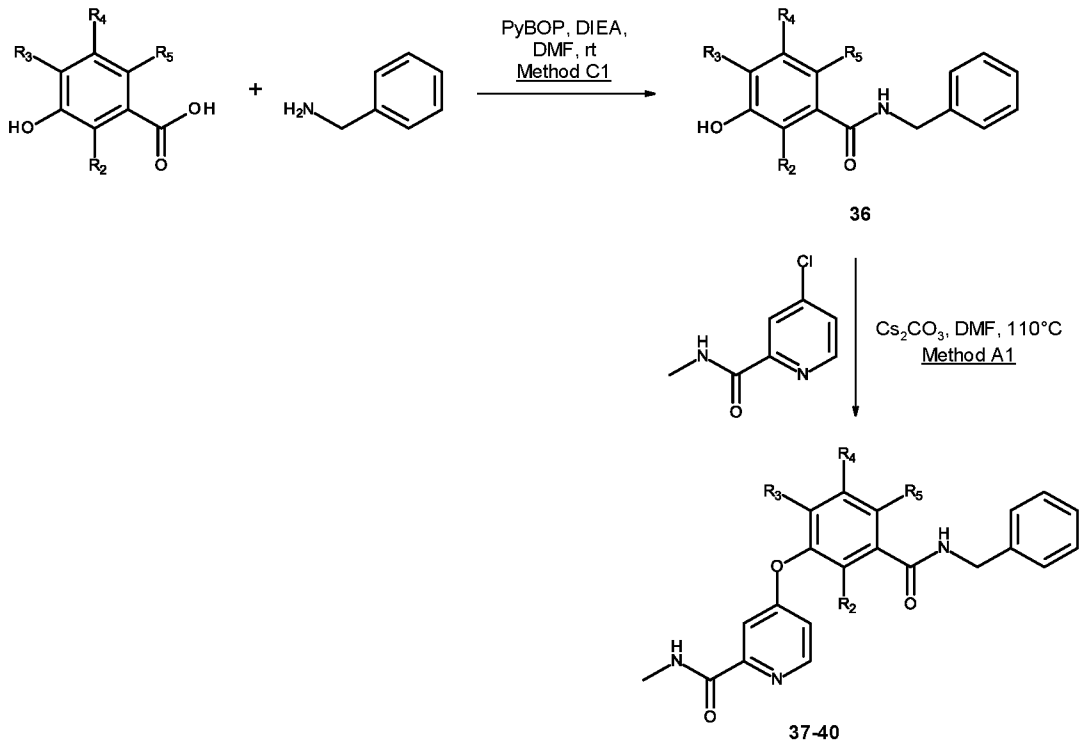
4-[3-(benzylcarbamoyl)-4-methoxy-phenoxy]-*N*-methyl-pyridine-2-carboxamide (**25**):



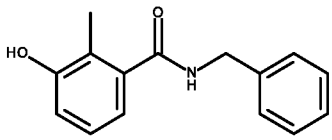
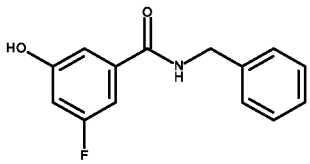
Compound **25** was synthesized from intermediate **2c** (0.25 mmol) and benzylamine (0.32 mmol) as a white solid in 67% yield according to the general method C3. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 8.37 (d, *J* = 5.6 Hz, 1H), 8.22 (t, *J* = 4.4 Hz, 1H), 8.01-7.98 (m, 2H), 7.62 (d, *J* = 2.5 Hz, 1H), 7.39-7.27 (m, 5H), 7.20 (dd, *J* = 8.9 Hz, 3.1 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.97 (dd, *J* = 5.6

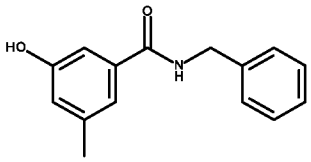
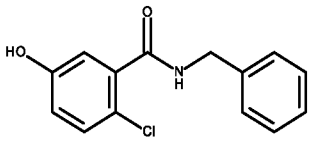
Hz, 2.6 Hz, 1H), 4.69 (d, *J* = 5.7 Hz, 2H), 3.96 (s, 3H), 3.00 (d, *J* = 5.1 Hz, 3H). ESI-MS: 392.30 $(M+H)^+$.

Example 23: General procedure for the preparation of analogues CC37-CC40



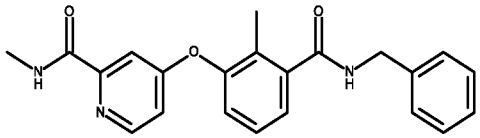
The following table illustrates intermediates **36** prepared from Method C1.

Intermediate	Structure	Synthesis procedure
Compound **36a**		Method C1
Compound **36b**		Method C1

Compound **36c**		Method C1
Compound **36d**		Method C1

The following compounds are examples illustrating the procedure A1:

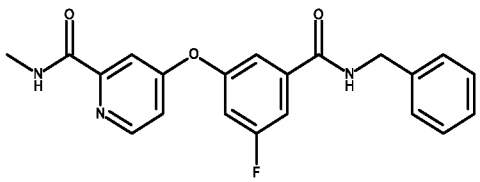
4-[3-(benzylcarbamoyl)-2-methyl-phenoxy]-N-methyl-pyridine-2-carboxamide (**37**):



Compound **37** was synthesized from intermediate **36a** (0.50 mmol) and 4-chloro-*N*-methylpyridine-2-carboxamide (0.50 mmol) as a white solid in 15% yield according to the general method A1.

ESI-MS: 376.40 $(M+H)^+$.

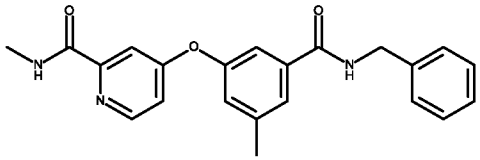
4-[3-(benzylcarbamoyl)-5-fluoro-phenoxy]-*N*-methyl-pyridine-2-carboxamide (**38**):



Compound **38** was synthesized from intermediate **36b** (0.50 mmol) and 4-chloro-*N*-methylpyridine-2-carboxamide (0.50 mmol) as a white solid in 34% yield according to the general method A1.

ESI-MS: 380.40 $(M+H)^+$.

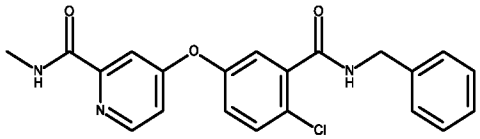
4-[3-(benzylcarbamoyl)-5-methyl-phenoxy]-*N*-methyl-pyridine-2-carboxamide (**39**):



Compound **39** was synthesized from intermediate **36c** (0.19 mmol) and 4-chloro-*N*-methylpyridine-2-carboxamide (0.19 mmol) as a white solid in 66% yield according to the general method A1.

ESI-MS: 376.40 $(M+H)^+$.

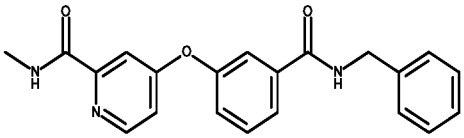
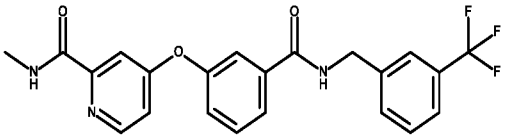
4-[3-(benzylcarbamoyl)-5-methyl-phenoxy]-*N*-methyl-pyridine-2-carboxamide (**40**):

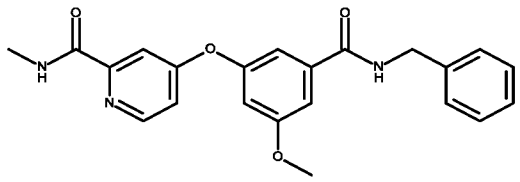
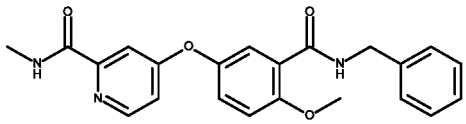
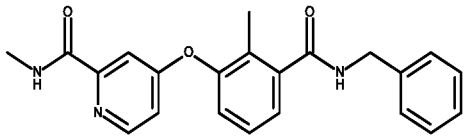
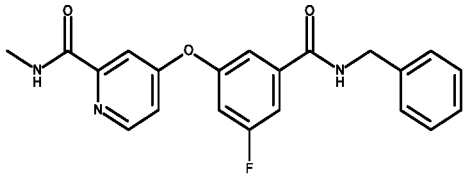
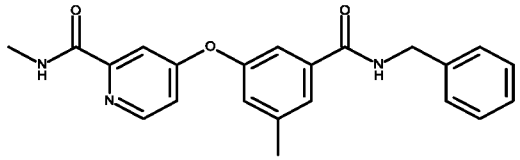
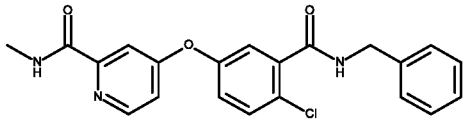
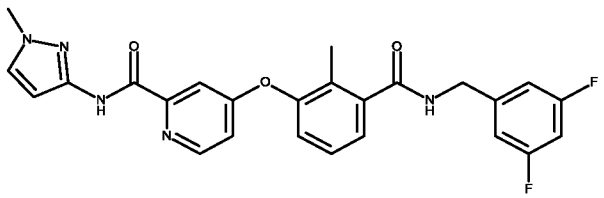


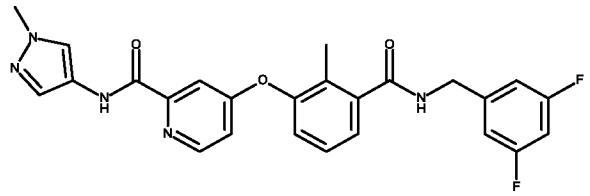
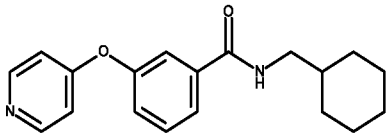
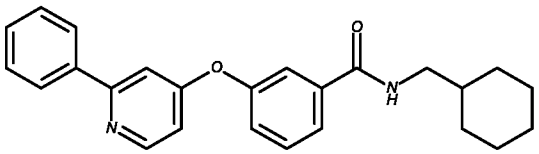
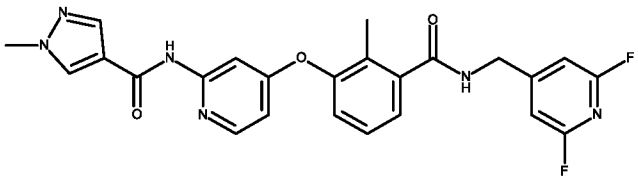
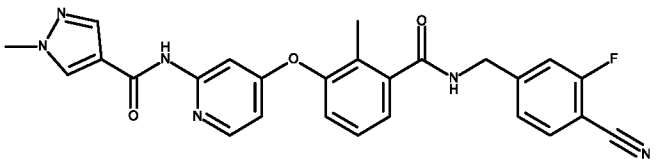
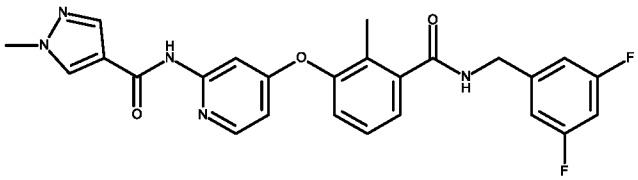
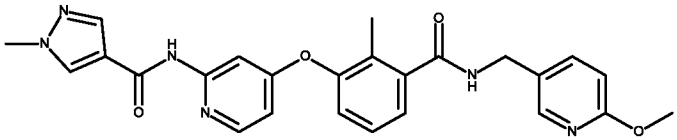
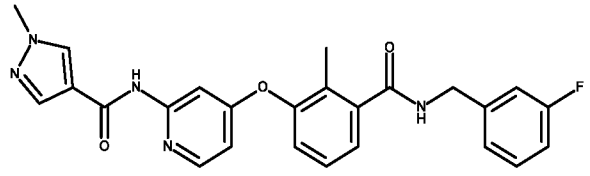
Compound **40** was synthesized from intermediate **36d** (0.50 mmol) and 4-chloro-*N*-methylpyridine-2-carboxamide (0.50 mmol) as a white solid in 32% yield according to the general method A1.

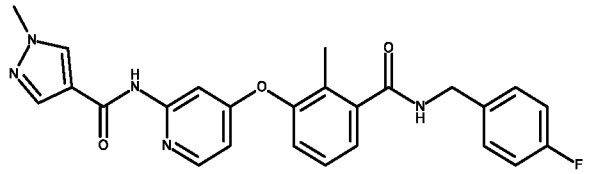
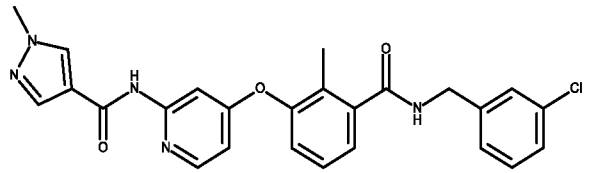
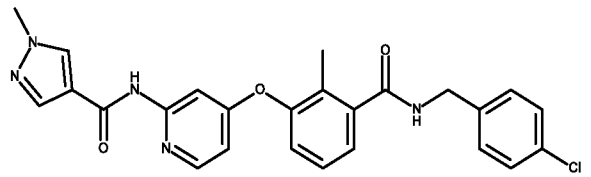
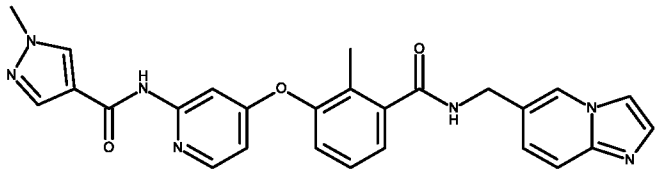
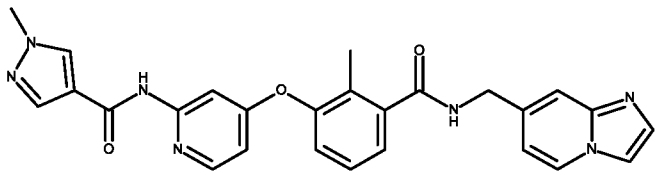
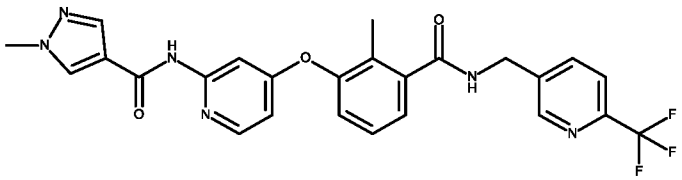
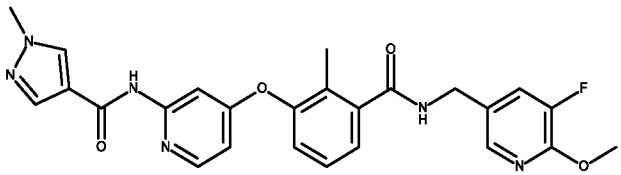
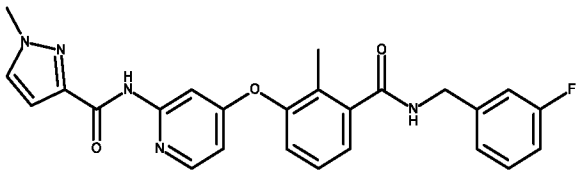
ESI-MS: 396.40 $(M+H)^+$.

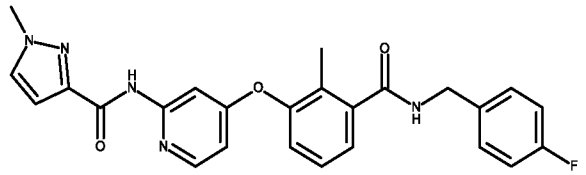
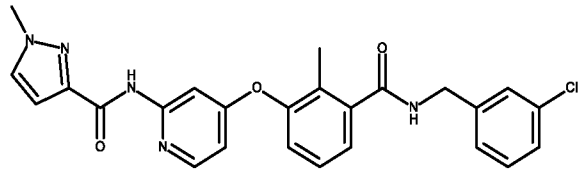
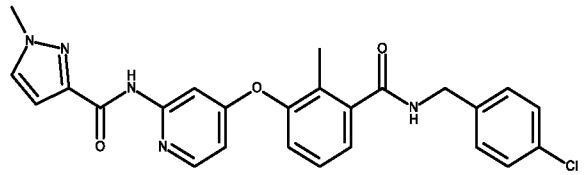
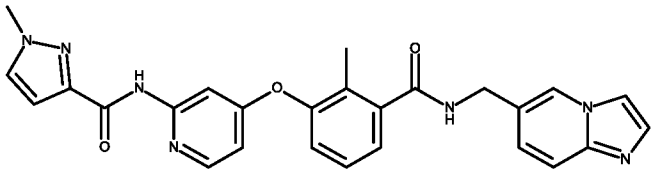
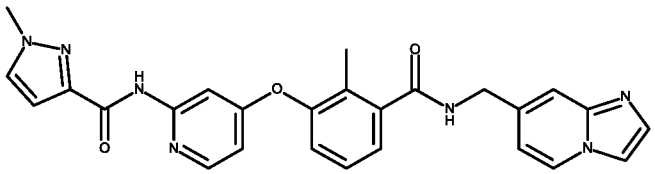
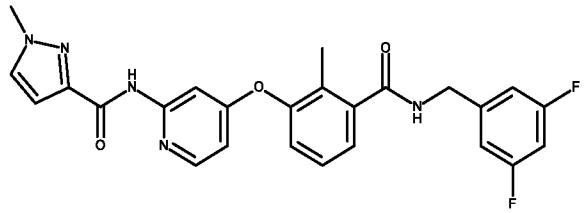
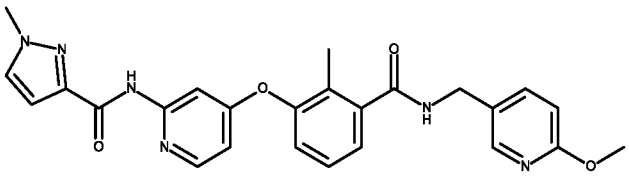
Table 1: Examples of compounds

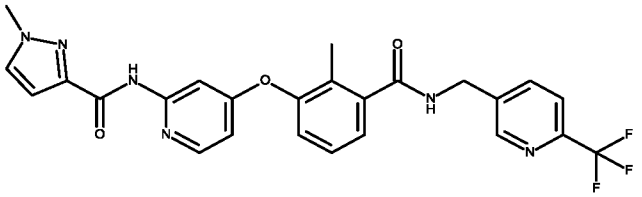
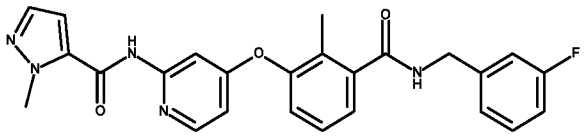
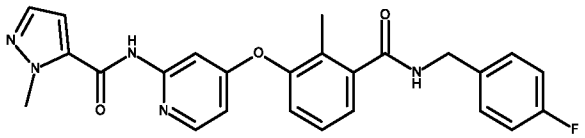
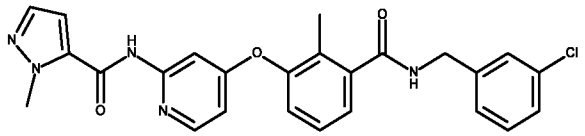
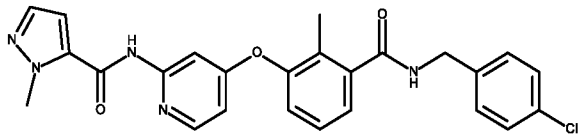
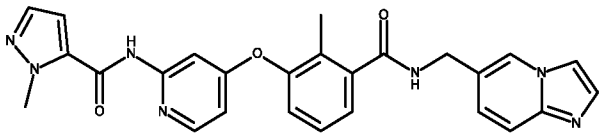
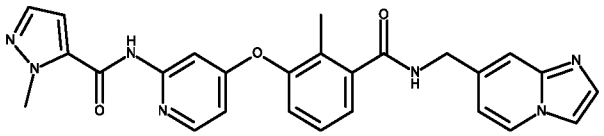
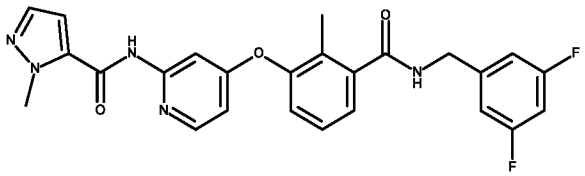
CC11	
CC20	

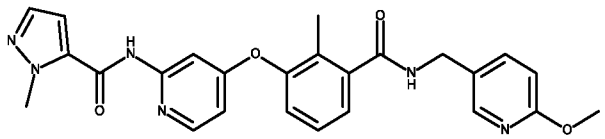
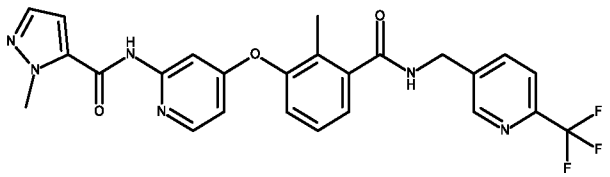
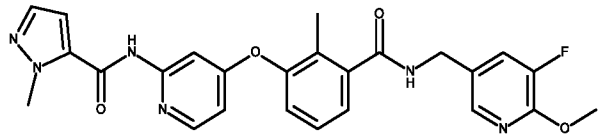
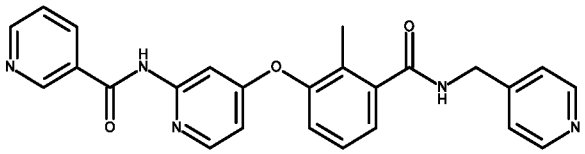
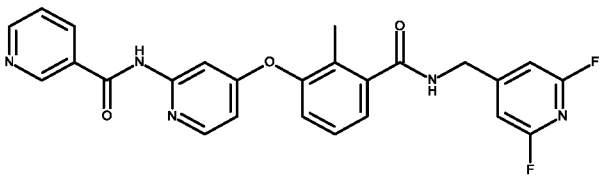
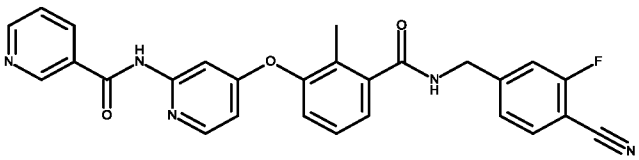
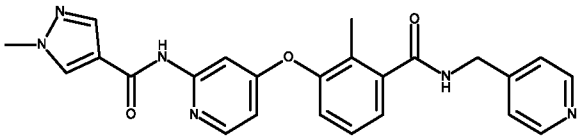
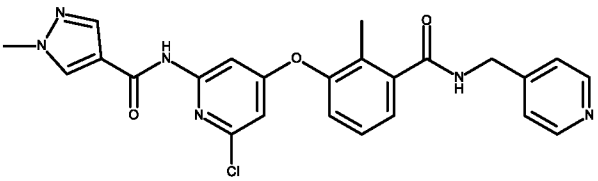
CC24	
CC25	
CC37	
CC38	
CC39	
CC40	
44	

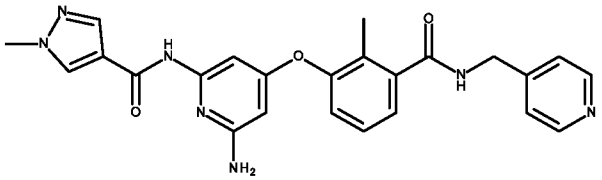
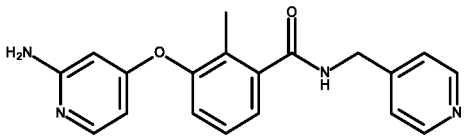
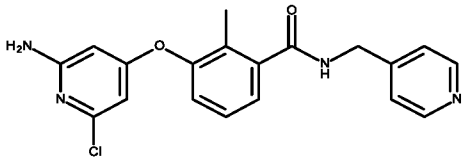
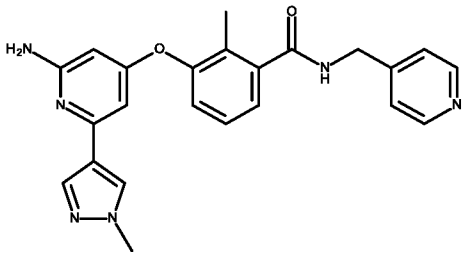
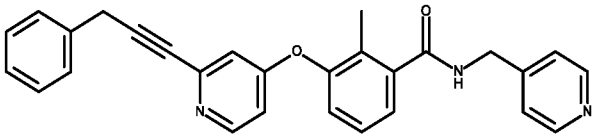
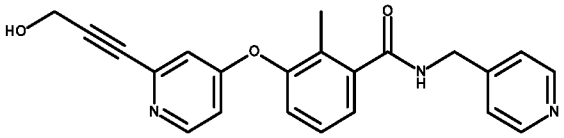
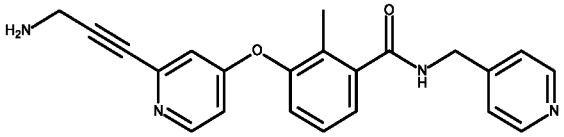
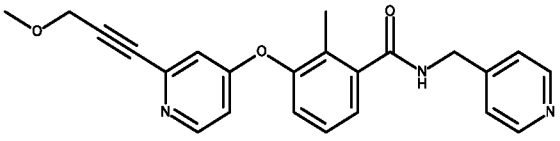
45	
49	
50	
68	
69	
70	
71	
72	

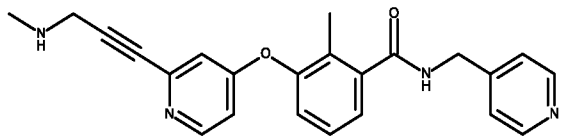
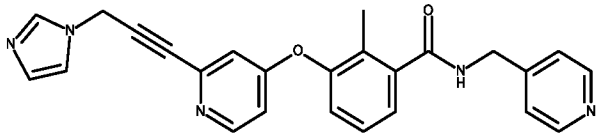
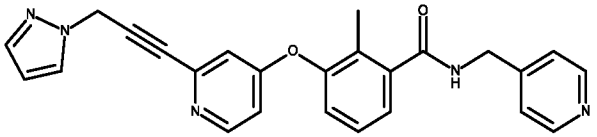
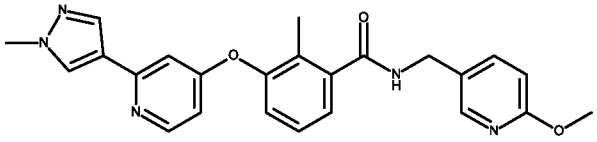
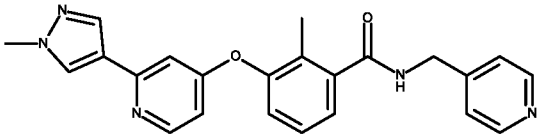
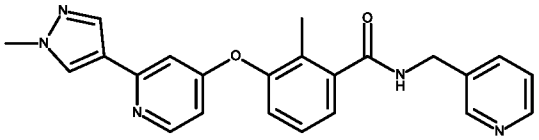
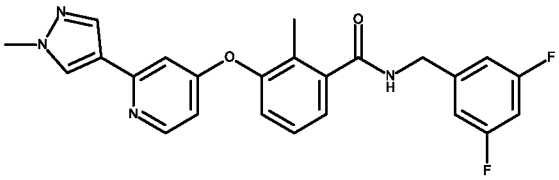
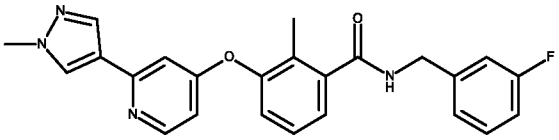
73	
74	
75	
76	
77	
78	
79	
80	

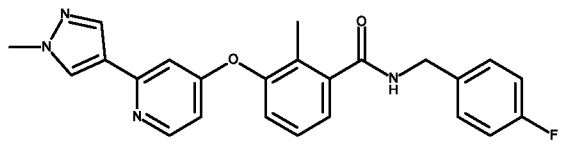
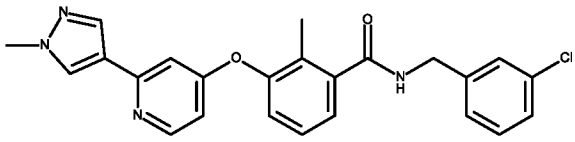
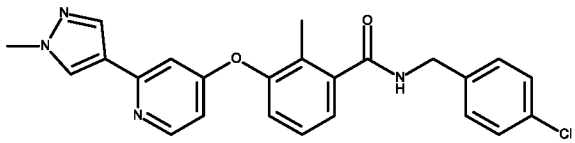
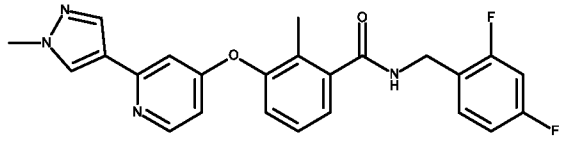
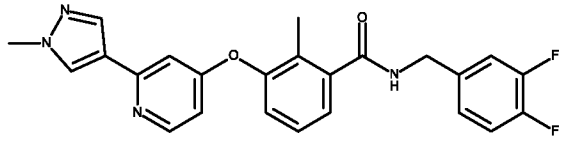
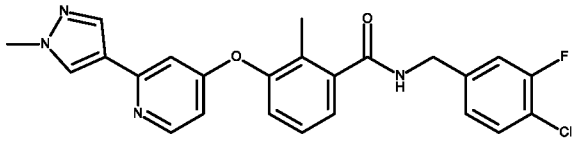
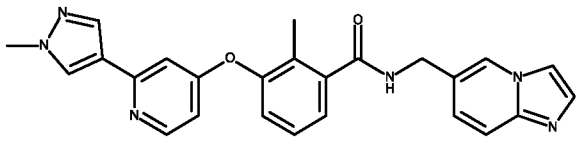
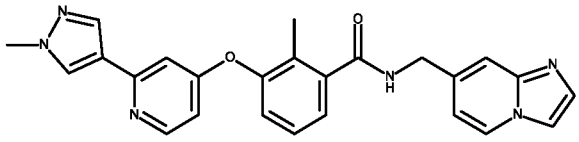
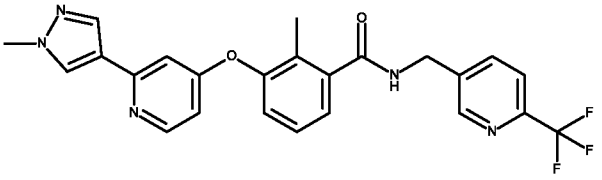
81	
82	
83	
84	
85	
86	
87	

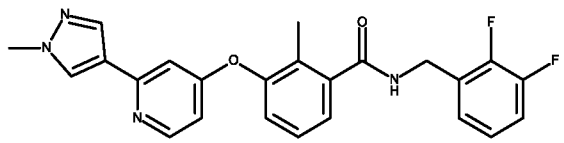
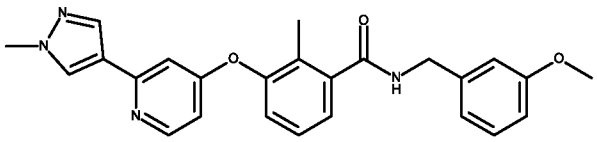
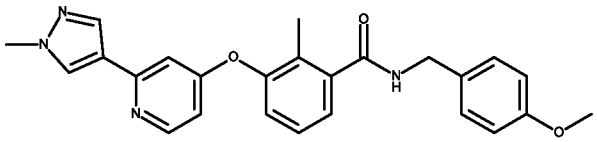
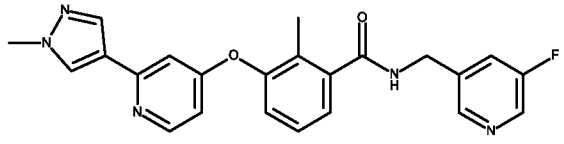
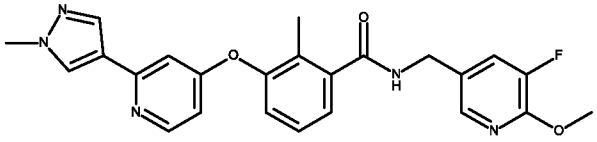
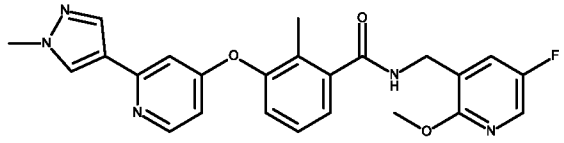
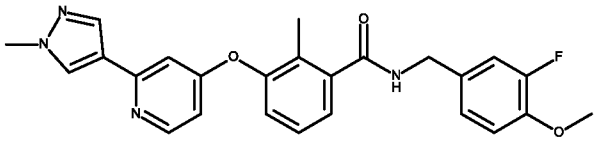
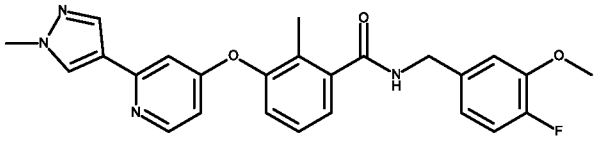
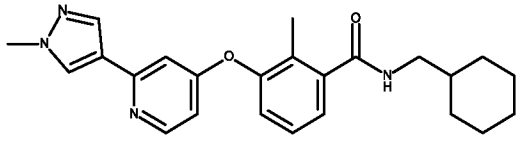
88	
89	
90	
91	
92	
93	
94	
95	

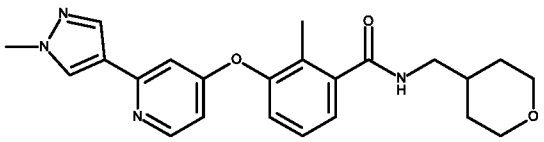
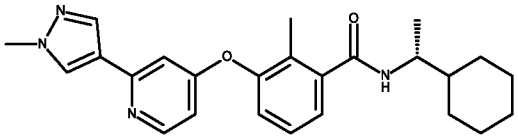
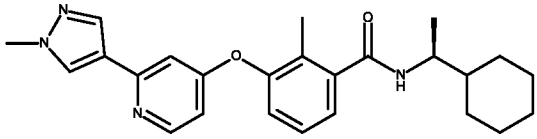
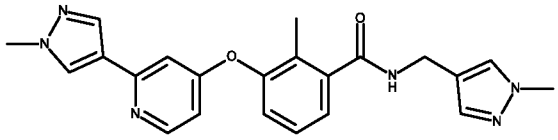
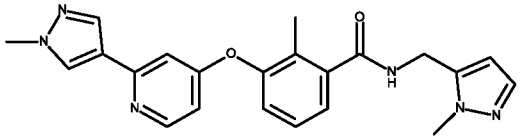
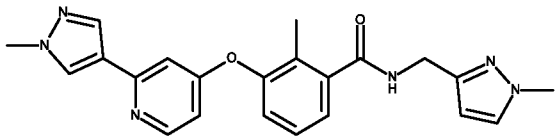
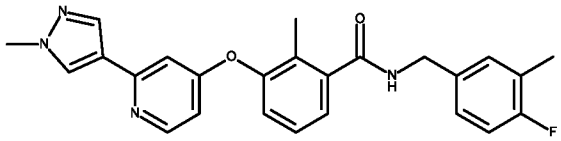
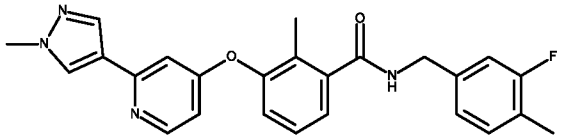
96	
97	
98	
99	
100	
101	
103	
104	

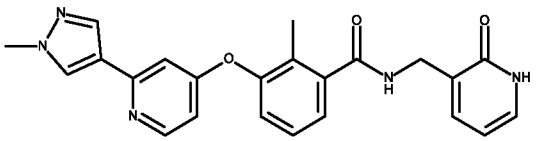
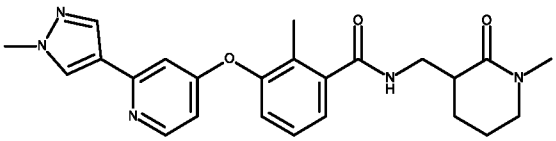
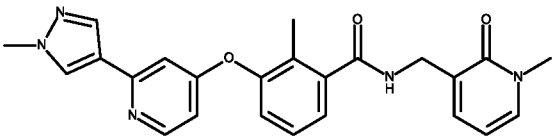
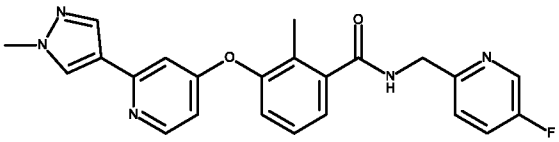
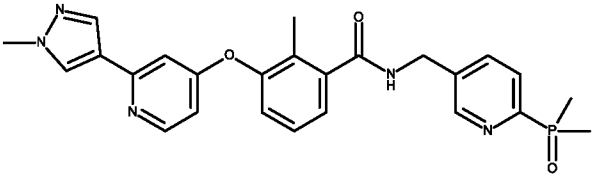
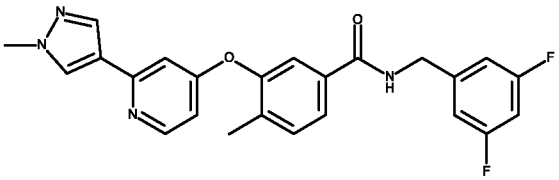
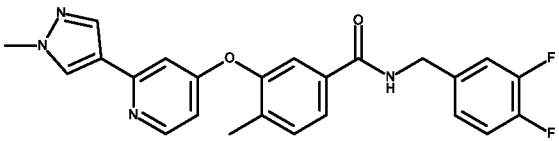
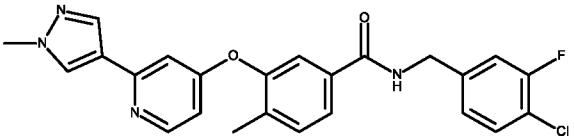
105	
106	
107	
108	
110	
111	
112	
113	

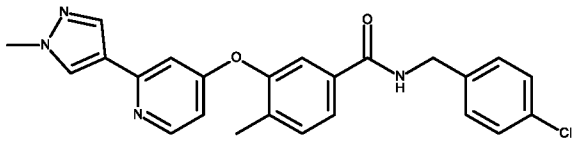
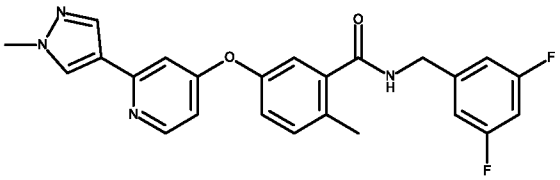
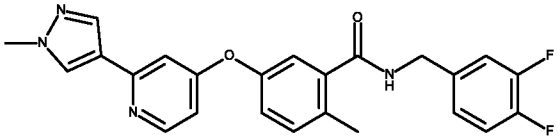
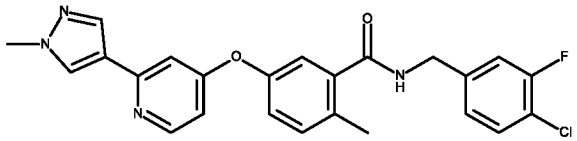
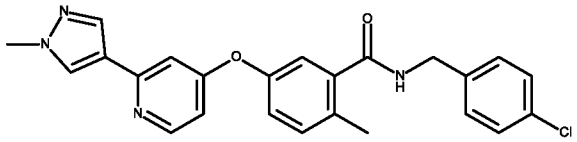
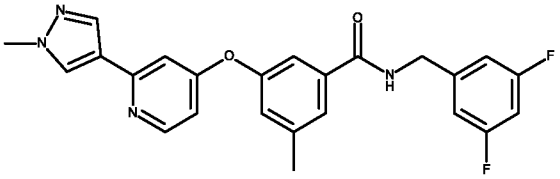
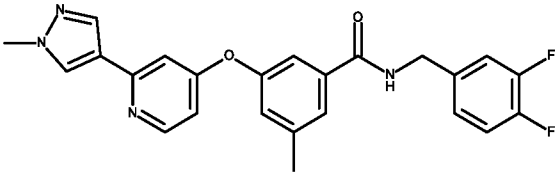
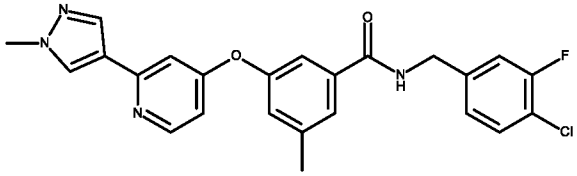
114	
115	
116	
120	
121	
122	
123	
124	

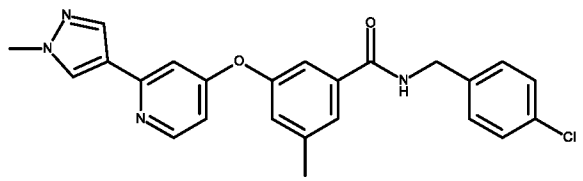
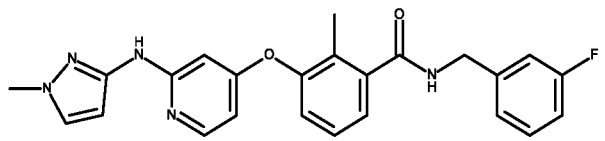
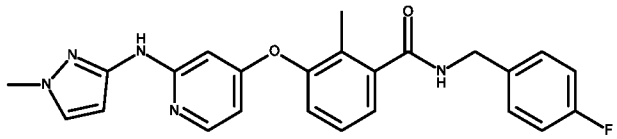
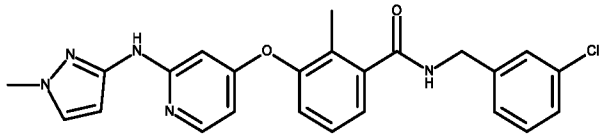
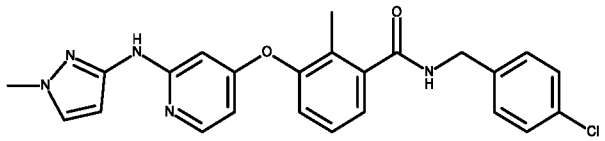
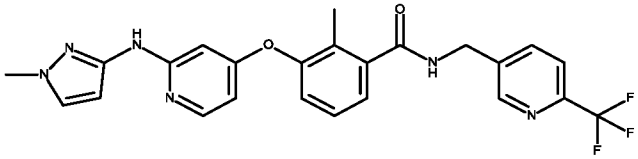
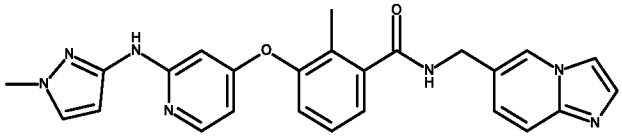
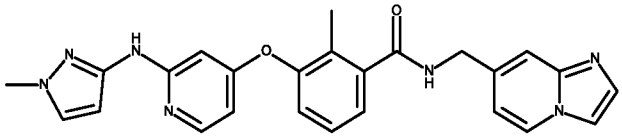
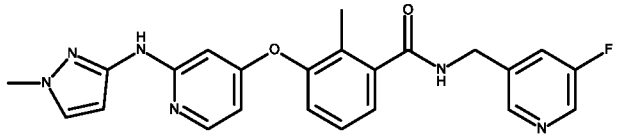
125	
126	
127	
128	
129	
130	
131	
132	
133	

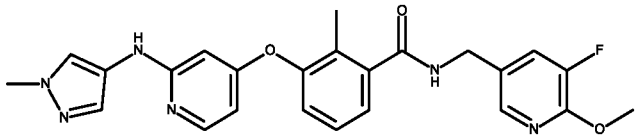
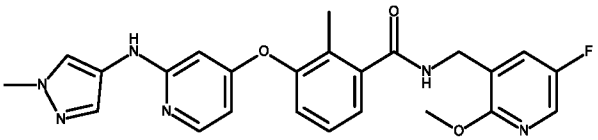
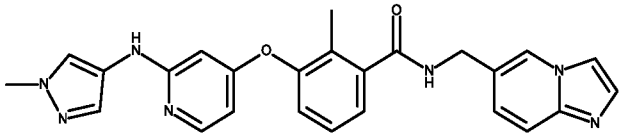
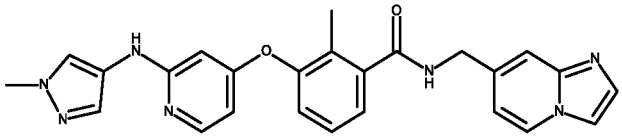
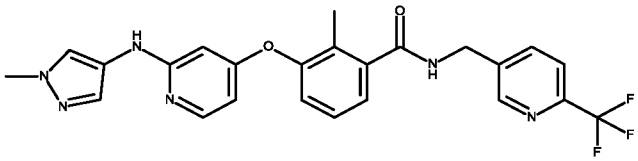
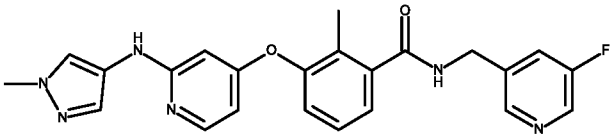
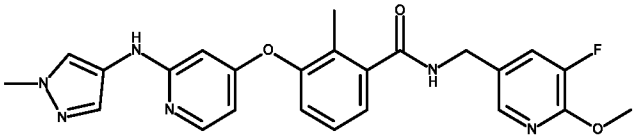
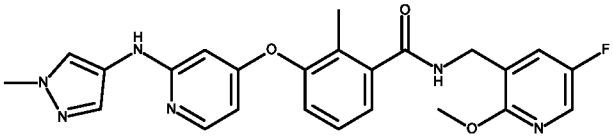
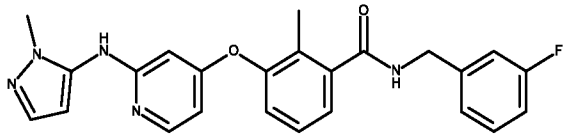
134	
135	
136	
137	
138	
139	
140	
141	
142	

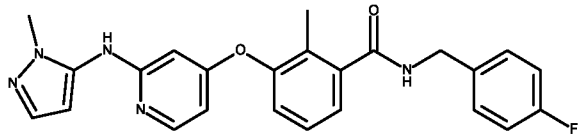
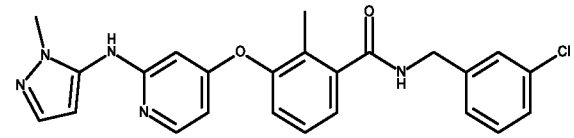
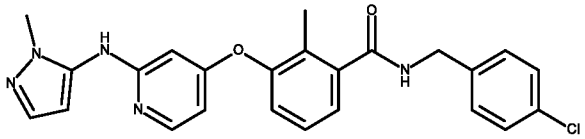
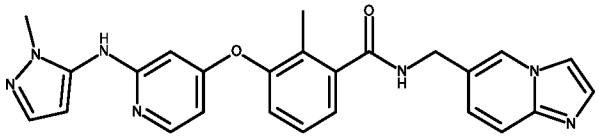
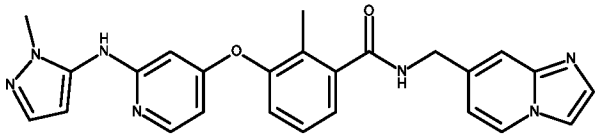
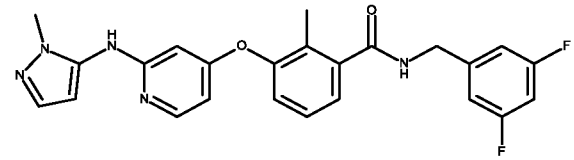
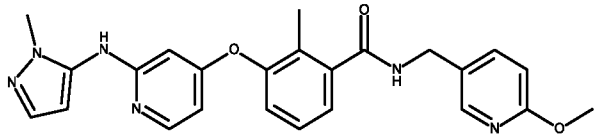
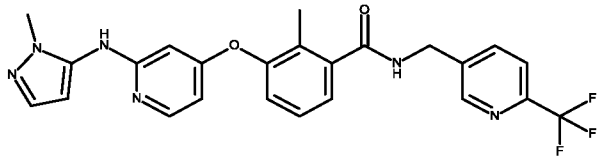
143	
144	
145	
146	
147	
148	
149	
150	

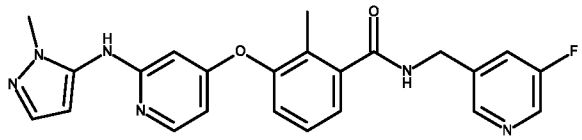
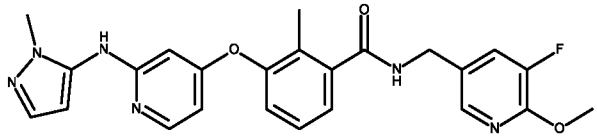
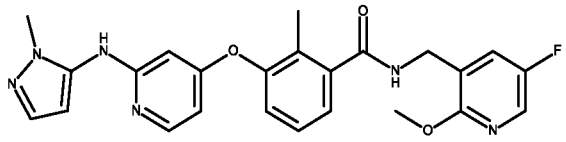
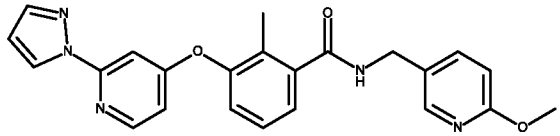
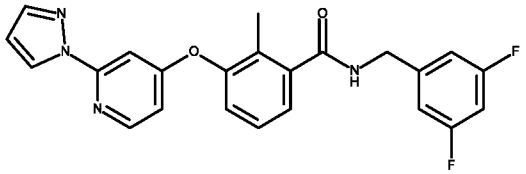
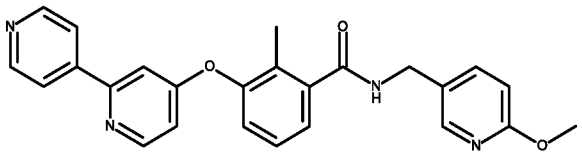
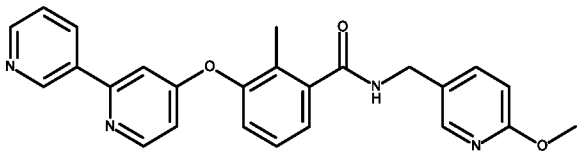
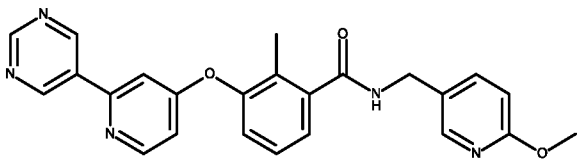
151	
152	
153	
154	
155	
156	
157	
158	

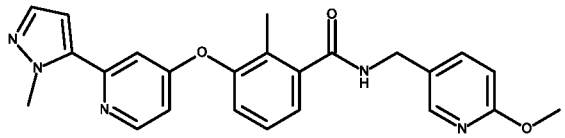
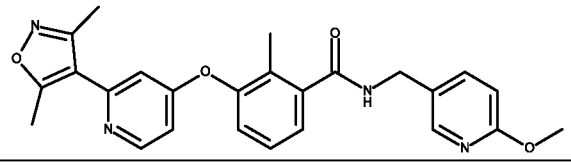
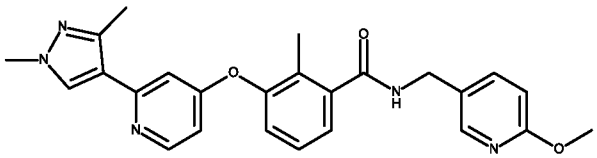
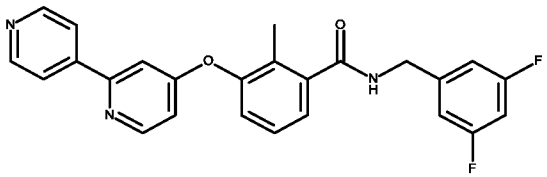
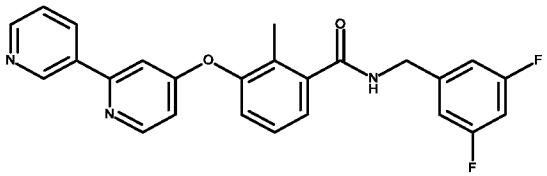
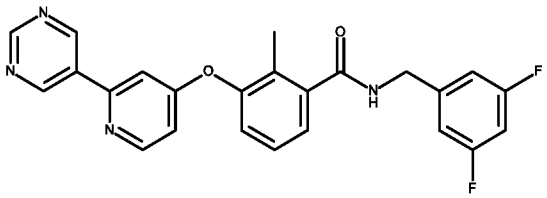
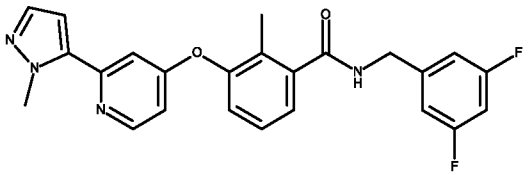
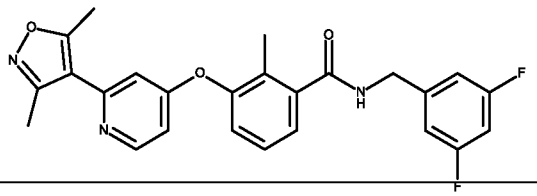
159	
160	
161	
162	
163	
164	
165	
166	

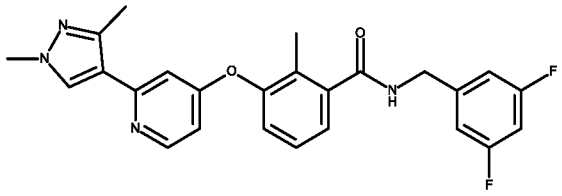
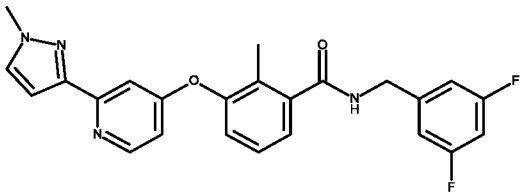
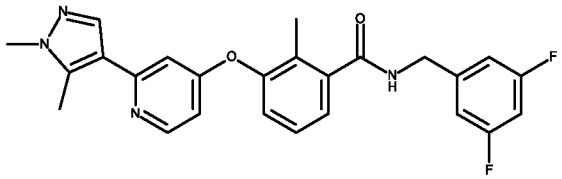
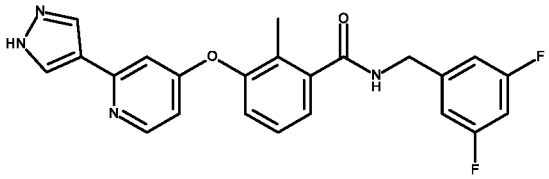
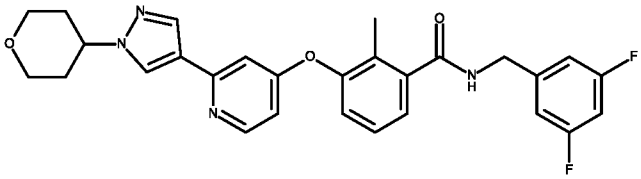
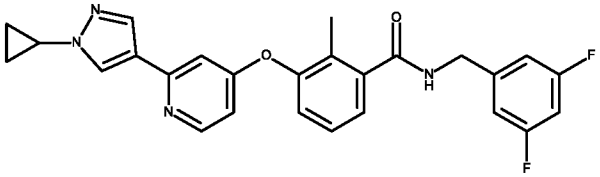
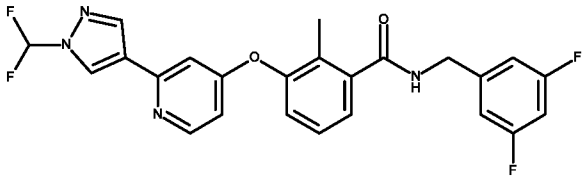
167	
168	
169	
170	
171	
172	
173	
174	
175	

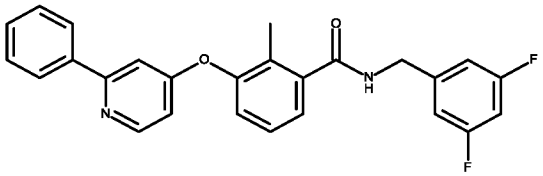
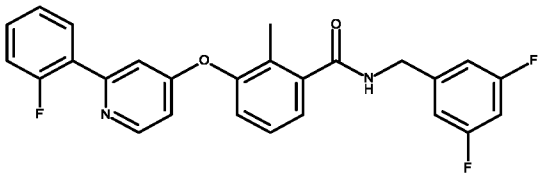
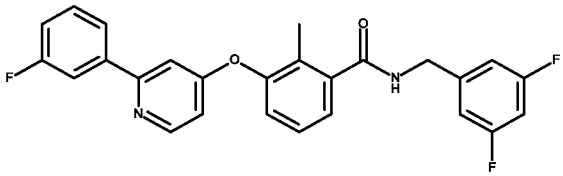
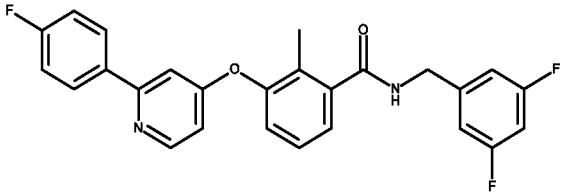
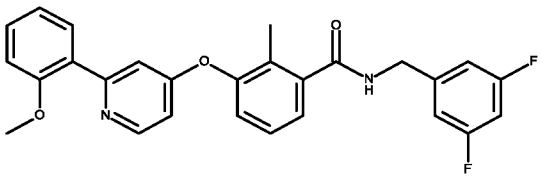
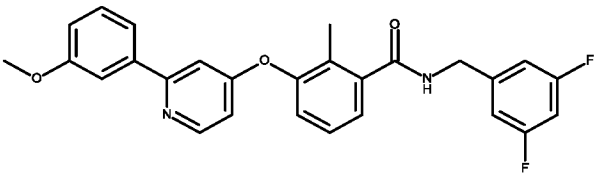
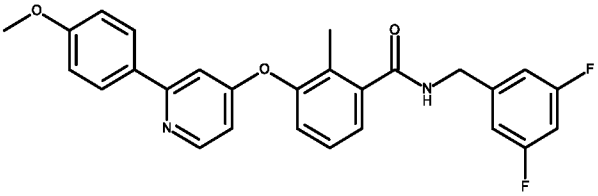
176	
177	
178	
179	
180	
181	
182	
183	
184	

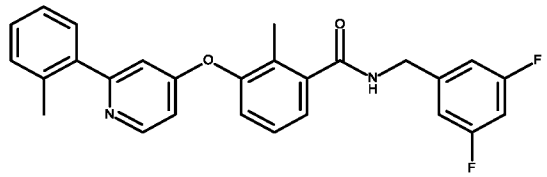
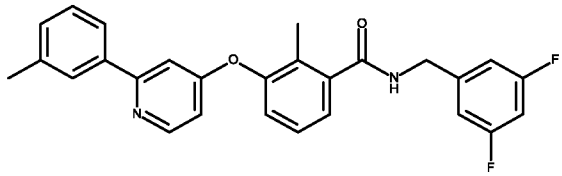
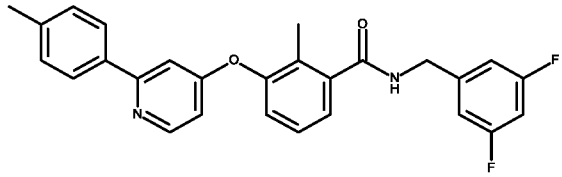
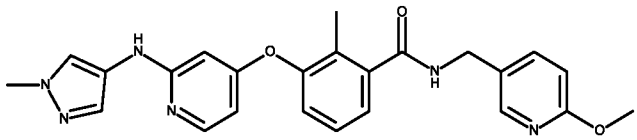
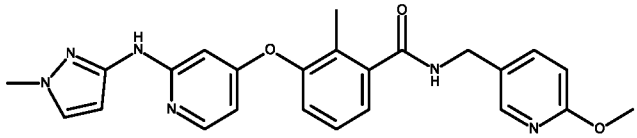
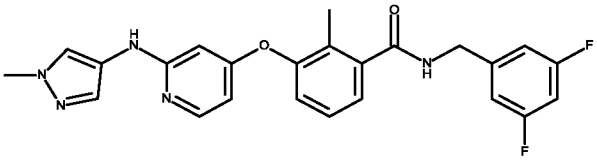
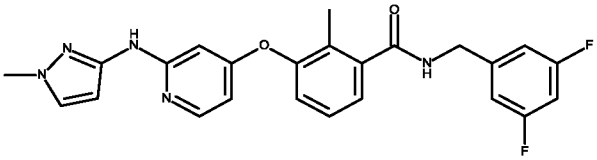
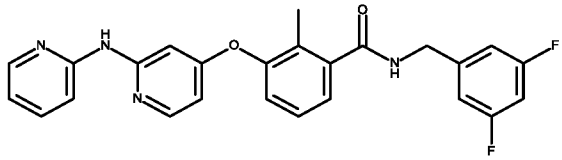
185	
186	
187	
188	
189	
190	
191	
192	

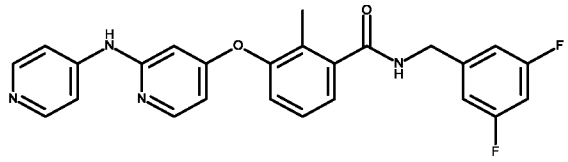
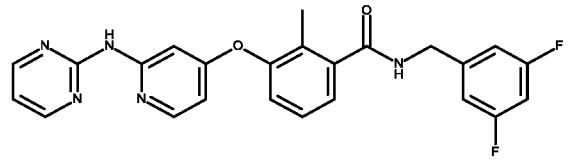
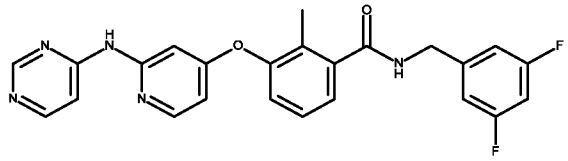
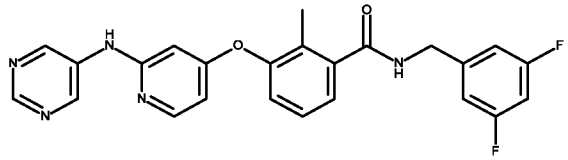
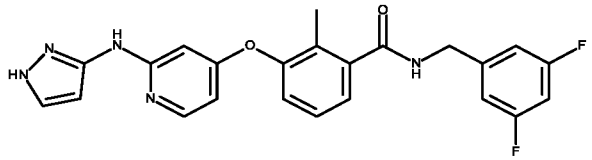
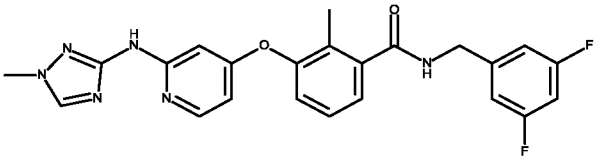
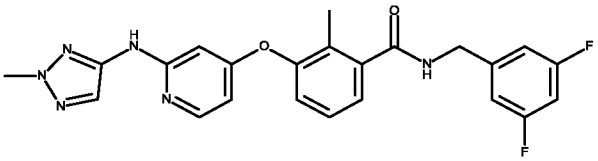
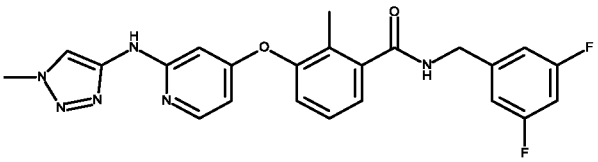
193	
194	
195	
196	
197	
200	
201	
202	

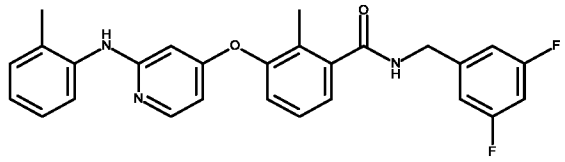
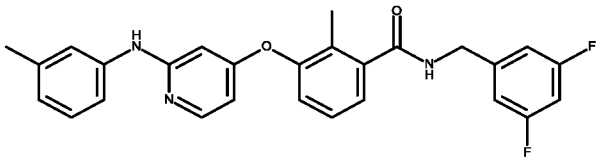
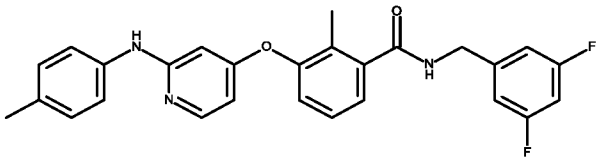
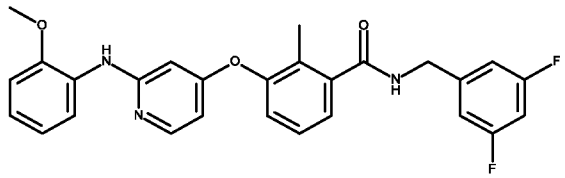
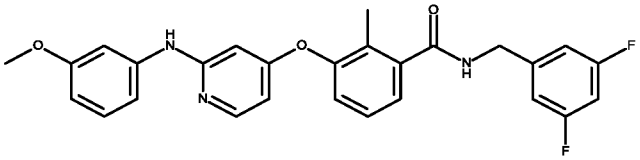
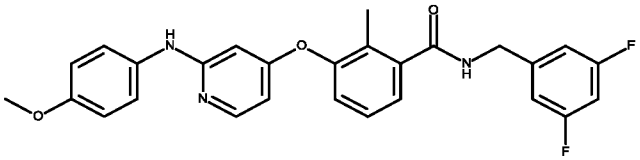
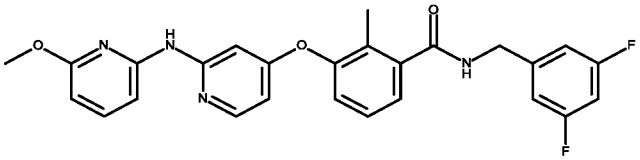
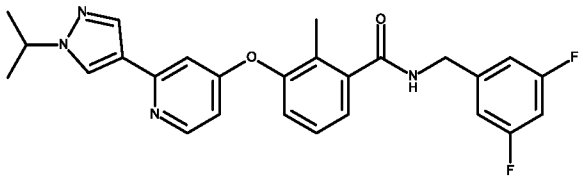
203	
204	
205	
206	
207	
208	
209	
210	

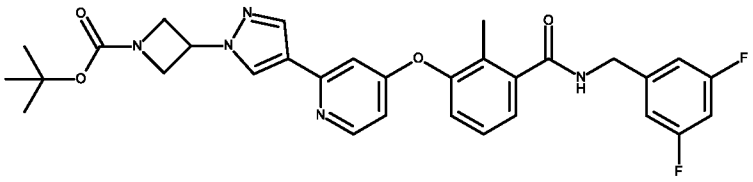
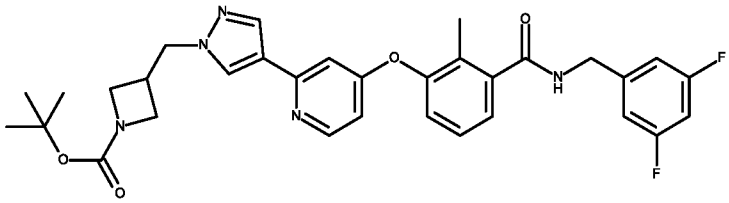
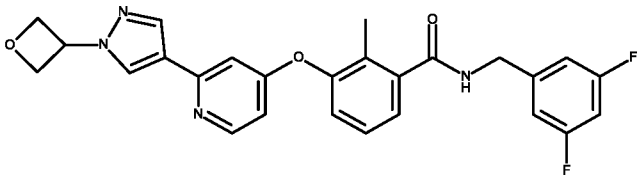
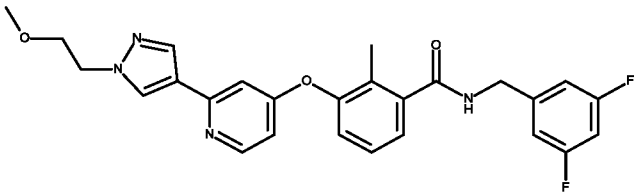
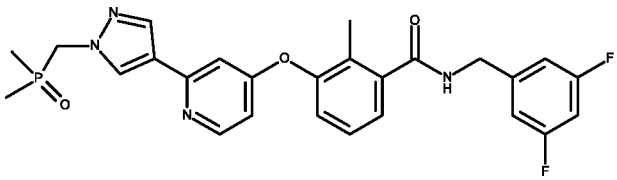
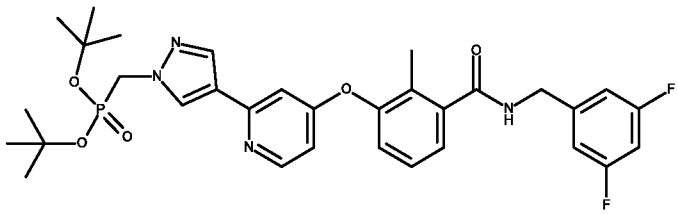
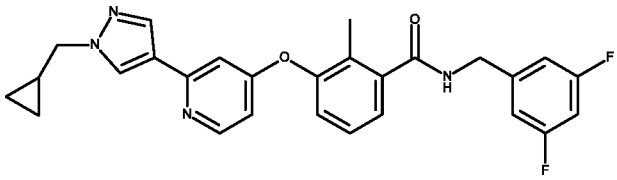
211	
212	
213	
214	
215	
216	
217	

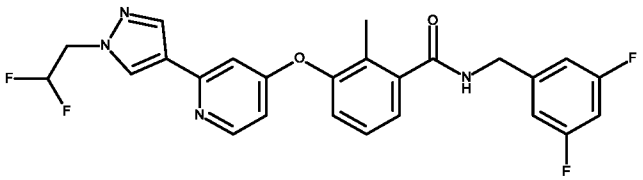
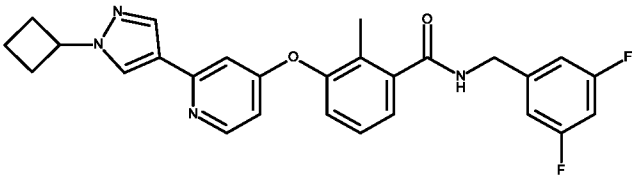
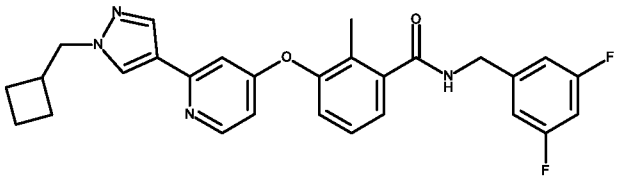
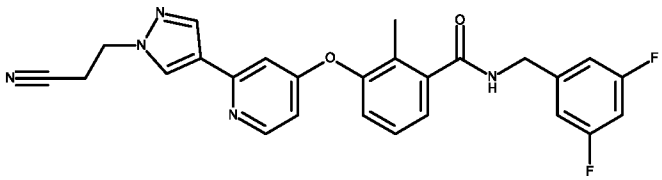
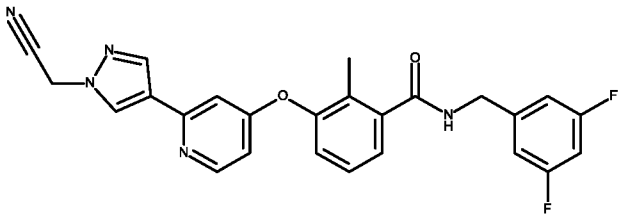
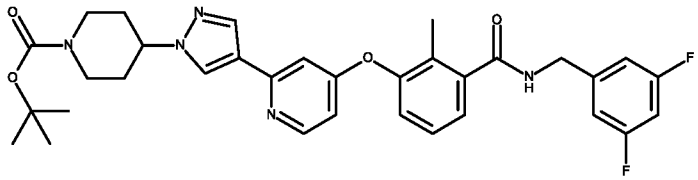
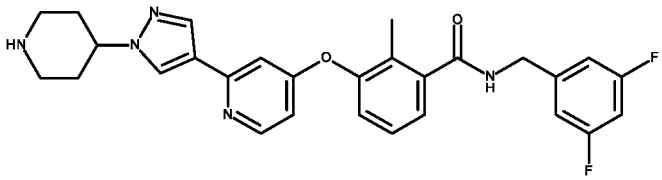
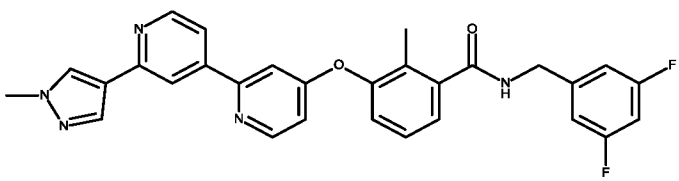
218	
219	
220	
221	
222	
223	
224	

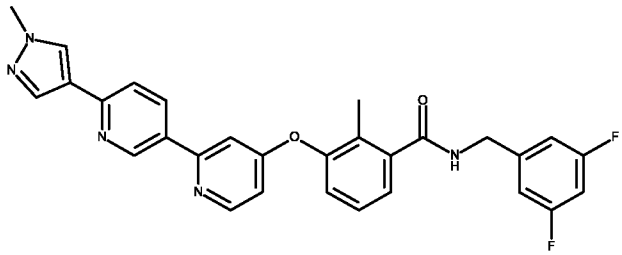
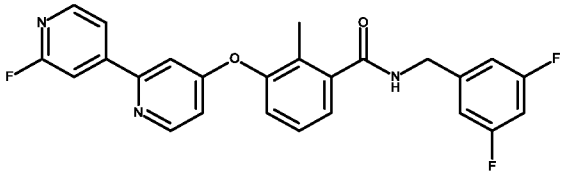
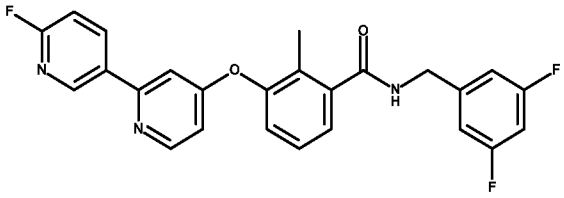
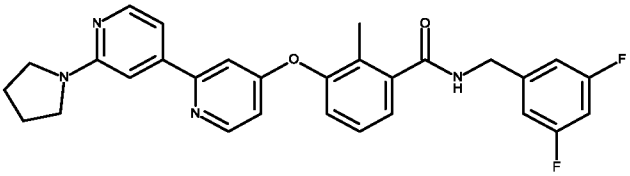
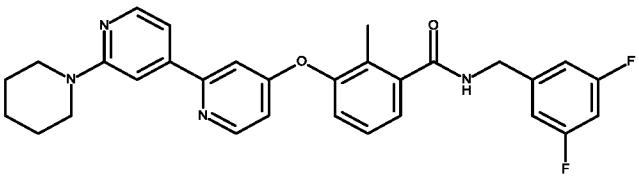
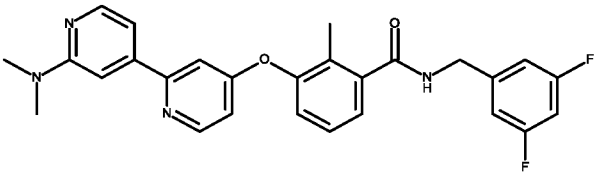
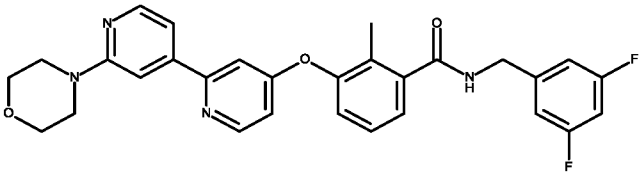
225	
226	
227	
228	
229	
230	
231	
232	

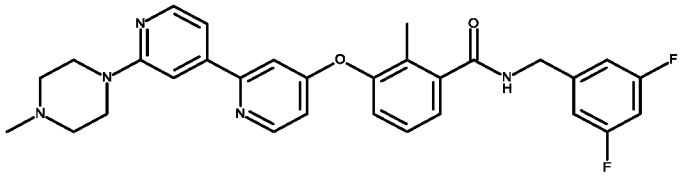
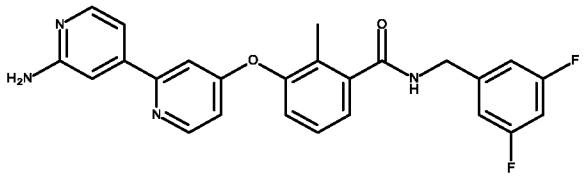
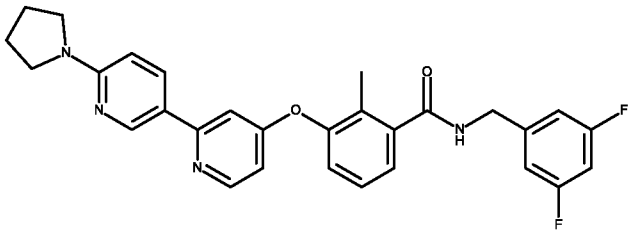
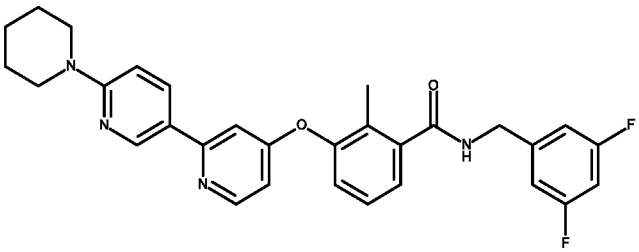
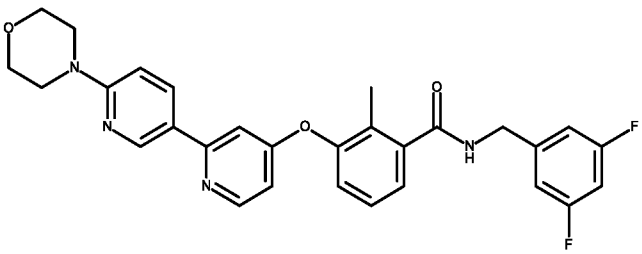
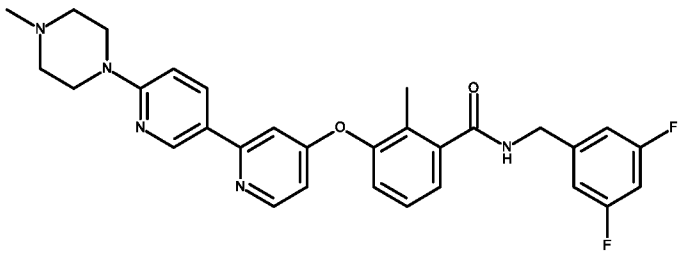
233	
234	
235	
236	
237	
238	
239	
240	

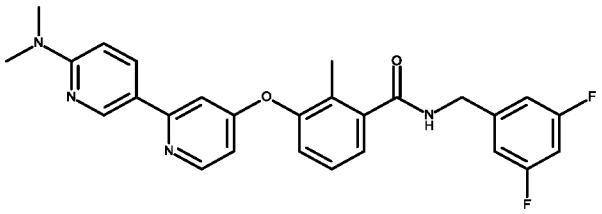
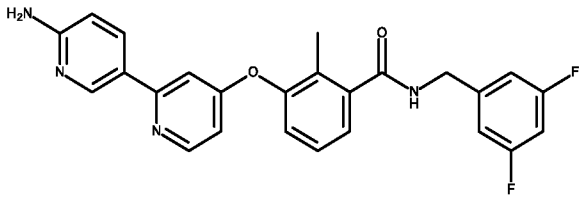
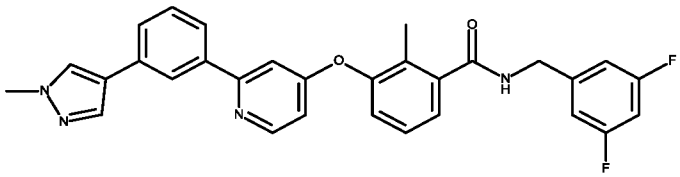
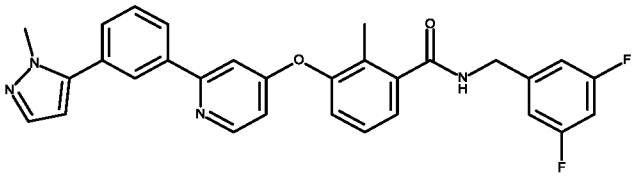
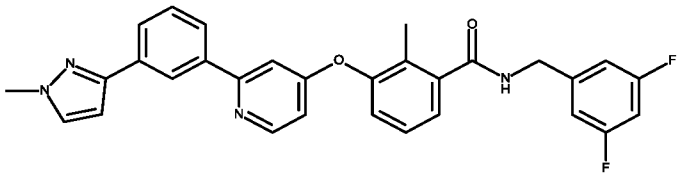
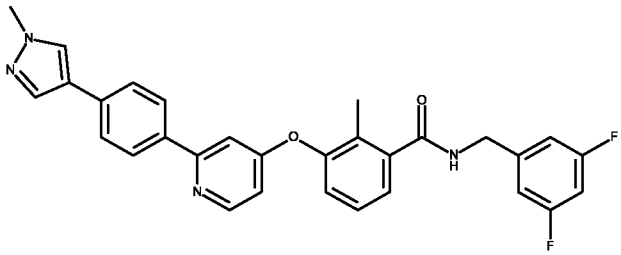
241	
242	
243	
244	
245	
246	
247	
248	

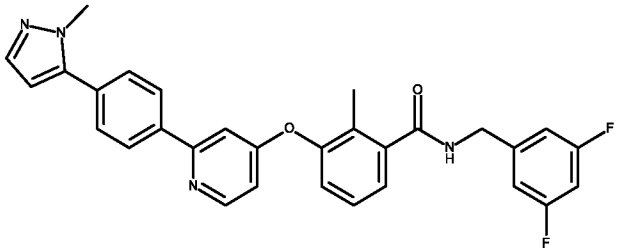
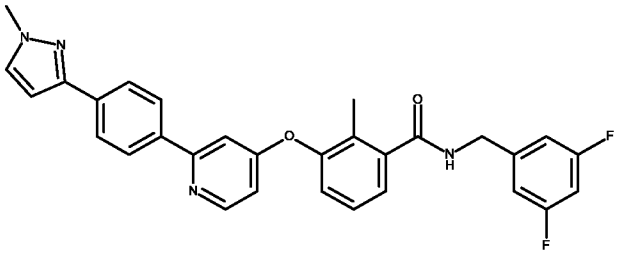
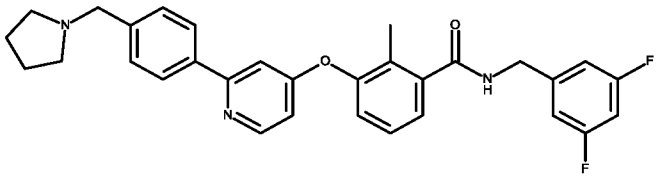
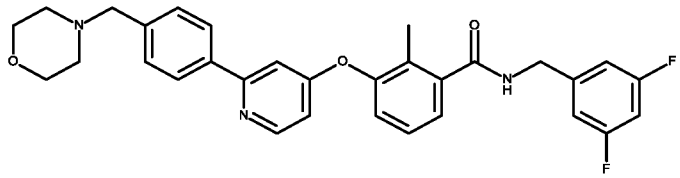
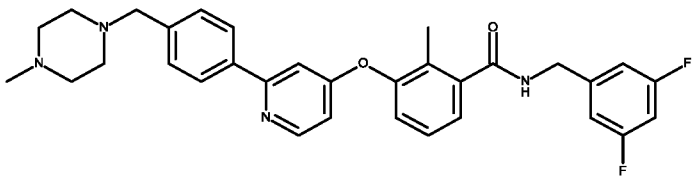
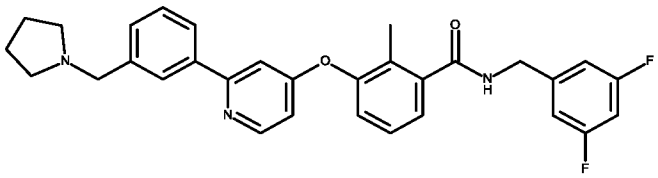
249	
250	
251	
252	
253	
254	
255	

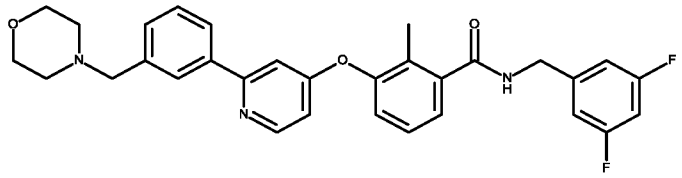
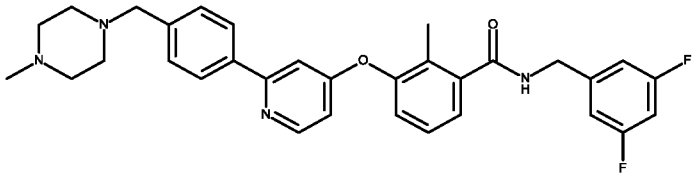
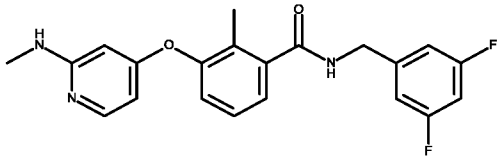
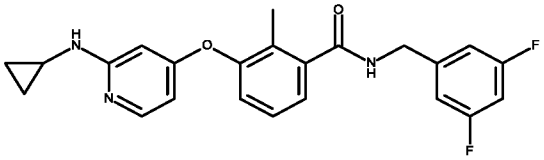
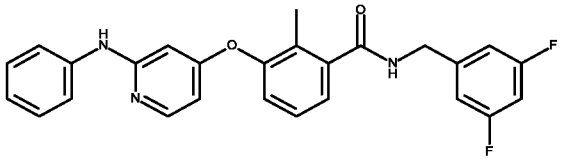
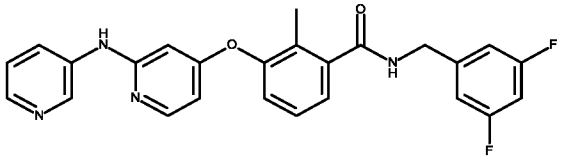
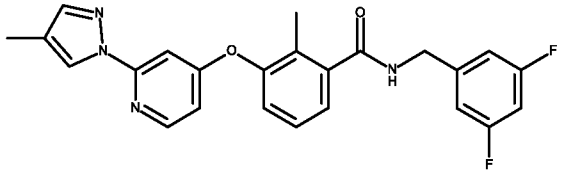
256	
257	
258	
259	
260	
261	
262	
263	

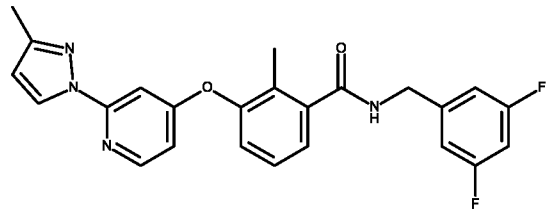
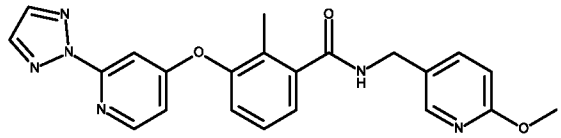
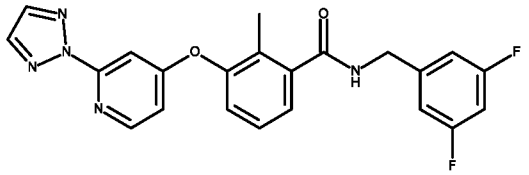
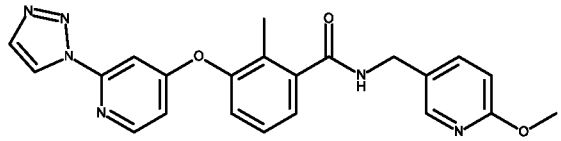
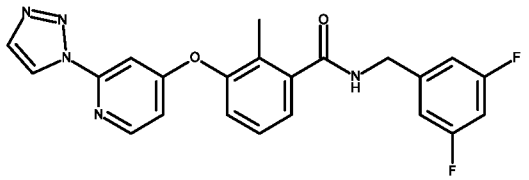
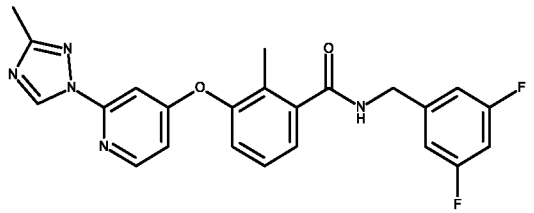
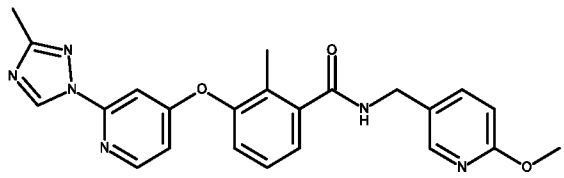
264	
265a	
265b	
266	
267	
268	
269	

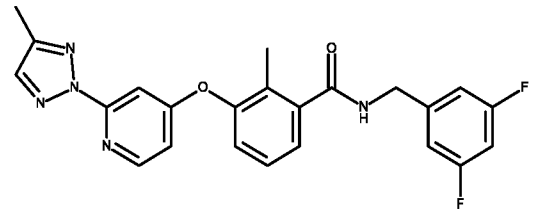
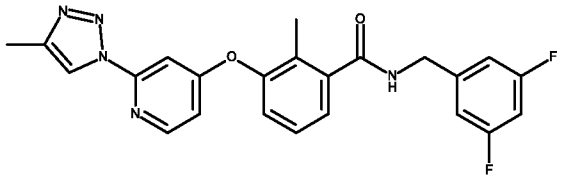
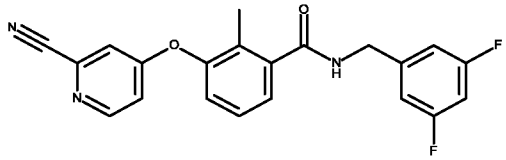
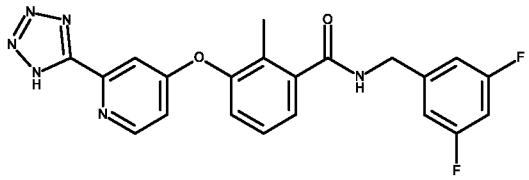
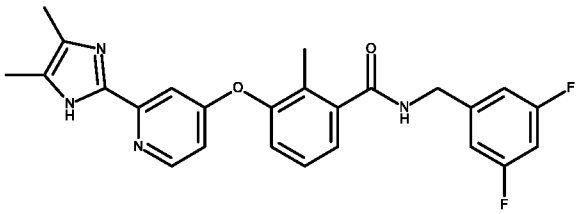
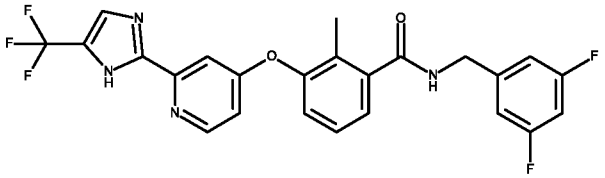
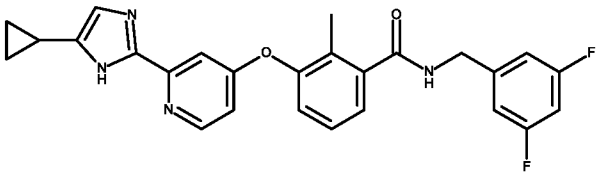
270	
271	
272	
273	
274	
275	

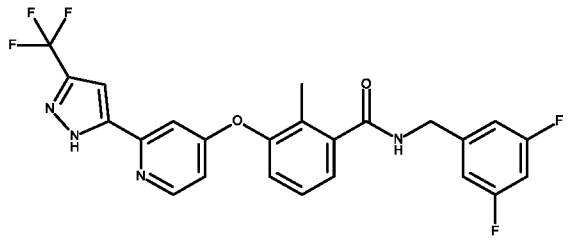
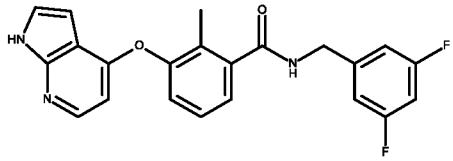
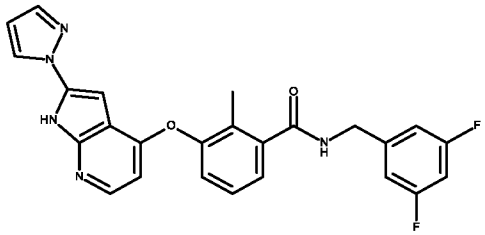
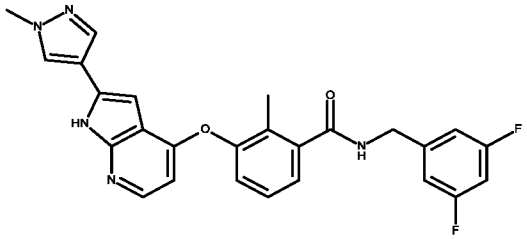
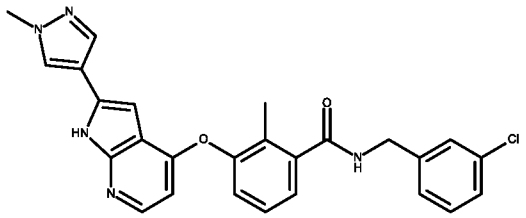
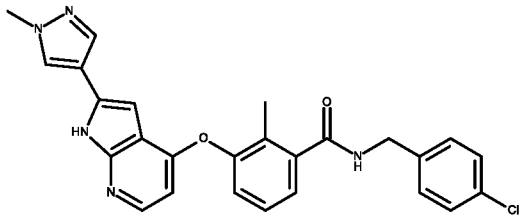
276	
277	
278	
279	
280	
281	

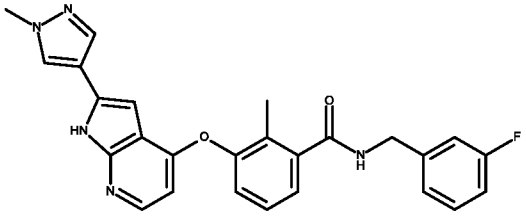
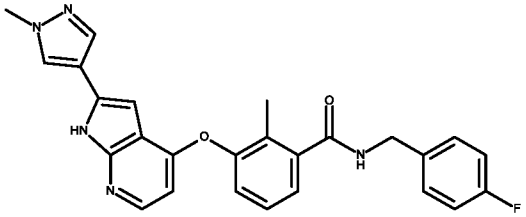
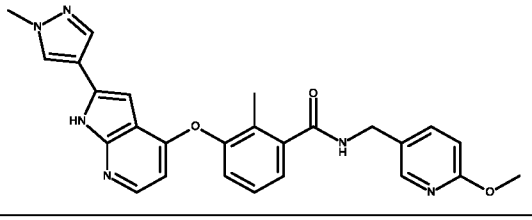
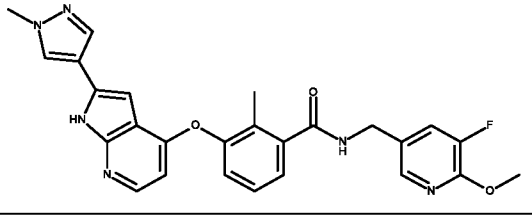
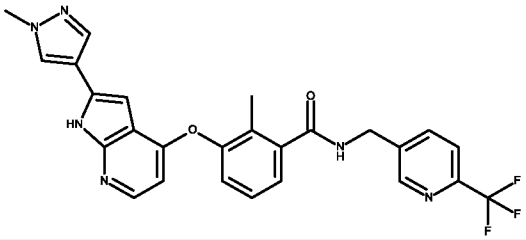
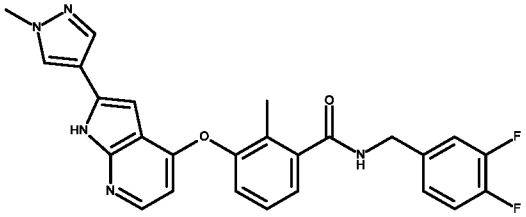
282	
283	
285	
286	
287	
288	

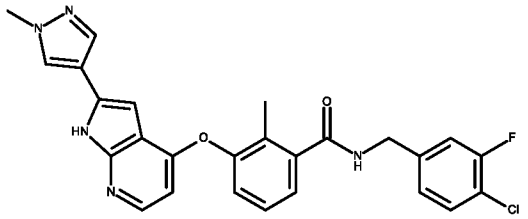
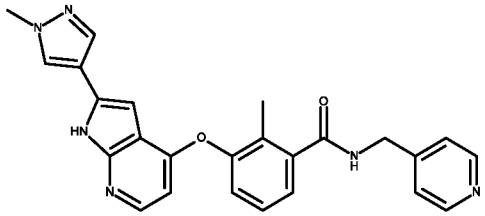
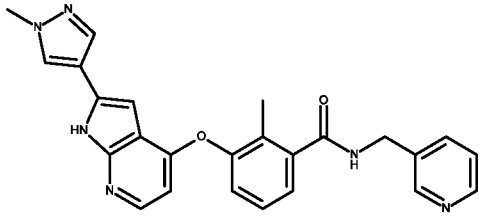
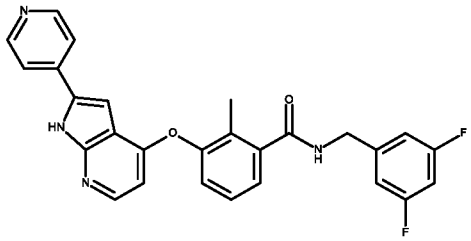
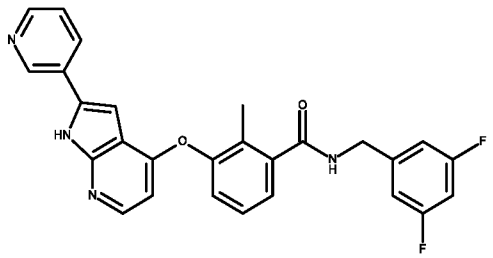
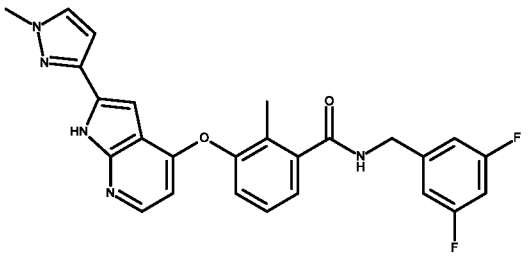
289	
290	
292	
293	
294	
295	
296	

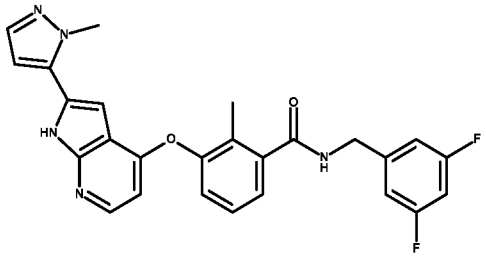
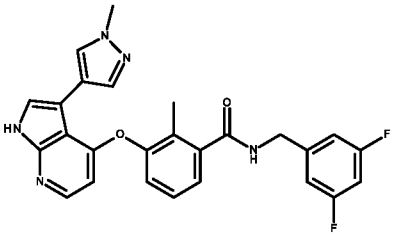
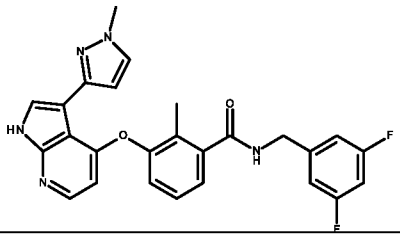
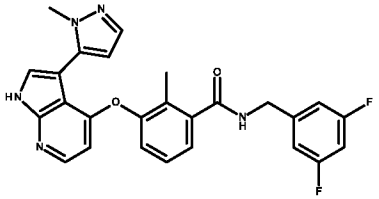
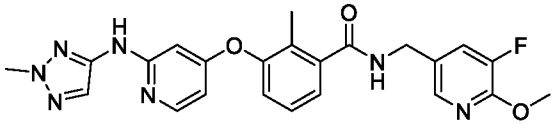
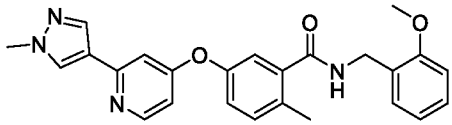
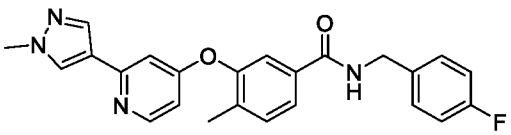
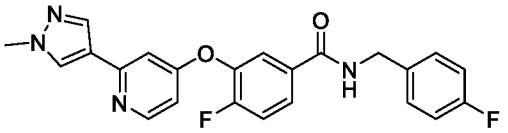
297	
302	
303	
304	
305	
306	
307	

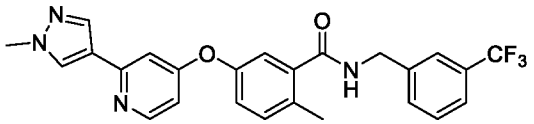
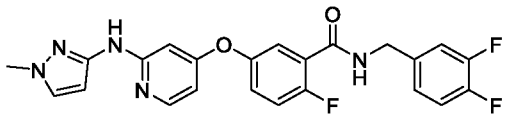
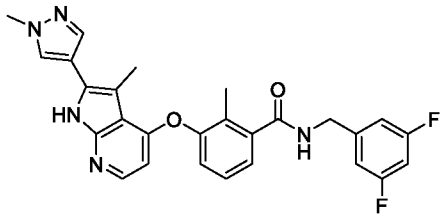
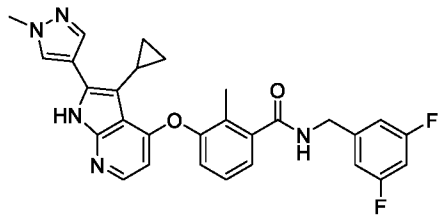
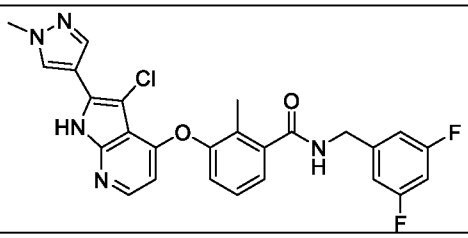
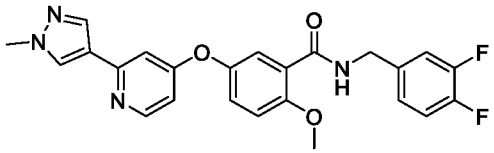
308	
309	
310	
311	
312	
313	
314	

318	
321	
322	
327	
328	
329	

330	
331	
332	
333	
334	
335	

336	
337	
338	
341	
342	
343	

344	
347	
348	
349	
350	
351	
352	
353	

354	
355	
356	
357	
358	
359	

Example 24: Cell-based assays: Biological assay measuring cell proliferation in cell lines

Compounds were evaluated in different cancer cell lines (Molm-13, M-NFS-60, HL-60 and P815) and in PDGFRα-BaF3 stable cell line. For each, cell proliferation were measured. The protocols of these assays are described below.

MOLM-13: Exponential growing MOLM-13 cells (DSMZ, ACC-554) were seeded at 2.10^4 per 200 µl of complete medium. 20 µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO_2.

Untreated cells and positive control (0,5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO_2, optical densities were measured at 450 nm and 620 nm for the background on microplate reader (Envision 2105, Perkinelmer).

M-NFS-60: Exponential growing M-NFS-60 cells (ATCC, CRL-1838) were seeded at 10^4 per 200 µl of complete medium with beta-mercaptoethanol and M-CSF (62 ng/mL) or IL34 (500 ng/mL). Twenty µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO_2. Untreated cells and positive control (0.5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO_2, optical densities were measured at 450 nm and 620 nm for the background on microplate reader (Envision 2105, Perkinelmer).

HL-60: Exponential growing HL-60 cells (DSMZ, ACC-3) were seeded at 2.10^4 per 200 µl of complete RPMI medium. 20 µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO_2. Untreated cells and positive control (0.5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO_2, optical densities were measured at 450 nm and 620 nm for the background on microplate reader (Envision 2105, Perkinelmer).

IC50 were measured and some biological results of these assays are presented in the following table.

P-815: Exponential growing P-815 cells (DSMZ, ACC-1) were seeded at 2.10^4 per 200 µl of complete RPMI medium. Twenty µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO2. Untreated cells and positive control (0,5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of

incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO2, optical densities were measured at 450 nm and 620 nm for the background on microplate reader (Envision 2105, Perkinelmer).

BaF3-PDGFRα: Exponential growing BaF3 cells stably transfected with a plasmid encoding the fusion gene GFP-ETV6-PDGFRA (ABMGood , T3082) were seeded at 5.10^3 per 200 µl of complete RPMI medium. Twenty µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO2. Untreated cells and positive control (0,5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO2, optical densities were measured at 450 nm and 620 nm for the background on microplate reader (Envision 2105, Perkinelmer).

IC50 were measured and some biological results of these assays are presented in the following table.

NB IC50 are reported as follows

> 1000 nM	*200-1000 nM*	*< 200 nM*

Table 2: Results biological cell-based assay measuring cell proliferation in cell lines

Compounds	MOLM-13	M-NFS-60	HL-60	P815	BaF3 PDGFRα
Pexidartinib					
Edicotinib					
Nintedanib			ND		
CC3					ND
CC7			ND	ND	
CC10			ND	ND	
CC11			ND	ND	
CC20			ND	ND	
CC24			ND	ND	
CC25			ND	ND	

CC37			ND	ND	
CC38			ND	ND	
CC39			ND	ND	
CC40			ND	ND	
44			ND		
45			ND		
51					ND
54					ND
58					ND
68					
69					
70					
71					
72					
73					
74					
75					
76					
77			ND		
78					
79			ND	ND	
80					
81					
82					
83					
84					
85			ND		
86					
87					
88					
89					
90					
91					
92					
93					
94					
95					
96					
97					
98			ND	ND	
99			ND		
100					

101					
103					
104					
105					
106			ND		
107			ND		
108			ND		
110			ND		
111			ND		
112			ND		
113			ND		
114			ND		
115			ND		
116			ND		
120					
121			ND		
122					
123					
124					
125					
126					
127					
128					
129					
130					
131			ND		
132			ND		
133			ND		
134			ND		
135			ND		
136			ND		
137			ND		
138			ND		
139			ND		
140			ND		
141			ND		
142			ND		
143			ND		
144			ND		
145			ND		
146			ND		
147			ND		

148			ND		
149			ND		
150			ND		
151			ND		
152			ND		
153			ND		
154			ND		
155			ND	ND	
156			ND	ND	
157			ND	ND	
158			ND	ND	
159			ND	ND	
160			ND	ND	
161			ND	ND	
162			ND	ND	
163			ND	ND	
164			ND	ND	
165			ND	ND	
166			ND	ND	
167			ND	ND	
168					
169					
170					
171					
172					
173					
174			ND		
175			ND		
176			ND		
177			ND		
178			ND		
179			ND		
180			ND		
181			ND		
182			ND		
183			ND		
184					
185					
186					
187					
188			ND		
189			ND		

190					
191			ND		
192			ND		
193			ND		
194			ND		
195			ND		
196			ND		
197			ND		
200			ND		
201			ND		
202			ND		
203			ND		
204			ND		
205					
206			ND		
207			ND		
208			ND		
209			ND		
210			ND		
211					
212			ND		
213			ND		
214			ND		
215			ND		
216			ND		
217			ND		
218			ND	ND	
219			ND	ND	
220			ND	ND	
221			ND	ND	
222			ND	ND	
223			ND	ND	
224			ND	ND	
225			ND	ND	
226			ND	ND	
227			ND	ND	
228					
229					
230					
231					
232					
233			ND		

234			ND	ND	
235			ND	ND	
236			ND	ND	
237			ND	ND	
238			ND	ND	
239			ND	ND	
240			ND	ND	
241			ND	ND	
242			ND	ND	
243			ND	ND	
244			ND	ND	
245			ND	ND	
246			ND	ND	
247			ND	ND	
248			ND	ND	
249			ND	ND	
250			ND	ND	
251			ND	ND	
252			ND	ND	
253			ND	ND	
254			ND	ND	
255			ND	ND	
256			ND	ND	
257			ND	ND	
258			ND	ND	
259			ND	ND	
260			ND	ND	
261			ND	ND	
262			ND	ND	
263			ND	ND	
264			ND	ND	
265a			ND	ND	
265b			ND	ND	
266			ND	ND	
267			ND	ND	
268			ND	ND	
269			ND	ND	
270			ND	ND	
271			ND	ND	
272			ND	ND	
273			ND	ND	
274			ND	ND	

275			ND	ND	
276			ND	ND	
277			ND	ND	
278			ND	ND	
279			ND	ND	
280			ND	ND	
281			ND	ND	
282			ND	ND	
283			ND	ND	
285			ND	ND	
286			ND	ND	
287			ND	ND	
288			ND	ND	
289			ND	ND	
290			ND	ND	
292			ND		
293			ND		
294			ND		
295			ND		
296			ND		
297			ND		
302			ND		
303			ND		
304			ND		
305			ND		
306			ND		
307			ND		
308			ND		
309			ND		
310			ND	ND	
311			ND	ND	
312			ND	ND	
313			ND	ND	
314			ND	ND	
318			ND	ND	
321			ND	ND	
322			ND	ND	
327			ND	ND	
328			ND	ND	
329			ND	ND	
330			ND	ND	
331			ND	ND	

332			ND	ND	
333			ND	ND	
334			ND	ND	
335			ND	ND	
336			ND	ND	
337			ND	ND	
338			ND	ND	
341			ND	ND	
342			ND	ND	
343			ND	ND	
344			ND	ND	
347			ND	ND	
348			ND	ND	
349			ND	ND	
350				ND	
351				ND	
352				ND	
353				ND	
354				ND	
355				ND	
356			ND	ND	
357			ND	ND	
358			ND	ND	
359			ND	ND	

Example 25: Cell-based assays: Biological assay measuring cell proliferation in non-cancer cell lines

CSF1R receptor has been expressed in HEK cell lines following the protocols below.

HEK-CSF1R-STAT5-Luc: Exponential growing HEK293T cells (ATCC® CRL-3216™), ectopically expressing human CSF1R receptor (Origene) and five copies of a STAT5 response element (STAT5 RE, promega) that drives transcription of the luciferase reporter were seeded at 5.10^3 per 20 µl of complete DMEM medium. The next day, 2.25 µL of test compound dilution were added to each well and stimulated with 600 ng/ml of M-CSF. The plates were incubated for 24 h at 37 °C, 5% CO2. Unstimulated and stimulated cells served as reference for maximum and minimum induction. At the end of incubation 25 µl of Steady-Glo® Luciferase Assay System (Promega) were added after 5 min of

lysis, luminescence was measured on microplate reader (Envision 2105, Perkinelmer).

HEK-CSF1R-WST-1: Exponential growing HEK293T cells (ATCC® CRL-3216™), were seeded at 5.10^3 per 200 µl of complete DMEM medium. The next day, twenty µL of test compound dilution were added to each well and the plates were incubated for 72 h at 37 °C, 5% CO2. Untreated cells and positive control (0,5% triton X-100, for the last 15 min) served as reference for maximum and minimum viability. At the end of incubation 100 µl of supernatant were removed and replaced by 10 µl of WST-1 solution (Cell Proliferation Reagent WST-1, Roche Applied Science). After 3 h incubation at 37 °C, 5% CO2, optical densities were measured at 450 nm and 620 nm for the background, on microplate reader (Envision 2105, Perkinelmer).

IC50 were measured and some biological results of these assays are presented in the following table.

NB IC50 are reported as follows

> 500 nM	*100-500 nM*	*< 100 nM*

Table 3: Results biological cell-based assay measuring cell proliferation in non-cancer cell lines

Compounds	HEK-CSF1R-STAT5 Luciferase	HEK-CSF1R-STAT5 WST-1
Pexidartinib		
Edicotinib		
Nintedanib		
CC7		
CC10		
CC11		
CC20		
CC24		
CC25		
CC37		

CC38		
CC39		
CC40		
44		
45		
68		
69		
70		
71		
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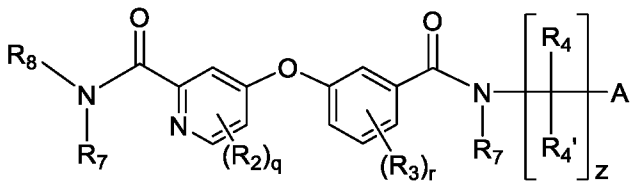
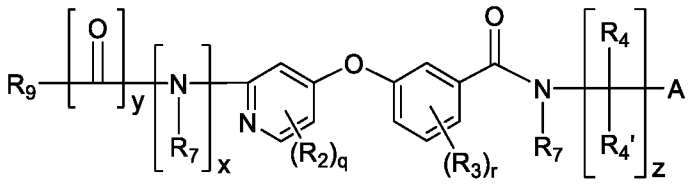
CLAIMS

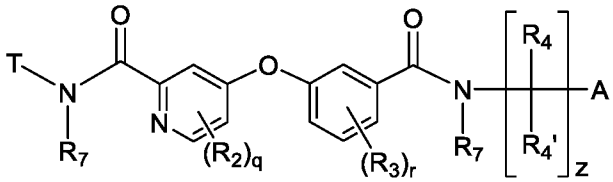
1. A compound (C) or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound (C) is chosen among those of formulae (I) to (VII):



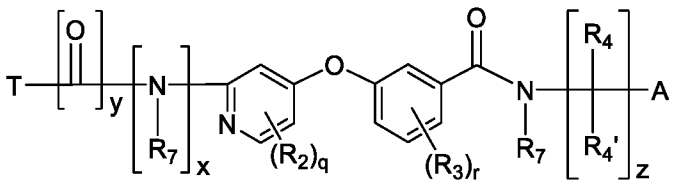
Formula (I)



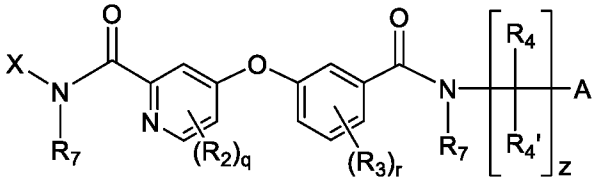
Formula (II)



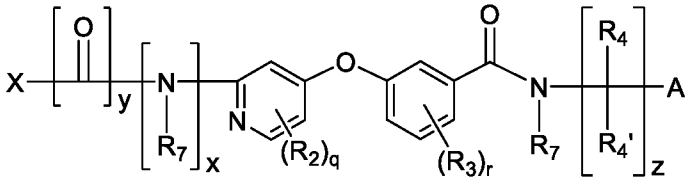
Formula (III)



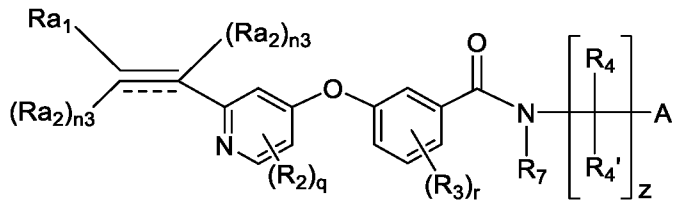
Formula (IV)



Formula (V)



Formula (VI)



Formula (VII)

wherein:

- each of A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $S(O)R_{12}$, SO_2R_{12}, $SO_2N(R_{11})_2$, $S(O)_3R_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, and heteroaryl substituents is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, COR_{11}, $CON(R_{11})_2$, $OC(O)R_{11}$, CN, or OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, C_{1-6} alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl.
- each of R_4 and R'_4, independently from each other and at each occurrence, are selected from hydrogen or C_{1-6} alkyl, and z is an integer in the range from 0 to 2; with the proviso that when z = 0, then A and R_7 may form together a saturated or unsaturated cyclic moiety;

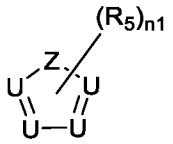
- each of R_7, independently from each other and at each occurrence is selected from hydrogen, C_{1-6} alkyl, cycloalkyl, wherein said alkyl and cycloalkyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, and CF_3;
- each of R_3, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{21}, SR_{21}, $N(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $OC(R_{21})_2O$, and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of r is an integer in the range from 0 to 3; with the proviso that when R_3 = NR_{21}, and R_7 = H, then R_3 and NR_7 may form together a saturated or unsaturated cyclic moiety;
- each of R_2, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CF_3, CN, NO_2, OR_{21}, SR_{21}, $N(R_{21})_2$, COR_{21}, $C(O)OR_{21}$, $CON(R_{21})_2$, $OC(O)R_{21}$, $OCON(R_{21})_2$, $NC(O)R_{21}$, $NCON(R_{21})_2$, $OC(R_{21})_2O$ and $OC(R_{21})_2C(R_{22})_2O$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, CF_3, COR_{21},

$CON(R_{21})_2$, $C(O)OR_{21}$, $N(R_{21})_2$, CN, or OR_{21}, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl substituent is further optionally substituted with heterocyclyl, $N(R_{11})_2$, or OR_{11}; and wherein each of R_{21} and R_{22}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl; each of q is an integer in the range from 0 to 2;

- each of x and y are independently integers equal to 0 or 1;
- R_8 is independently selected from the group consisting of C_{6-12} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl and heterocyclyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl;
- R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, $N(R_{11})_2$ and CN, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, an aryl group, an aralkyl group, an heterocyclyl group, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl,

heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl optionally substituted with a C_{1-4} alkyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, alkyl or aryl or heteroaryl amide, OR_{31} or $N(R_{32})_2$, wherein each of R_{31} and R_{32}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen and C_{1-4} alkyl, with the proviso that if x = 1 and y = 0, R_9 is different from heterocyclyl, and from C_{1-6} alkyl wherein said alkyl is optionally substituted with heterocyclyl; and with the proviso that if x=0 and y=0, R_9 is different from hydrogen, and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$; with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.

- each of T is independently the moiety of formula (T-a) herein below:



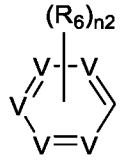
(T-a)

wherein:

- each of U, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen or C_{1-4} alkyl; with the proviso that at least one U is different from N;
- each of Z, independently from each other and at each occurrence is selected from $C(R)_2$, O, S and NR_7, wherein R, independently from each other and at each occurrence is selected from hydrogen or an C_{1-6} alkyl

which is optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein R_7 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, cycloalkyl, heterocyclyl, aryl, aralkyl and CF_3;

- each of R_5, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n1 is an integer in the range from 0 to 2;
- each of X is independently the moiety of formula (X-a) herein below:



(X-a)

wherein :

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is selected from hydrogen, OR_{11}, $N(R_{11})_2$, a C_{1-6} alkyl or a cycloalkyl which are optionally substituted by a halogen atom, an aryl group or an aralkyl group, wherein each of R_{11}, independently from each other and at each occurrence, is selected from hydrogen or C_{1-4} alkyl;
- each of R_6, independently from each other and at each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, SR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and

wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n2 is an integer in the range from 0 to 4;

- the dash bond represents an optional triple bond;
- R_{a1} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, , cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl.
- each of R_{a2}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, $C(O)OR_{11}$, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, COR_{11}, and $C(O)OR_{11}$, and each optional alkyl, alkenyl, cycloalkyl, phenyl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, phenyl, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl, wherein said alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl or heterocyclyl; and wherein n3 is an integer equal to 0 or 1; with the proviso that when the dash bond represents a triple bond, n3 is 0;

wherein said cycloalkyl is a monocyclic, bicyclic or tricyclic ring system of 3-6 ring members per ring; said heterocyclyl is a saturated, partially saturated or completely saturated monocycle, bicycle or tricycle containing 3 to 12 carbon atoms and 1 or 2 heteroatoms independently selected from O or N; said aryl is phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of 5-7 ring members; said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

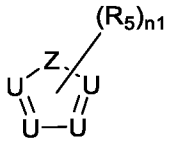
2. The compound (C) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein x and y are as defined as in claim 1 and wherein:

- each of A is independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, wherein said cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl are optionally substituted with one or more substituents independently selected from the group consisting of halo, NO_2, C_{1-6} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR_{11}, SR_{11}, $N(R_{11})_2$, $OC(R_{11})_2O$, $OC(R_{11})_2C(R_{11})_2O$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$ $NR_{11}COR_{12}$, COR_{11}, $C(O)OR_{11}$, $CON(R_{11})_2$, $OC(O)R_{11}$, and $OCON(R_{11})_2$, and each optional alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl substituent is further optionally substituted with halo, NO_2, C_{1-6} alkyl, cycloalkyl, aryl, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11} and R_{12}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and CF_3, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, or heterocyclyl;
- each of R_4 and R'_4, independently from each other and at each occurrence, are selected from hydrogen or C_{1-6} alkyl; and wherein z is an integer equal to 1;

- each of R_7, independently from each other and at each occurrence is hydrogen or C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl and the like;
- each of R_3, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, CF_3, CN, OR_{21}, and $N(R_{21})_2$, wherein said alkyl, cycloalkyl and heterocyclyl, are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, CF_3, $N(R_{21})_2$, CN, or OR_{21}; and wherein each of R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl, and wherein said alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl substituents are optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, or aryl; each of r is an integer equal to 0 or 1
- each of R_2, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, halo, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, CN, OR_{21}, and $N(R_{21})_2$, wherein said alkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from halo, C_{1-6} alkyl, cycloalkyl, $N(R_{21})_2$, CN, or OR_{21}; wherein R_{21}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, and aralkyl.
- R_8 is selected from the group consisting of C_{6-12} alkyl, cycloalkyl and heterocyclyl, wherein said alkyl, cycloalkyl, and heterocyclyl are optionally substituted by a halogen atom, CF_3, $N(R_{11})_2$, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, and C_{1-6} alkyl.
- R_9 is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, $N(R_{11})_2$, and CN, wherein said alkyl, and cycloalkyl, are optionally substituted by a halogen atom, CF_3, CN, or OR_{11}; and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and CF_3, wherein

said alkyl, and alkenyl substituents are optionally substituted with an heteroaryl group optionally substituted with a C_{1-4} alkyl with the proviso that if x=0 and y=0, R_9 is different from hydrogen and C_{1-6} alkyl, wherein said alkyl is optionally substituted with heterocyclyl and $N(R_{11})_2$ and with the proviso that when x=0 and y=0, R_9 and R_2 may form together a saturated or an unsaturated cyclic moiety; with the proviso that when x=0 and y=0 and when R_9 and R_2 form together a saturated or an unsaturated cyclic moiety, R_9 is NR_{11}; with the proviso that when x=1 and y=1, R_9 is different from $N(R_{11})_2$; and with the proviso that when x=0, y=0 and z=0, R_9 is different from pyrrole.

- each of T is independently the moiety of formula (T-a) herein below:



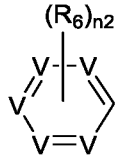
(T-a)

wherein:

- each of U is selected independently from each other and at each occurrence, from C, C-halo, C-R, or N; wherein R is hydrogen or C_{1-4} alkyl with the proviso that at least one U is different from N. More preferably, each of U is selected, independently from each other and at each occurrence, from C, C-R or N; wherein R is hydrogen or C_{1-4} alkyl with the proviso that at least one U is different from N;
- each of Z, is, independently from each other and at each occurrence, preferably selected from the group consisting of CH_2, and O, S and NR_7, wherein R_7 is an hydrogen, or a C_{1-4} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, and isobutyl;
- each of R_5, independently from each other and at each occurrence is preferably selected from the group consisting of C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$,

$P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; each of n1 is an integer equal to 1 or 2

- each of X is independently the moiety of formula (X-a) herein below:



(X-a)

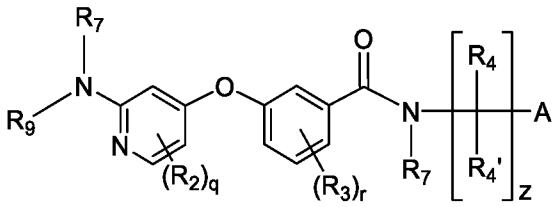
wherein :

- each of V, independently from each other and at each occurrence, is selected from the group consisting of C, C-halo, C-R, and N; wherein R is hydrogen or C_{1-4} alkyl ;
- each of R_6, independently from each other and at each occurrence is preferably selected from the group consisting of C_{1-6} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, halo, CF_3, OR_{11}, $N(R_{11})_2$, $COOR_{11}$, $CO(R_{11})_2$, $CON(R_{11})_2$, and each optional alkyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl substituent is further optionally substituted with halo, C_{1-6} alkyl, cycloalkyl, aryl, heterocyclyl, $N(R_{11})_2$, CN, OR_{11}, $C(=O)OR_{11}$, $P(=O)(OR_{11})_2$, $P(=O)(R_{11})_2$, CN or CF_3 and wherein each of R_{11}, independently from each other and at each occurrence, is selected from the group consisting of hydrogen, C_{1-6} alkyl, cycloalkyl, and heterocyclyl; and wherein n2 is an integer equal to 0, 1 or 2
- the dash bond represents an optional triple bond;
- R_{a1} is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-4} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, or C_{1-4} alkyl.
- each of R_{a2} is independently selected from the group consisting of C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, wherein said alkyl

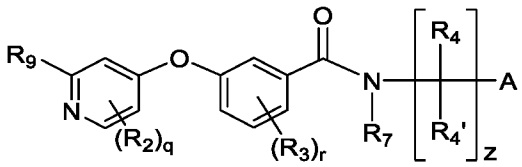
cycloalkyl, heterocyclyl, aryl, heteroaryl and aralkyl are optionally substituted by halo, NO_2, C_{1-4} alkyl, cycloalkyl, heterocyclyl, phenyl, heteroaryl, CF_3, CN, OR_{11}, $N(R_{11})_2$, and wherein each of R_{11} is selected from the group consisting of hydrogen, or C_{1-4} alkyl.

wherein said cycloalkyl is a monocyclic, bicyclic or tricyclic ring system of 3-6 ring members per ring; said heterocyclyl is a saturated, partially saturated or completely saturated monocycle, bicycle or tricycle containing 3 to 12 carbon atoms and 1 or 2 heteroatoms independently selected from O or N; said aryl is phenyl, naphthyl or anthracenyl optionally carbocyclic fused with a cycloalkyl or heterocyclyl of 5-7 ring members; said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

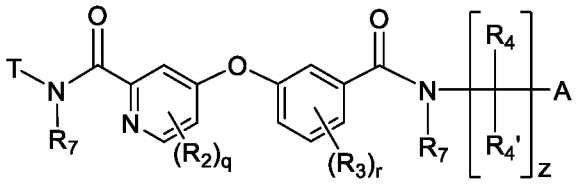
3. The compound (C) of formulae (II) or (III), according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (II-a) or (II-b) [compounds (C) of class (II) hereinafter] or of formula (III-a) [compounds (C) of class (III) hereinafter] :



Formula (II-a)



Formula (II-b)

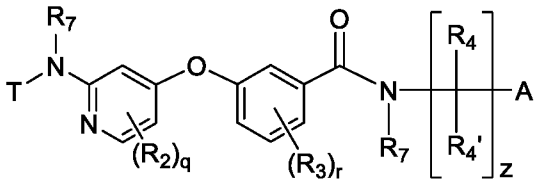


Formula (III-a)

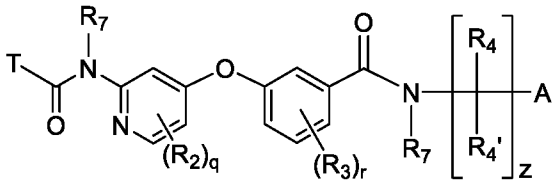
wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, R_9 and T are as defined as in claim 1 or in

claim 2.

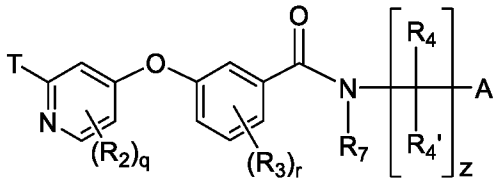
4. The compound (C) of formula (IV) or formula (VI), according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (IV-a) to (IV-c) [compounds (C) of class (IV) hereinafter] or of formula (VI-a) to (VI-c) [compounds (C) of class (VI) hereinafter]:



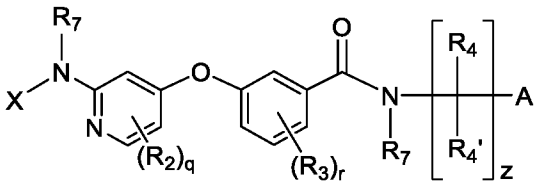
Formula (IV-a)



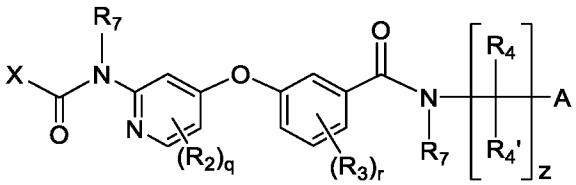
Formula (IV-b)



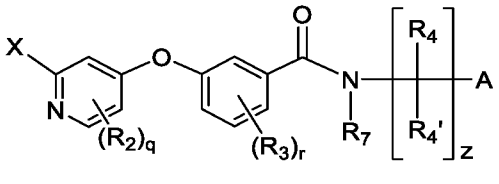
Formula (IV-c)



Formula (VI-a)



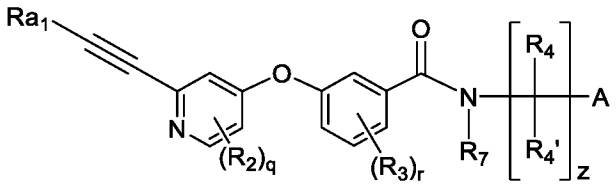
Formula (VI-b)



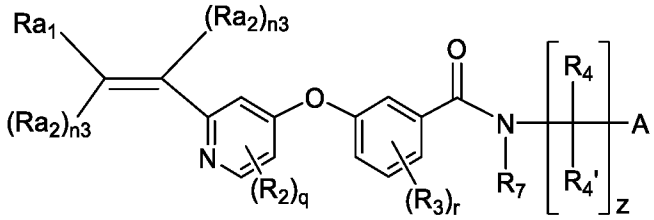
Formula (VI-c)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, T, and X are as defined as in claim 1 or in claim 2.

5. The compound (C) of formula (VII), according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (VII-a) or (VII-b) [compounds (C) of class (VII) hereinafter] :



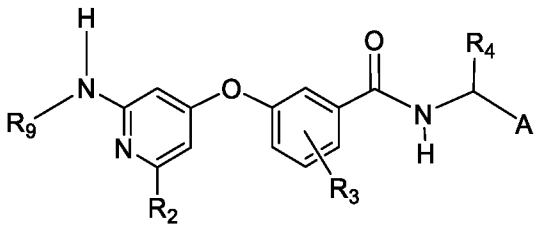
Formula (VII-a)



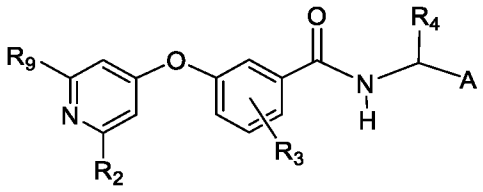
Formula (VII-b)

wherein A, R_4, R_4', z, R_7, R_3, r, R_2, q, R_{a1}, R_{a2} and n3 are as defined as in claim 1 or in claim 2.

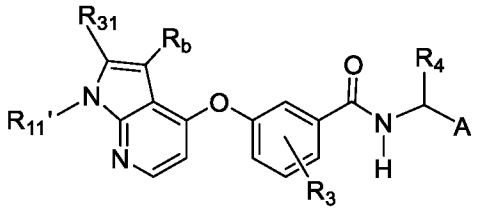
6. The compound (C) of formulae (II) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (II-a-1) or (II-b-1) or (II-c-1) [compounds (C) of class (II) hereinafter]:



Formula (II-a-1)



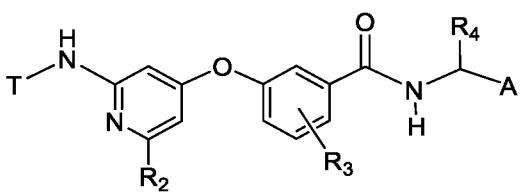
Formula (II-b-1)



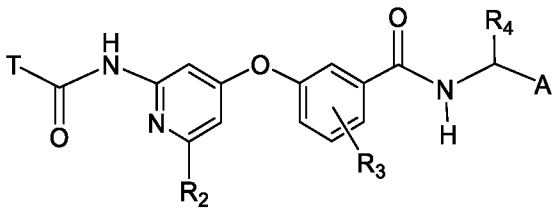
Formula (II-c-1)

wherein A, R_4, R_3, R_2, and R_9 have the same meaning as defined above for formula (II); wherein R_{31} is a heteroaryl which is optionally substituted with a C_{1-4} alkyl, wherein R_{11}' is hydrogen or C_{1-4} alkyl; and wherein R_b is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-6} cycloalkyl.
wherein said heteroaryl is a monocyclic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing 1-3 heteroatoms independently selected from O or N.

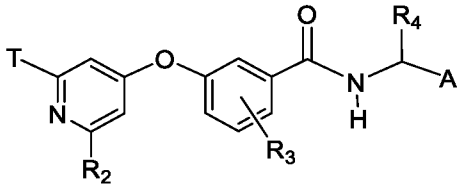
7. The compound (C) of formulae (IV) or (VI) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (IV-a-1) to (IV-c-1) [compounds (C) of class (IV) hereinafter] or of formula (VI-a-1) to (VI-c-1) [compounds (C) of class (VI) hereinafter]:



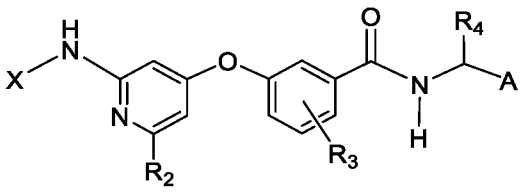
Formula (IV-a-1)



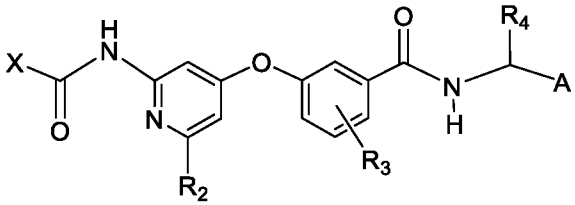
Formula (IV-b-1)



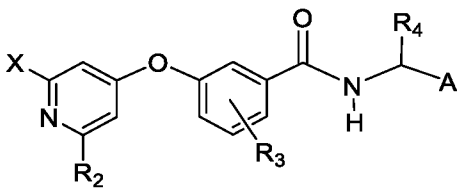
Formula (IV-c-1)



Formula (VI-a-1)



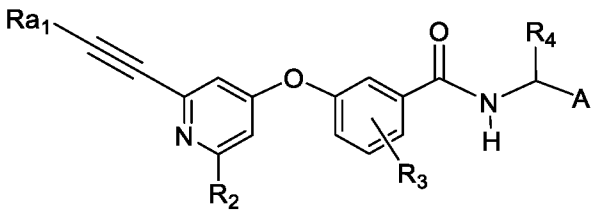
Formula (VI-b-1)



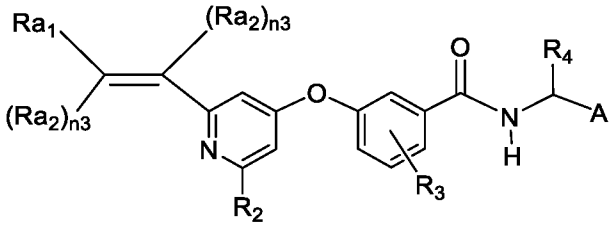
Formula (VI-c-1)

wherein A, R_4, R_3, R_2, T, and X are as defined as in claim 1 or in claim 2.

8. The compound (C) of formula (VII) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (VII-a-1) or (VII-b-1) [compounds (C) of class (VII) hereinafter]:



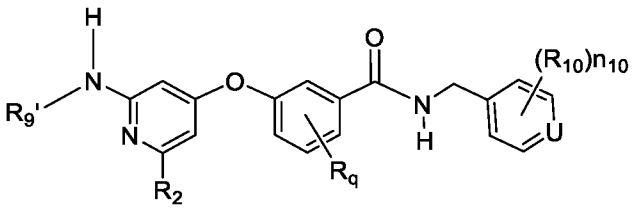
Formula (VII-a-1)



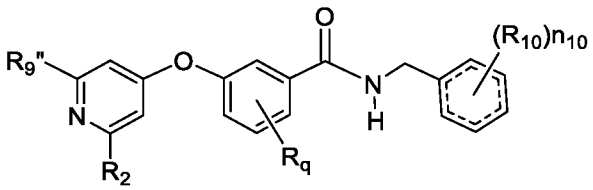
Formula (VII-b-1)

wherein A, R_4, R_3, R_2, R_{a1}, R_{a2}, and n3 are as defined as in claim 1 or in claim 2.

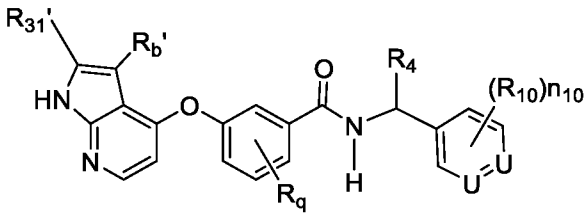
9. The compound (C) of formula (II) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (II-a-2), or (II-b-2), or (II-c-2) [compounds (C) of class (II) hereinafter]:



Formula (II-a-2)



Formula (II-b-2)

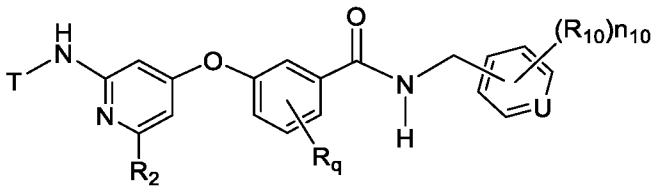


Formula (II-c-2)

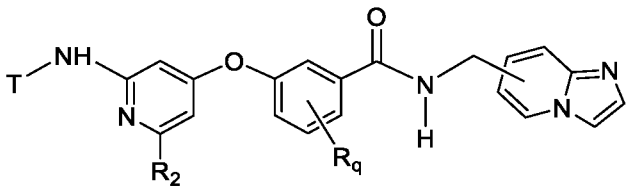
wherein:

- each of R_9' is selected from the group consisting of hydrogen, CN and C_{3-6} cycloalkyl such as cyclopropyl;
- each of R_9" is selected from the group consisting of hydrogen, C_{1-4} alkyl, CN and C_{3-6} cycloalkyl such as cyclopropyl;
- each of R_2 is independently selected from hydrogen or halo;
- each of R_q is independently selected from the group consisting of hydrogen, CH_3, OCH_3, and halo, such as F or Cl;
- each of R_{10} is independently selected from the group consisting of H, F, Cl, OCH_3, or CF_3;
- each of U is selected from the group consisting of C, C-R_{10} and N;
- n_{10} is an integer equal to 0, 1 or 2;
- each of R_{31}' is selected from the group consisting of pyrazyl, N-methylpyrazyl, and pyridyl.
- R_b' is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, and C_{1-4} cycloalkyl; preferably R_b' is selected from the group consisting of Cl, CH_3, and cyclopropyl;
- the dash bond represents an optional double bond.

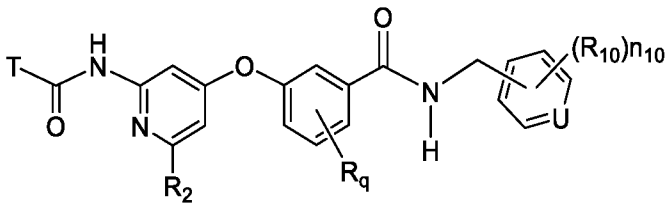
10. The compound (C) of formula (IV) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein said compound is of formula (IV-a-2-1), (IV-a-2-2), (IV-b-2-1), (IV-b-2-2), or (IV-c-2-1) to (IV-c-2-4) [compounds (C) of class (IV) hereinafter]:



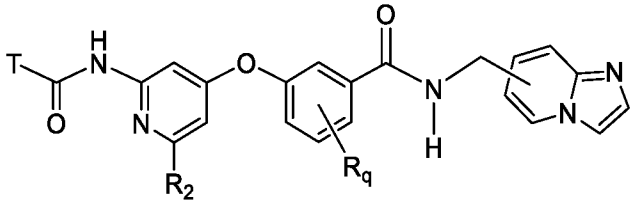
Formula (IV-a-2-1)



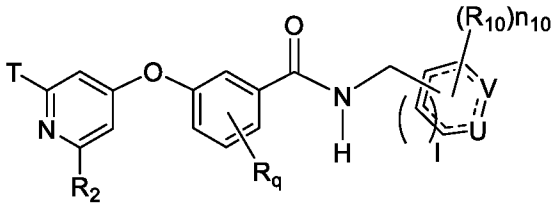
Formula (IV-a-2-2)



Formula (IV-b-2-1)



Formula (IV-b-2-2)



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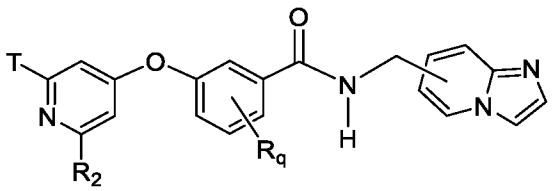
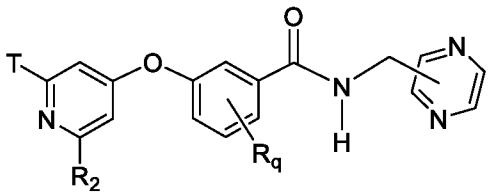
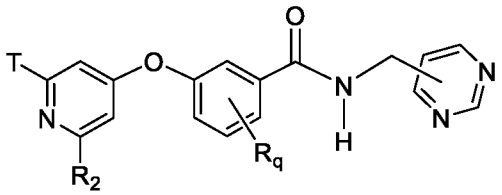


Formula (IV-c-2-2)



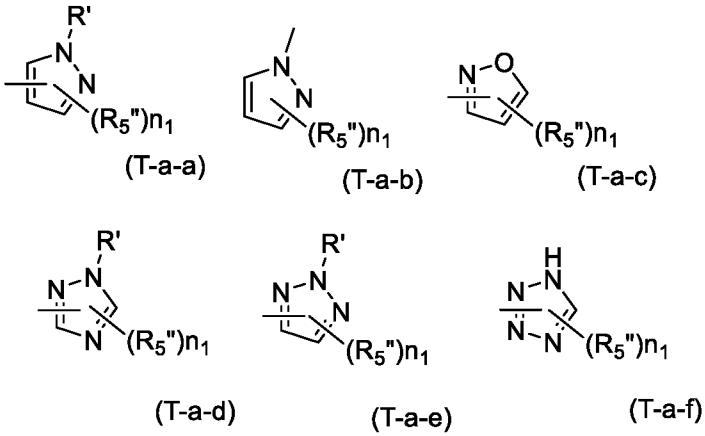
Formula (IV-c-2-3)



Formula (IV-c-2-4)

wherein:

- T is, independently from each other and at each occurrence, selected from the moiety of formula (T-a-a) to (T-a-f) herein below:

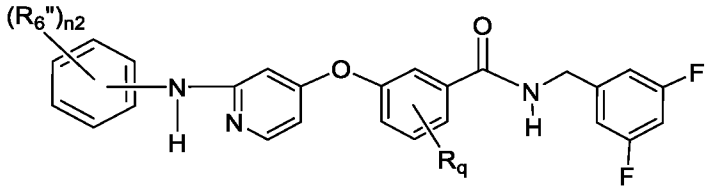


wherein:

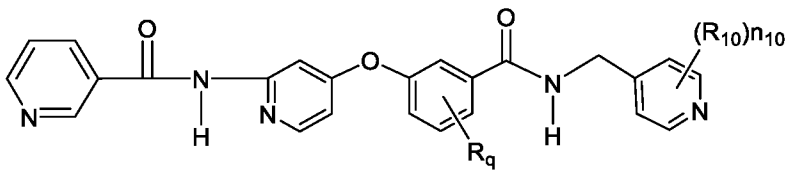
- each of R' is independently hydrogen, C_{1-4} alkyl, cycloalkyl selected from the group consisting of cyclopropyl and cyclobutyl; heterocyclyl selected from the group consisting of oxetanyl, tetrahydropyranyl, azetdinyl, and piperidinyl; wherein said alkyl is further optionally substituted with F, OC_{1-4} alkyl, $P(=O)(OC_{1-4}alkyl)_2$, $P(=O)(C_{1-4}alkyl)_2$, CN, cyclopropyl, or cyclobutyl; and wherein said heterocyclyl is further optionally substituted with $C(=O)(OC_{1-4}alkyl)$,
- each of $R"_5$ is independently selected from the group consisting of hydrogen, C_{1-4} alkyl, CF_3 and cyclopropyl;
- each of n1, independently from each other and at each occurrence is an integer equal to 0, 1 or 2.
- R_2 is independently hydrogen, halo, or NH_2;
- each of R_q is independently selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl;
- each of R_{10} is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, CF_3, OC_{1-4}alkyl, CN,
- each of U and V are independently C, C-R_{10} or N;
- n_{10} is an integer equal to 0, 1 or 2.

11. The compound (C) of formula (VI) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or

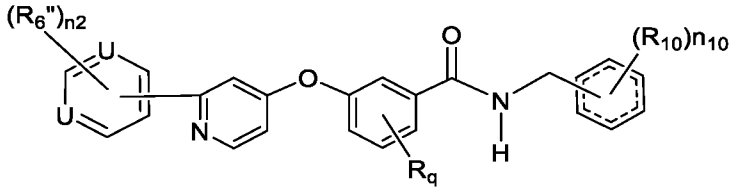
stereoisomer thereof, wherein said compound is of formula (VI-a-2) to (VI-c-2) [compounds (C) of class (VI) hereinafter]:



Formula (VI-a-2)



Formula (VI-b-2)



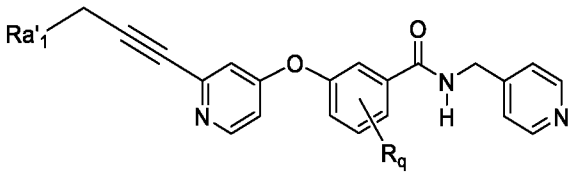
Formula (VI-c-2)

wherein

- each of R"$_6$ is independently selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, $N(R_{21})_2$, OR_{21}; heterocyclyl selected from the group consisting of pyrrolidyl, piperidyl, morpholinyl, piperazyl and a pyrazyl, wherein said heterocyclyl and pyrazyl are optionally substituted with C_{1-4} alkyl, and wherein R_{21} is a C_{1-4} alkyl.
- each of R_q is independently selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl.
- each of R_{10} is independently selected from the group consisting of hydrogen, halo, OC_{-4} alkyl, and CN;
- each of U is independently C, C-R_{10} or N;
- n_{10} is an integer equal to 0, 1 or 2
- n_2 is an integer equal to 0, 1 or 2.

12. The compound (C) of formula (VII) according to claim 1, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or

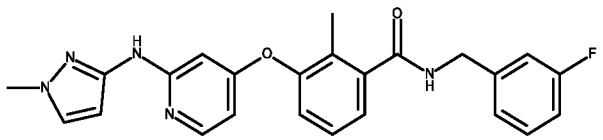
stereoisomer thereof, wherein said compound is of formula (VII-a-2) [compounds (C) of class (VI) hereinafter]:



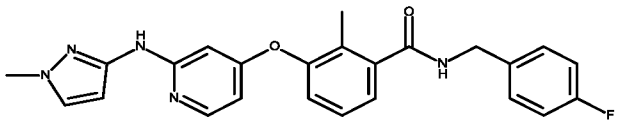
Formula (VII-a-2)

wherein Ra'_1 is selected from the group consisting of benzyl, pyrazyl, OH, OC_{1-4} alkyl, NH_2, and $NH(C_{1-4}$ alkyl) and wherein R_q is selected from the group consisting of H, CH_3, OCH_3, and halo, such as F or Cl; preferably R_q is H or CH_3..

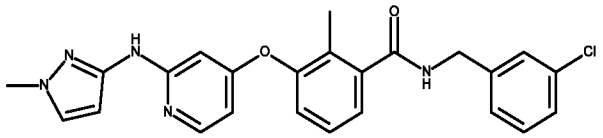
13. The compound (C) of formulae (IV-a-1), (IV-b-1), or (IV-c-1), (VI-a-1), (VI-b-1) or (VI-c-2) according to claim 7, or the N-oxide, pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or stereoisomer thereof, wherein compound of formulae (IV-a-1), (IV-b-1), (IV-c-1), (VI-a-1), (VI-b-1) or (VI-c-2) is a compound according to formula (XXXVII) to (CCLX) herein below:



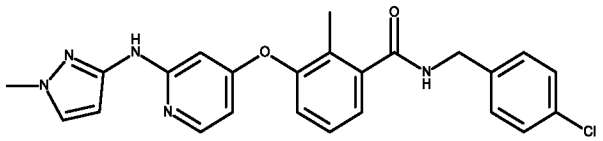
Formula (XXXVII)



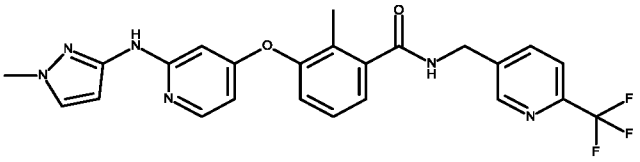
Formula (XXXVIII)



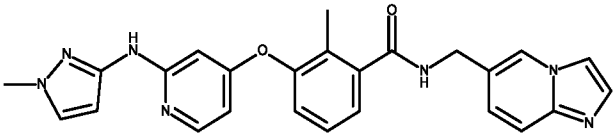
Formula (XXXIX)



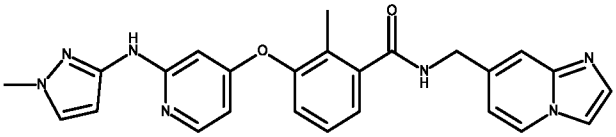
Formula (XL)



Formula (XLI)



Formula (XLII)



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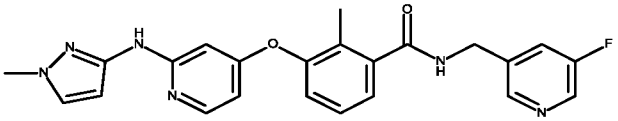

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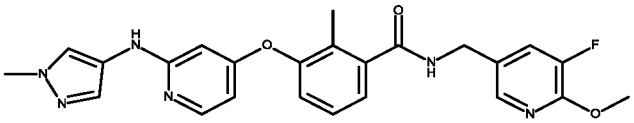
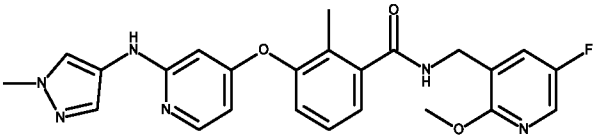
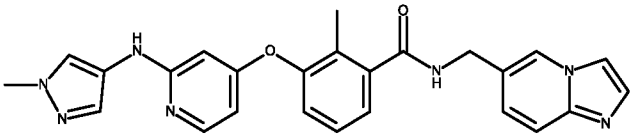


Formula (XLV)



Formula (XLVI)



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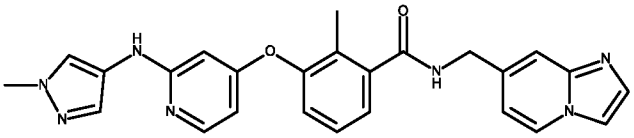

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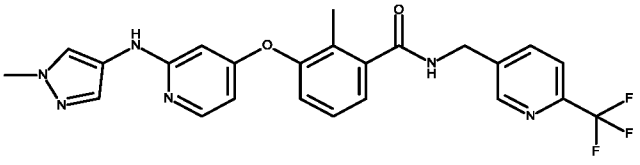

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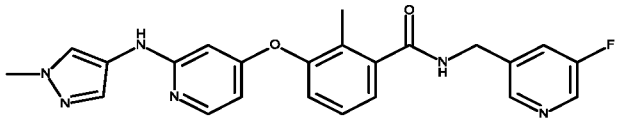
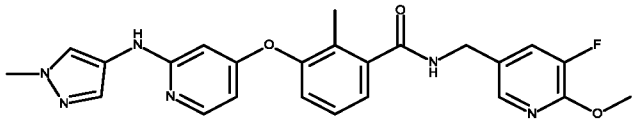
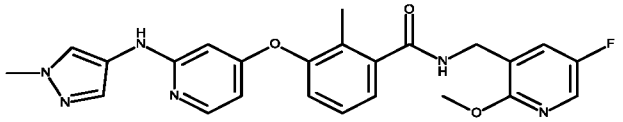


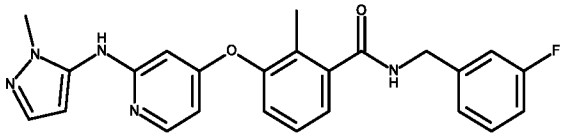
Formula (L)



Formula (LI)



Formula (LII)



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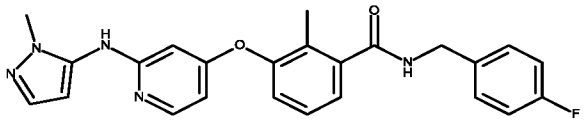

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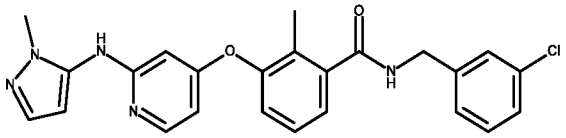
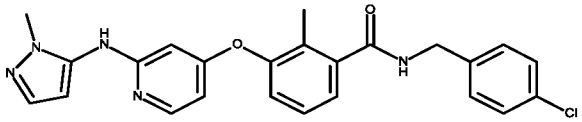


Formula (LV)



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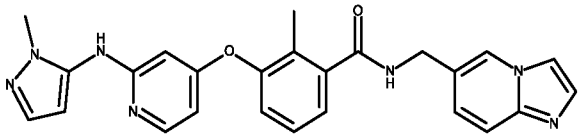

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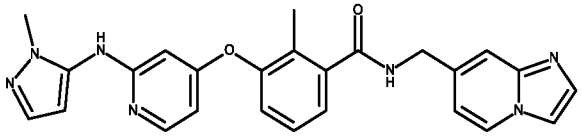

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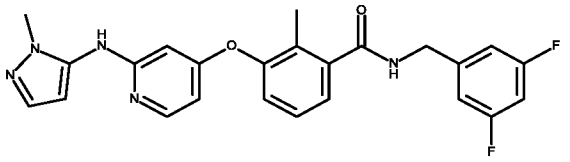

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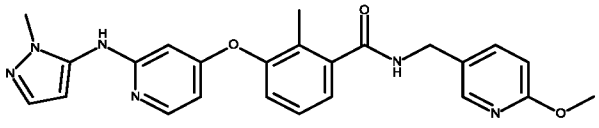

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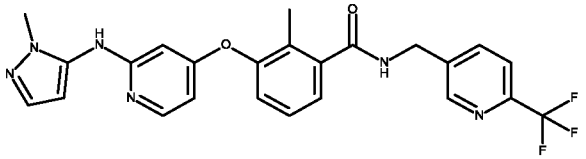
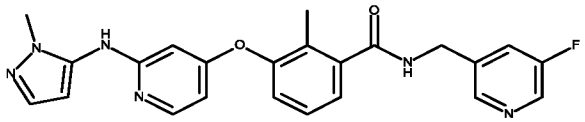


Formula (LXI)



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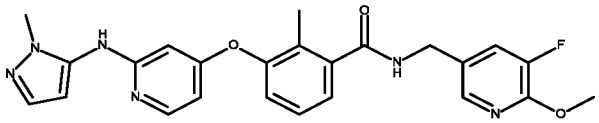

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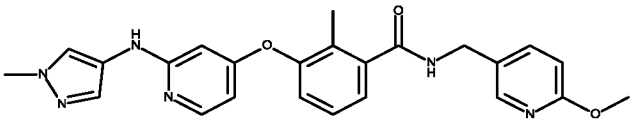

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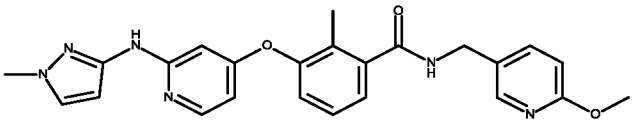

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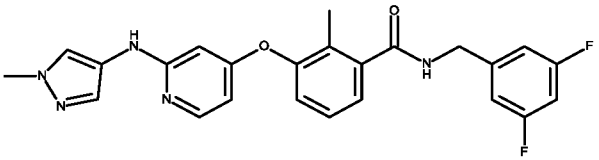
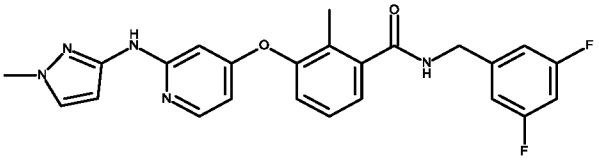


Formula (LXVI)



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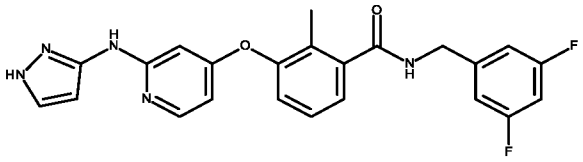

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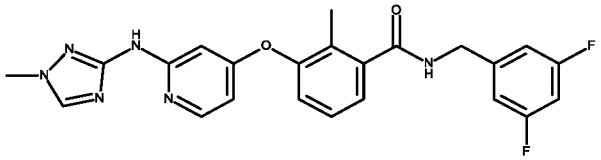

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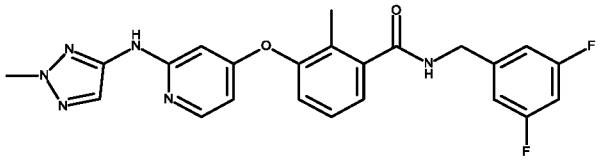

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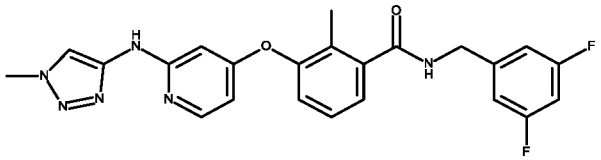

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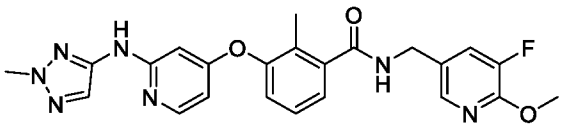

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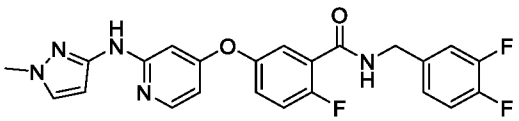

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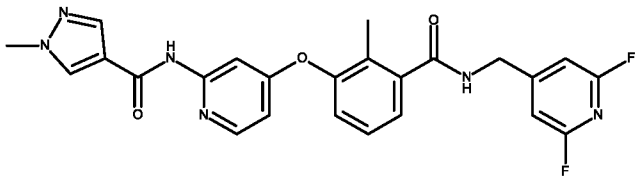

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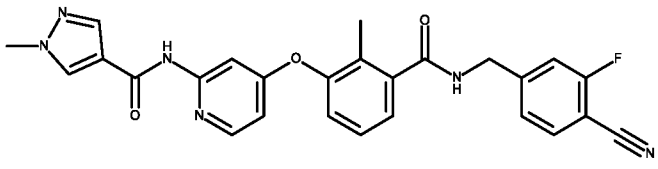

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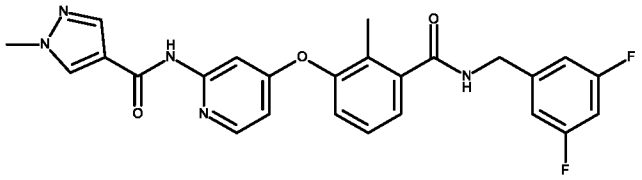

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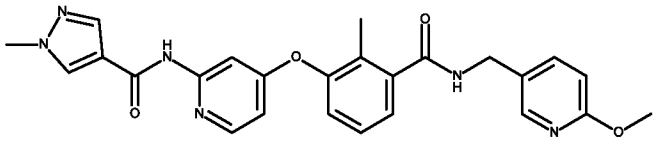

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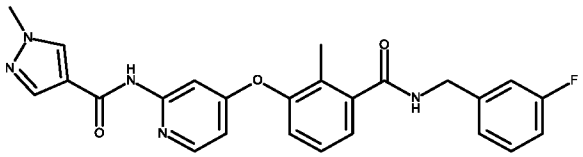
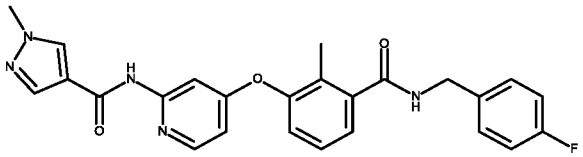


Formula (LXXVI)



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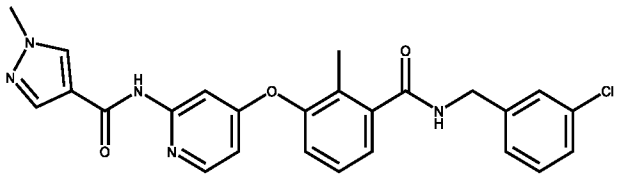

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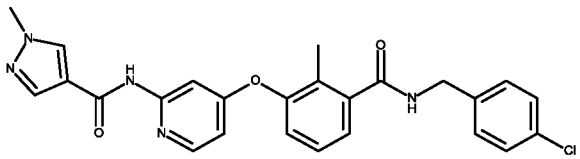

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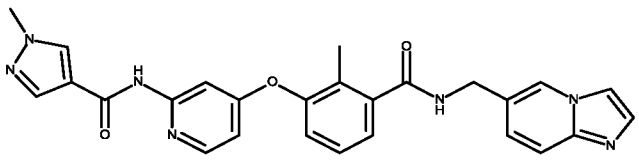

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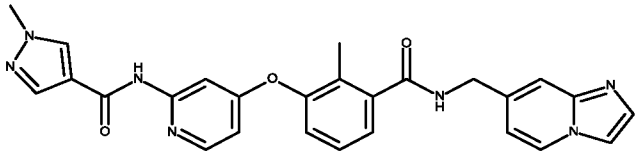

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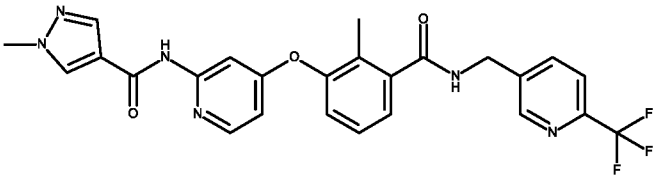

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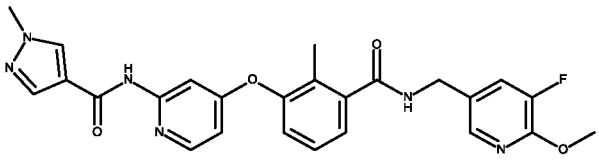

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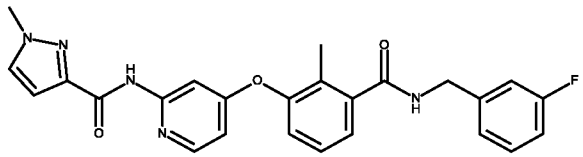

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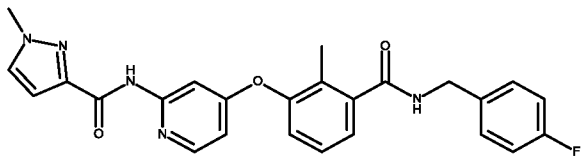

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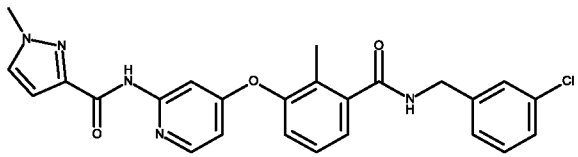

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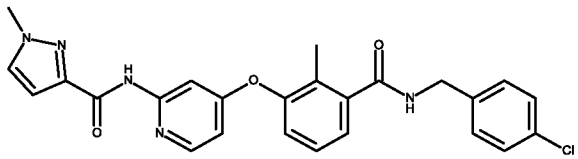

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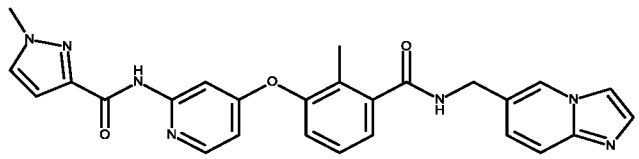

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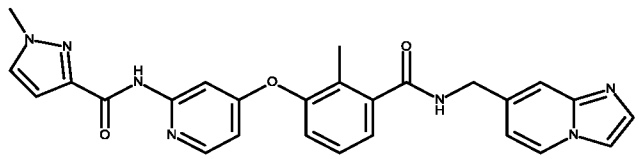

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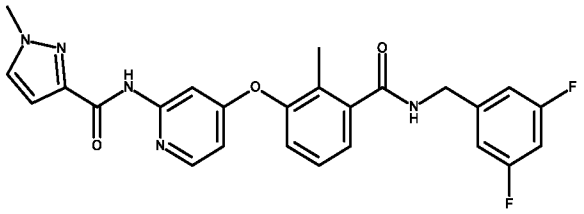
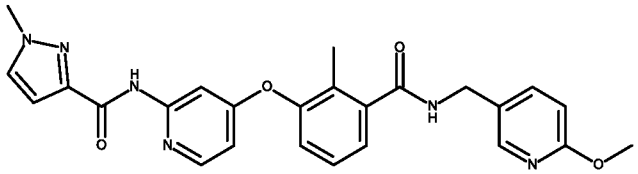


Formula (XC)



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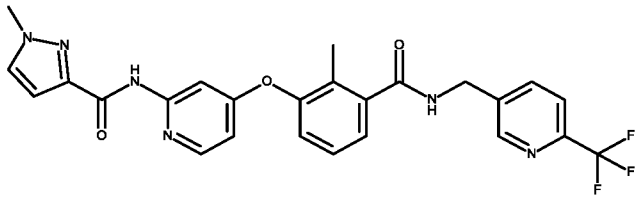
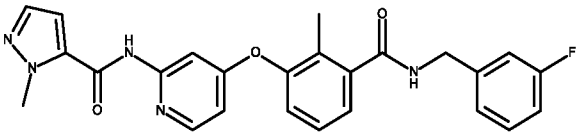


Formula (XCII)



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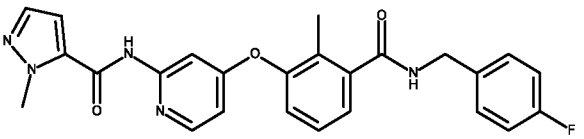

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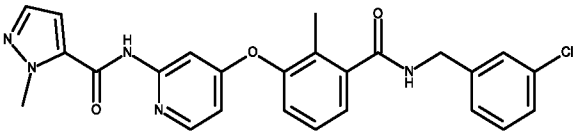

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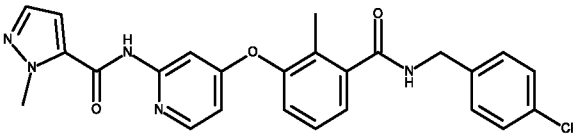

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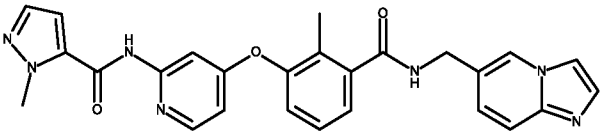
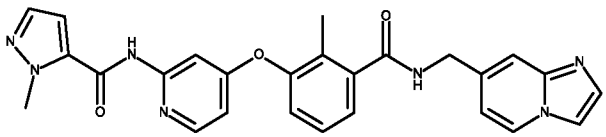


Formula (XCVII)



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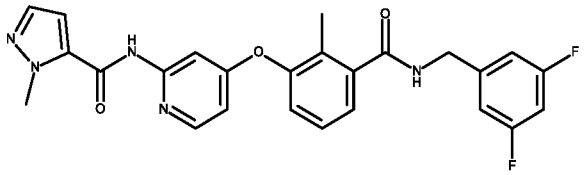

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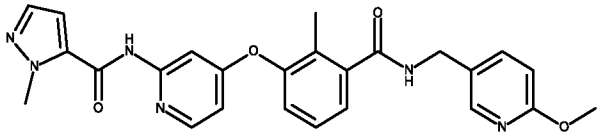
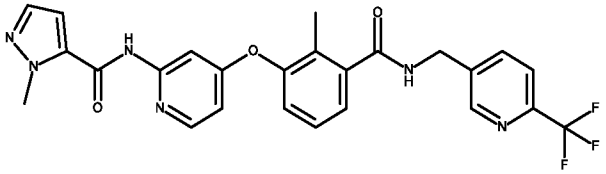


Formula (C)



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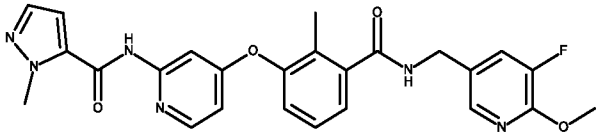

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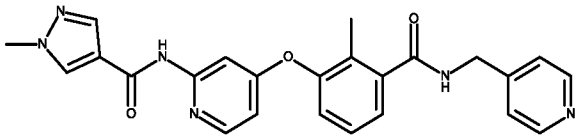

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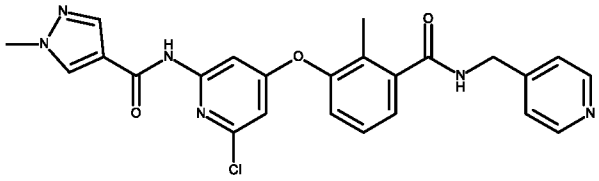
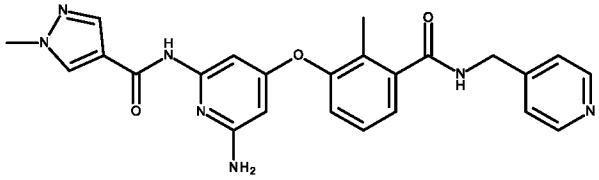
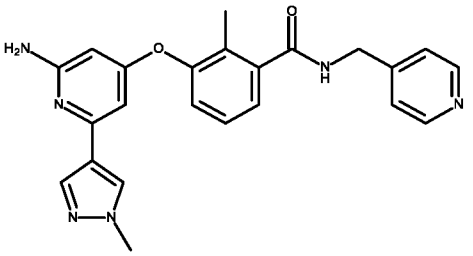


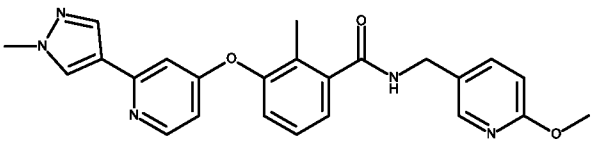
Formula (CIV)



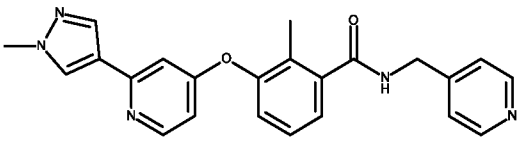
Formula (CV)



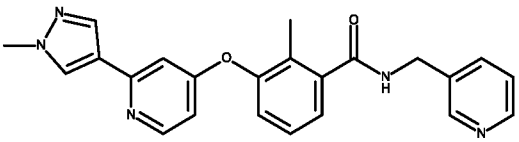
Formula (CVI)



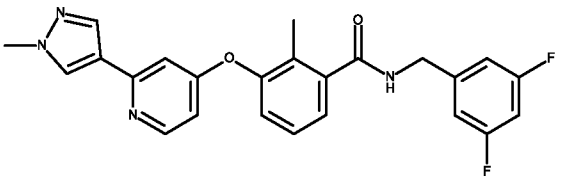
Formula (CVI-1)



Formula (CVII)



Formula (CVIII)



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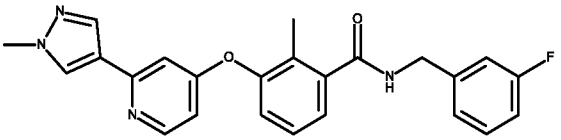
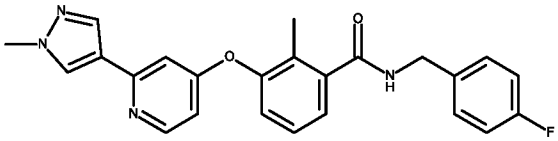
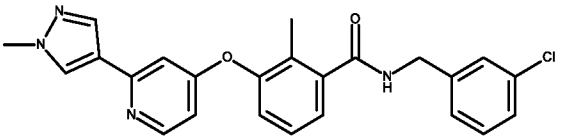


Formula (CX)



Formula (CXI)



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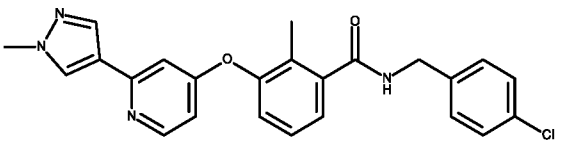

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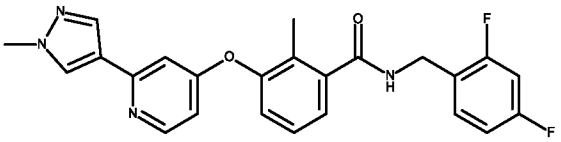

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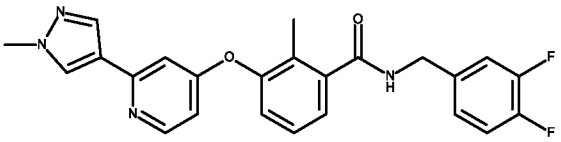

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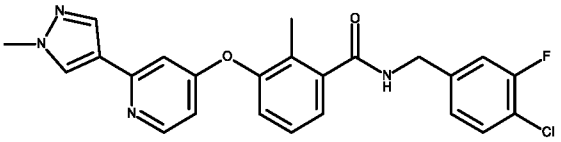

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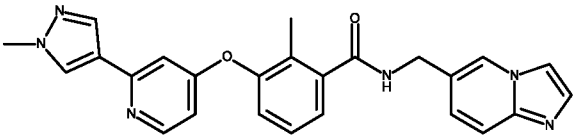

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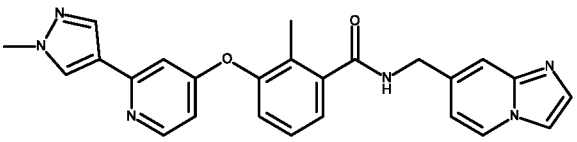

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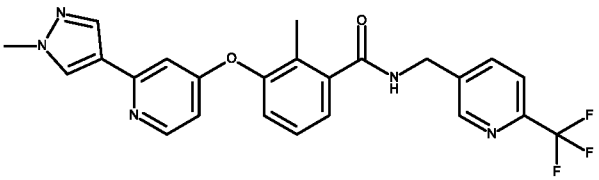

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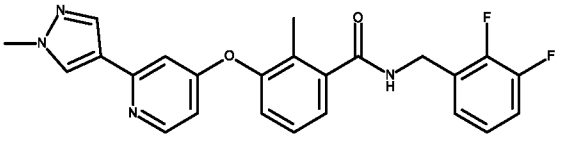

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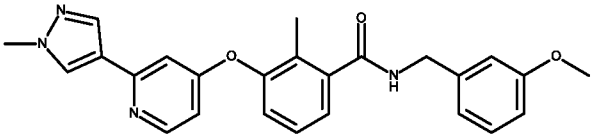

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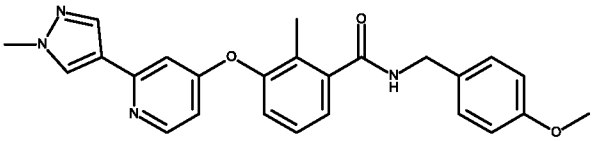

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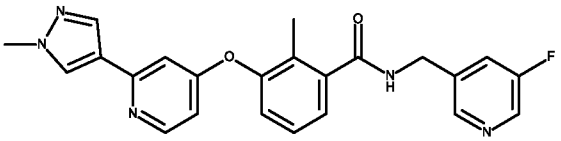

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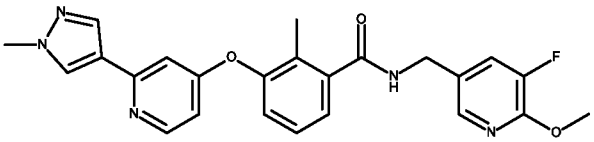

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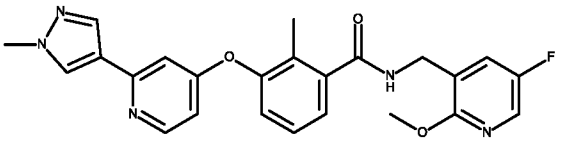

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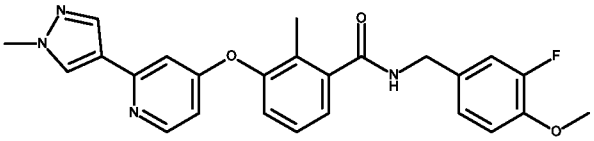

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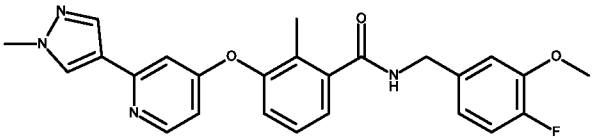

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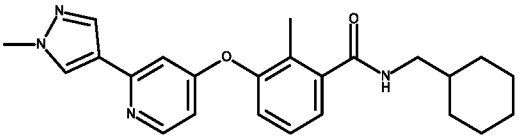

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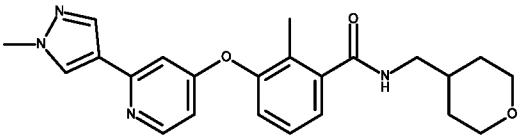

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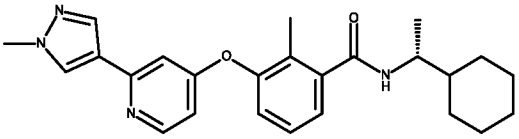

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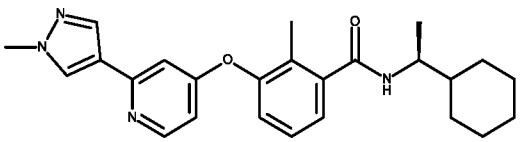

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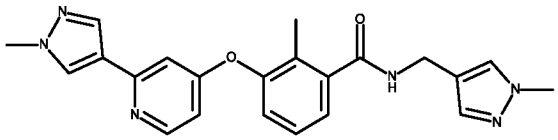

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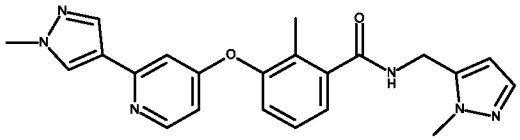

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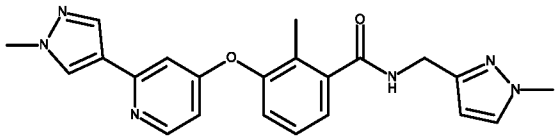

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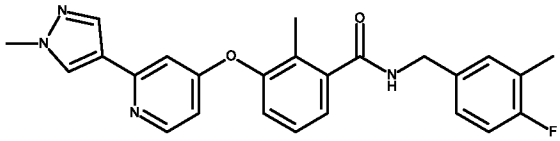

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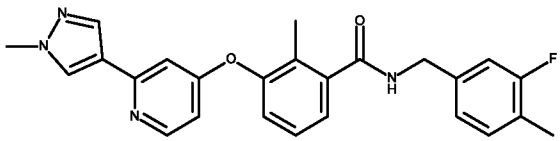

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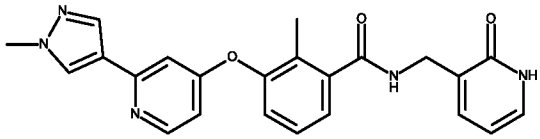

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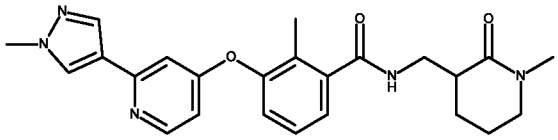

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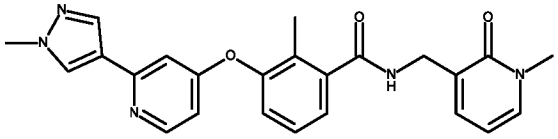

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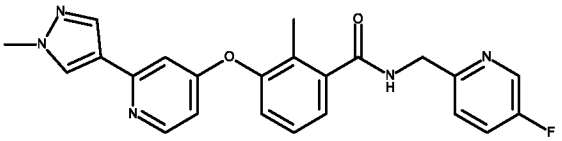

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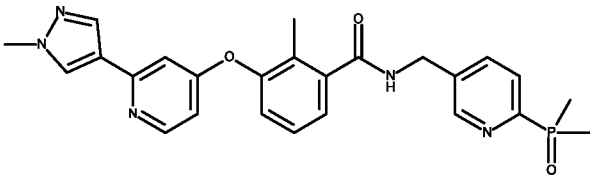

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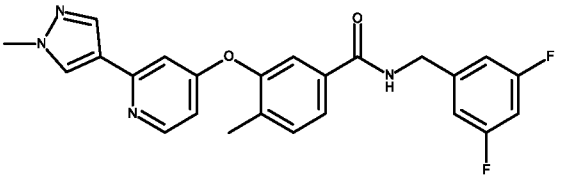

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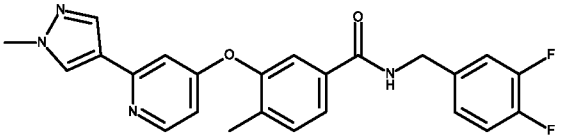

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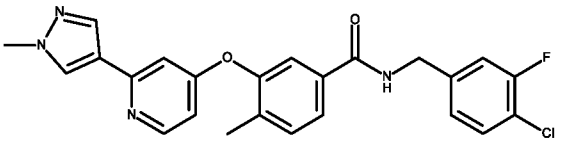

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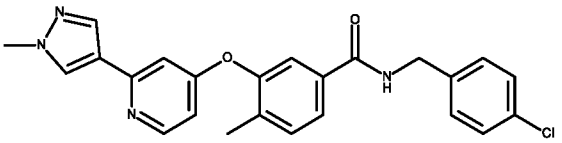

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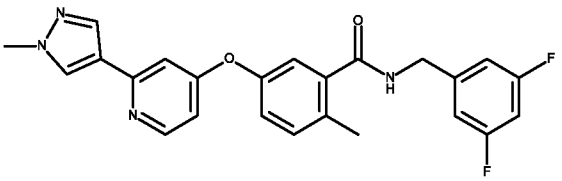

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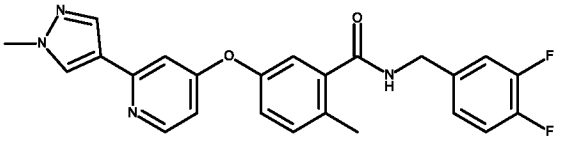

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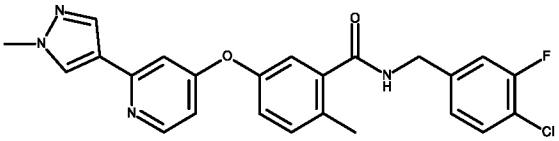

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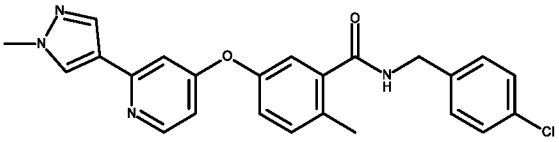

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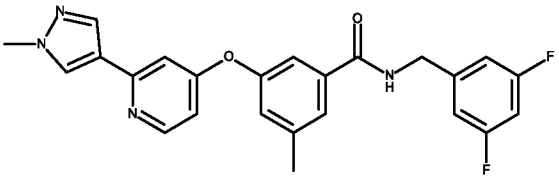
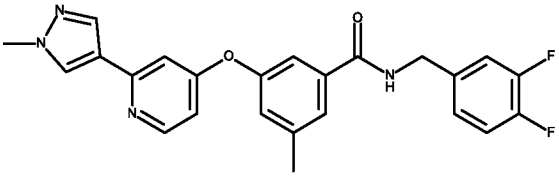


Formula (CL)



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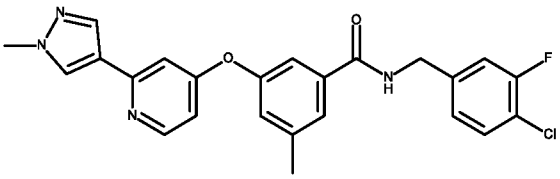

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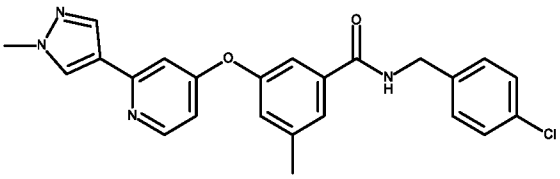

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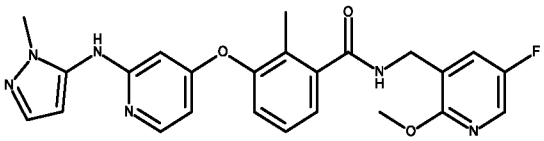

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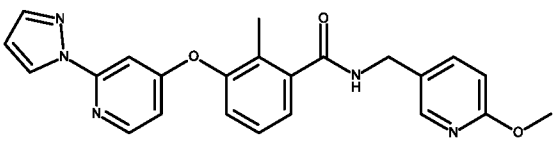

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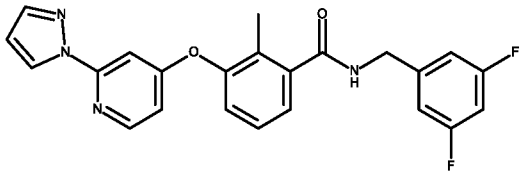

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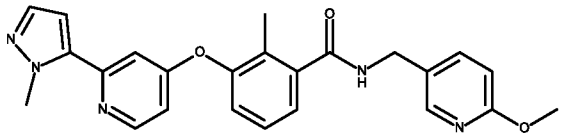

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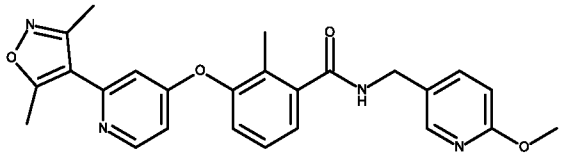

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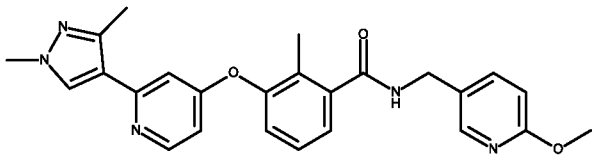
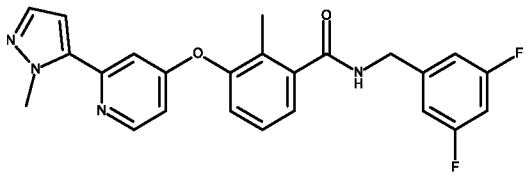


Formula (CLIX)



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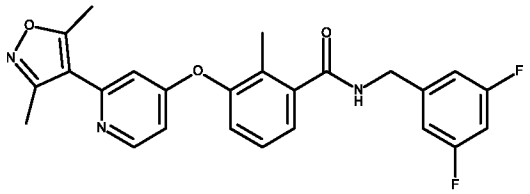
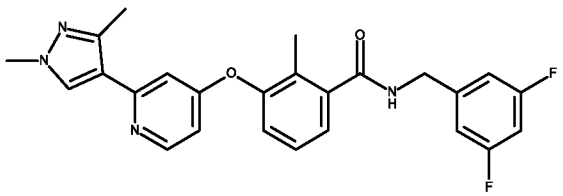


Formula (CLXI)



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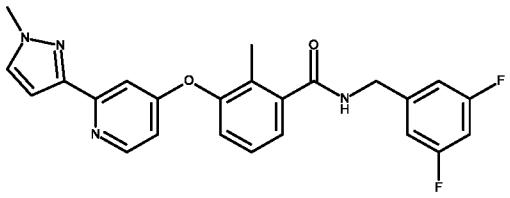

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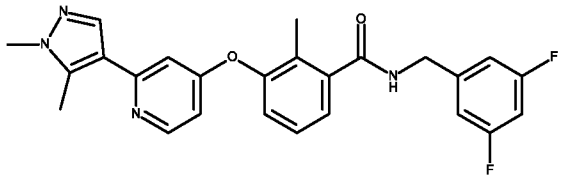

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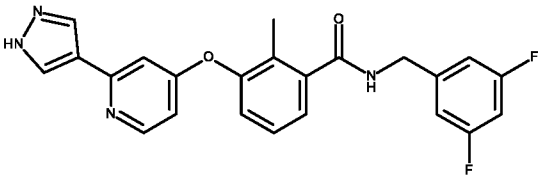

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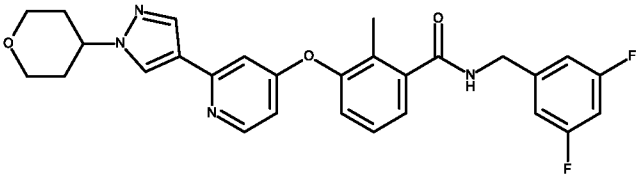

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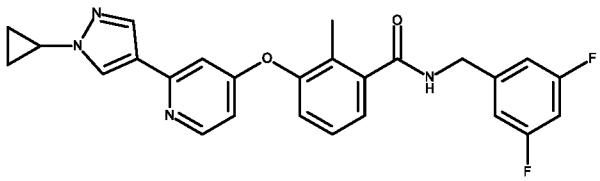

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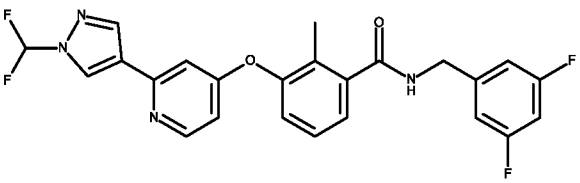

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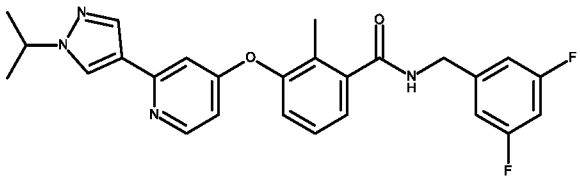

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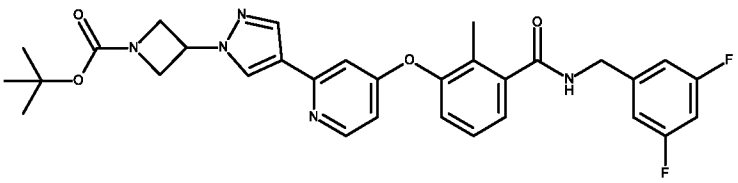

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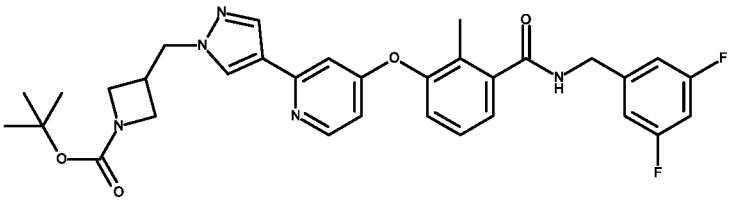

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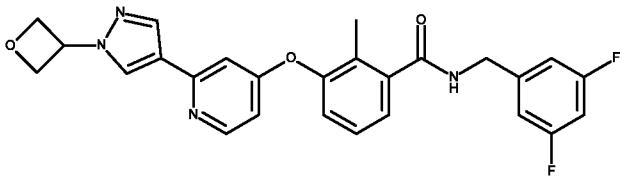

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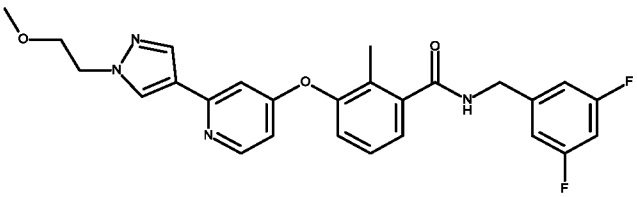

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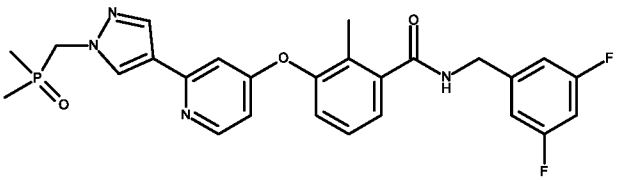

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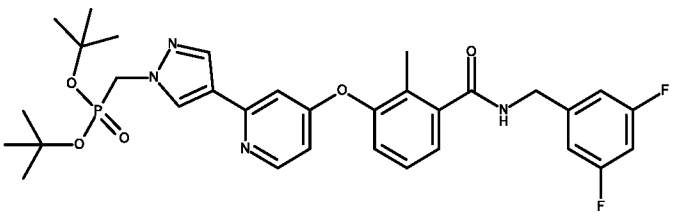

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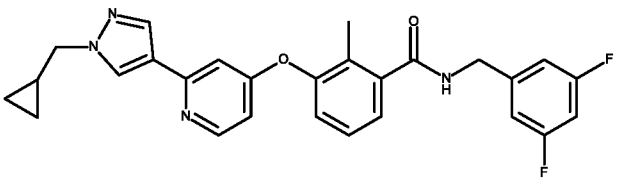

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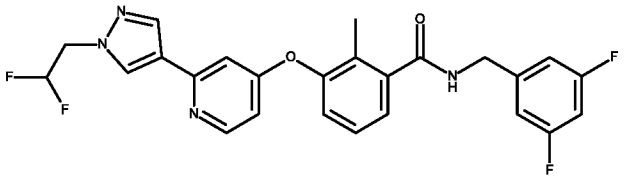

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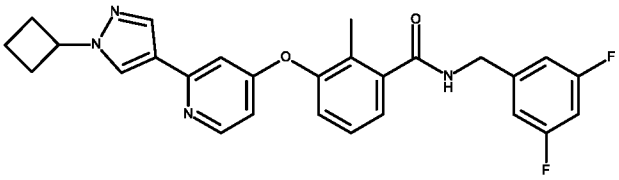

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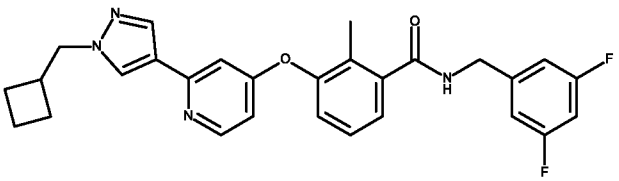

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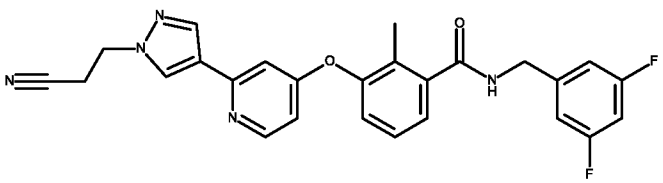

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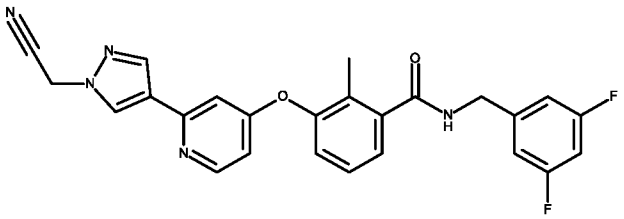

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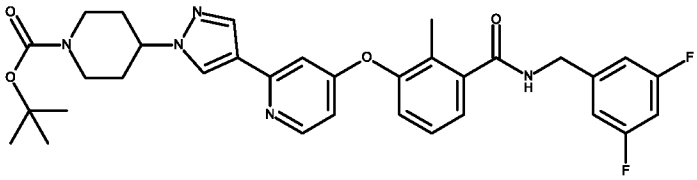

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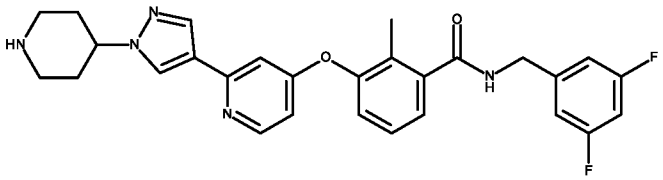

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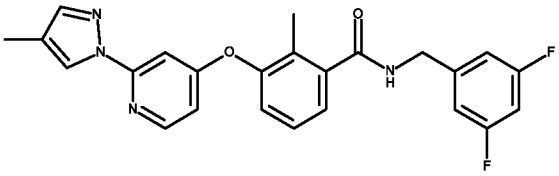

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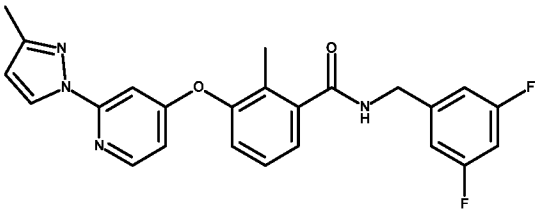

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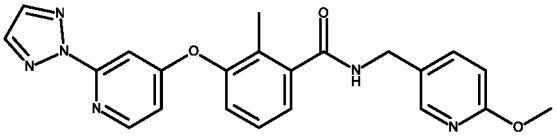

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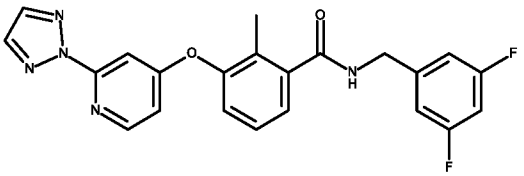

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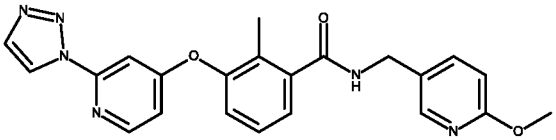

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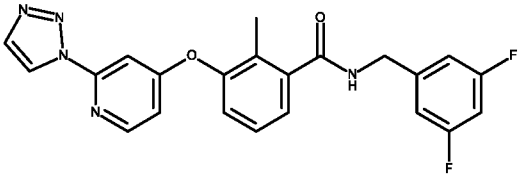

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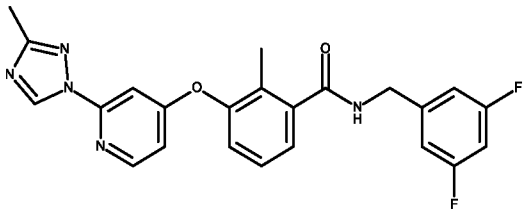

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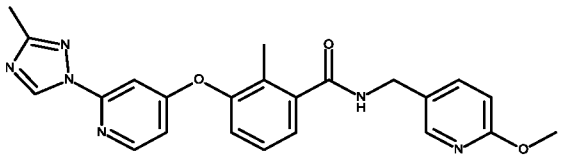

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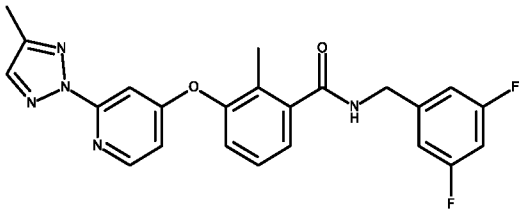
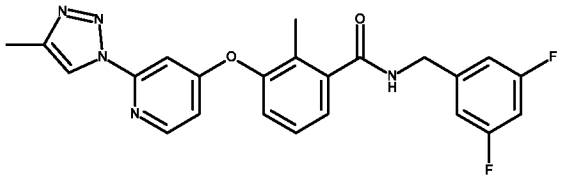


Formula (CXCII)



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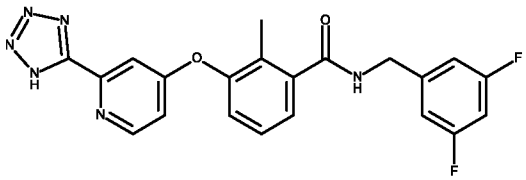

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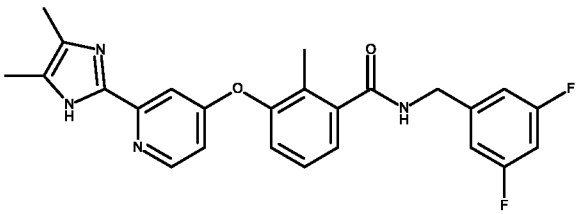

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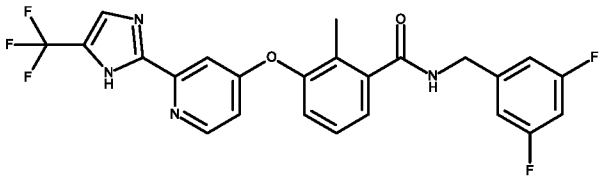

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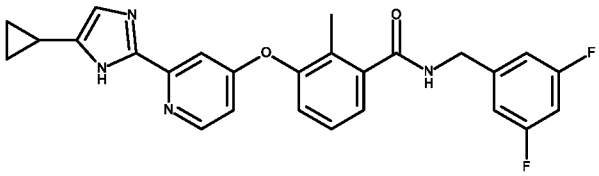

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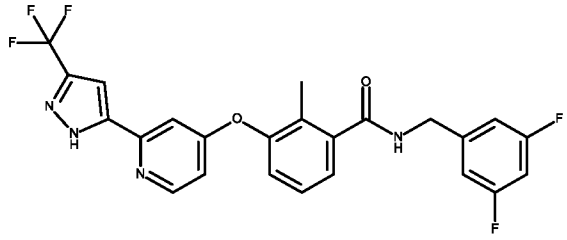

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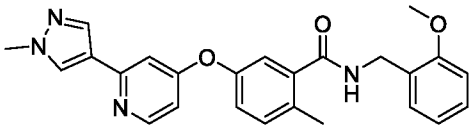
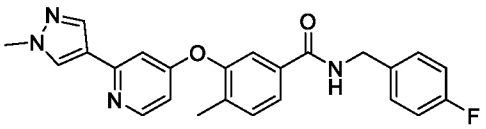
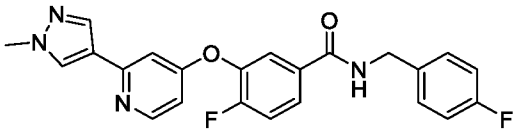


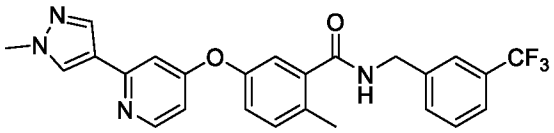
Formula (CXCVIII-1)



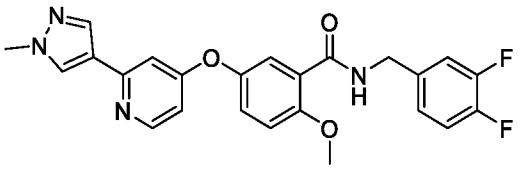
Formula (CXCVIII-2)



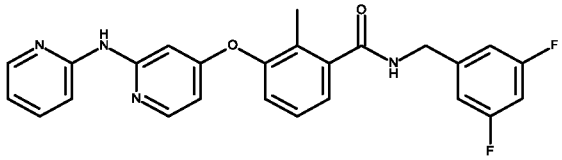
Formula (CXCVIII-3)



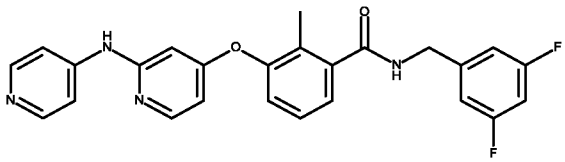
Formula (CXCVIII-4)



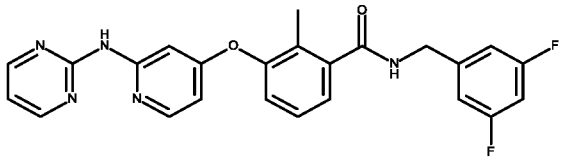
Formula (CXCVIII-5)



Formula (CXCIX)



Formula(CC)



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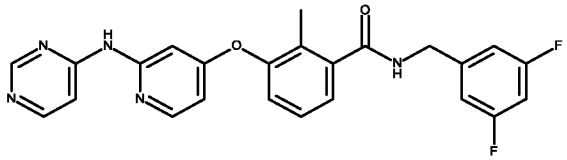
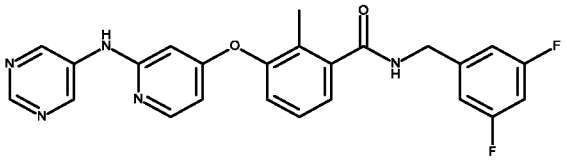


Formula (CCII)



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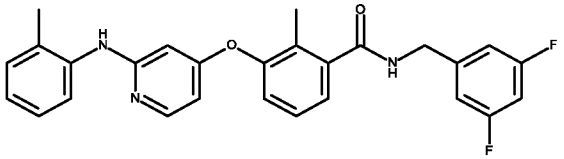

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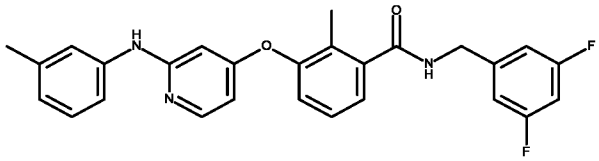

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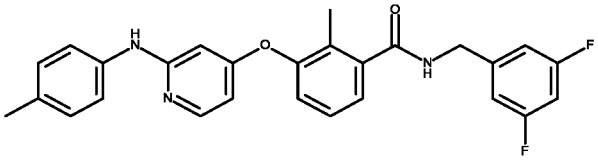

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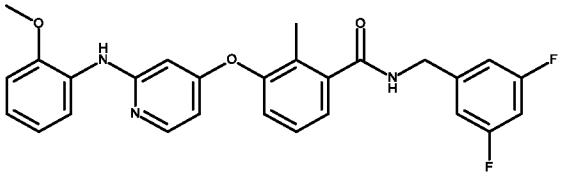

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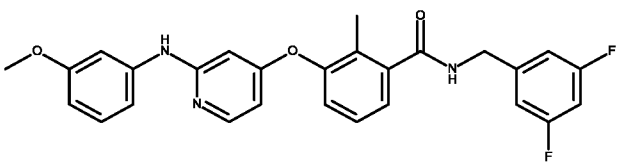

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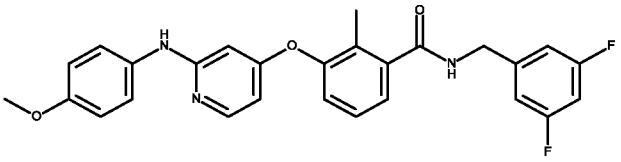

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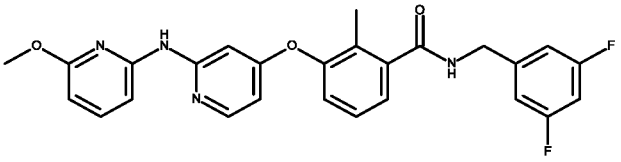

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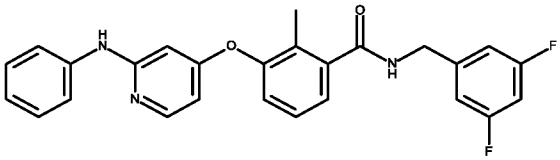

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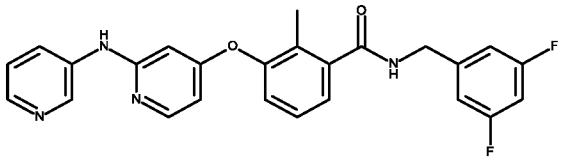

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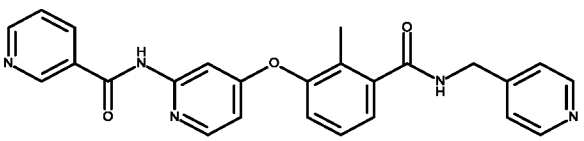

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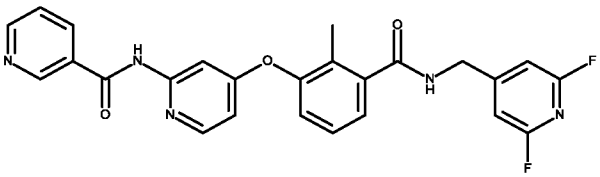

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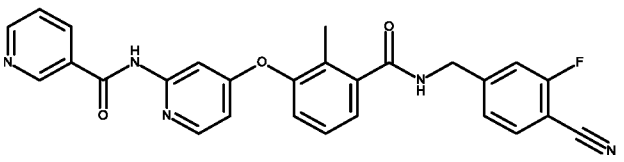

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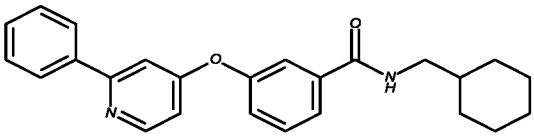

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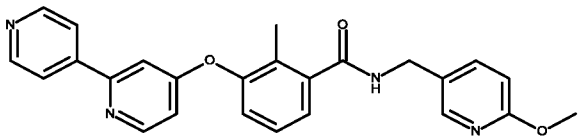

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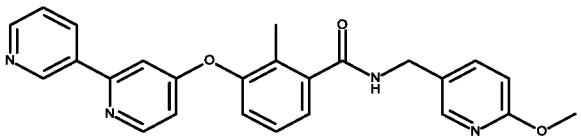

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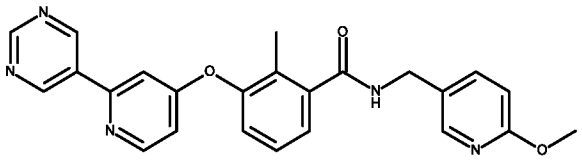

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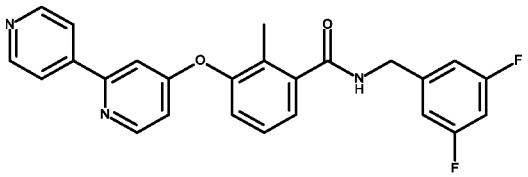

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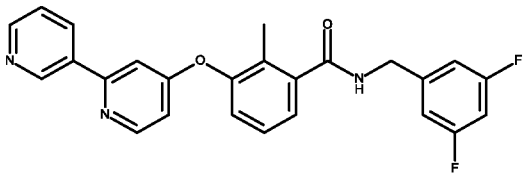

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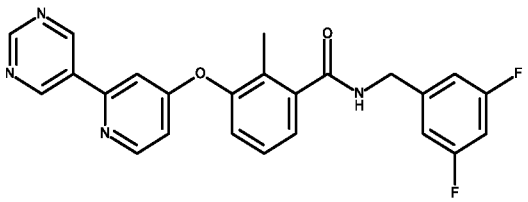

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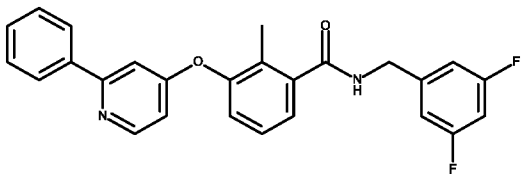

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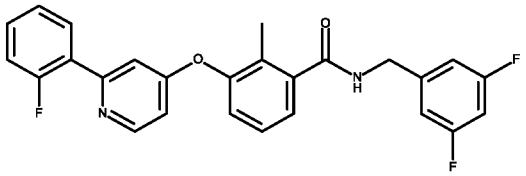

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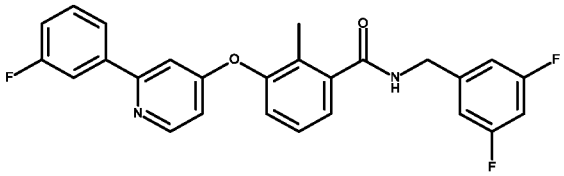

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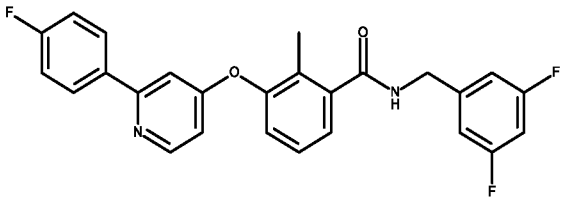

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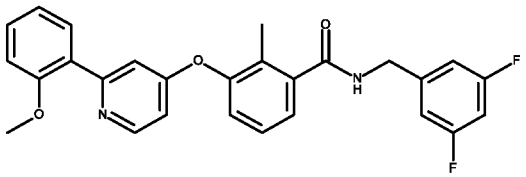

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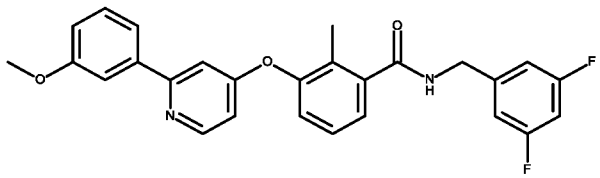

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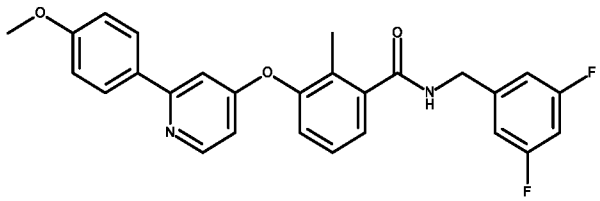

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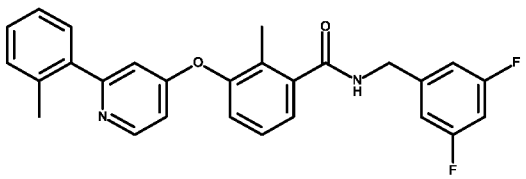

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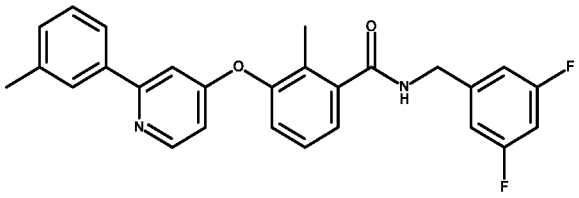

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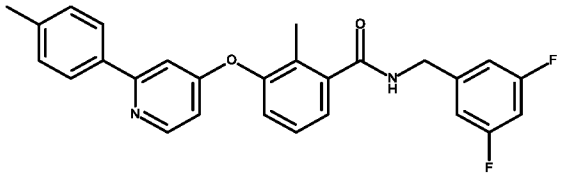

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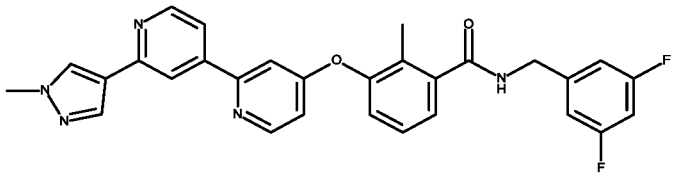

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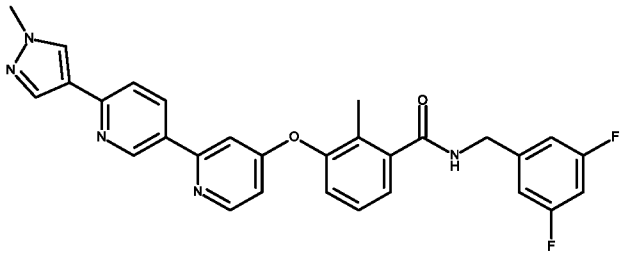

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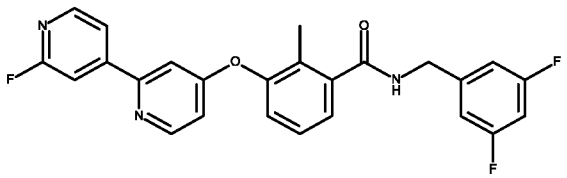

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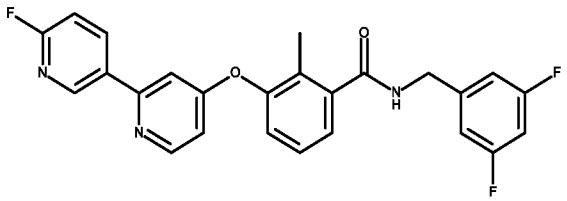

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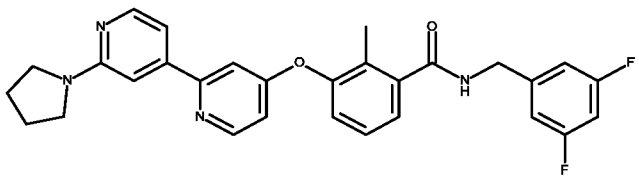

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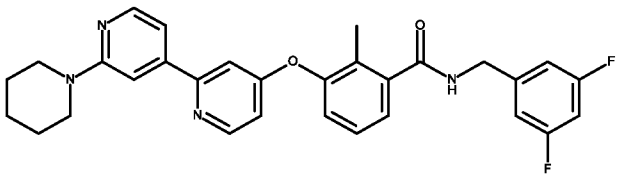

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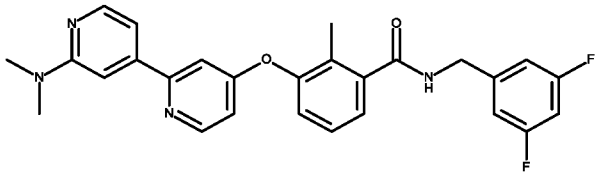

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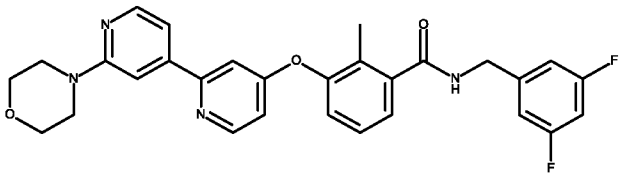

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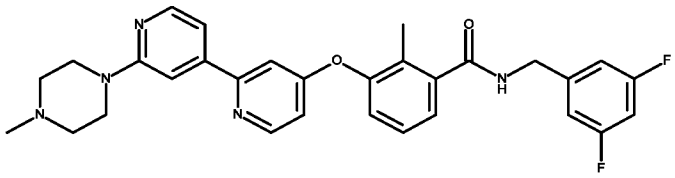

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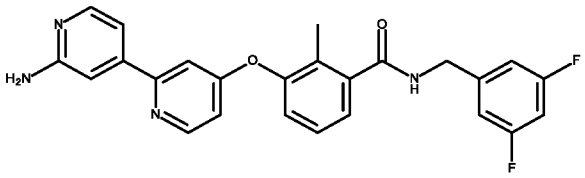

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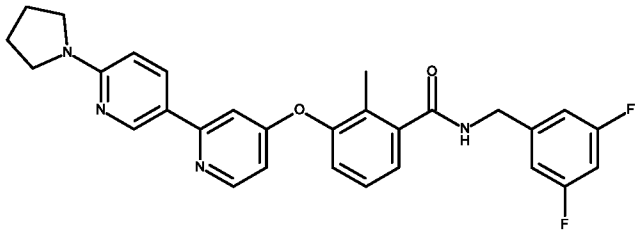

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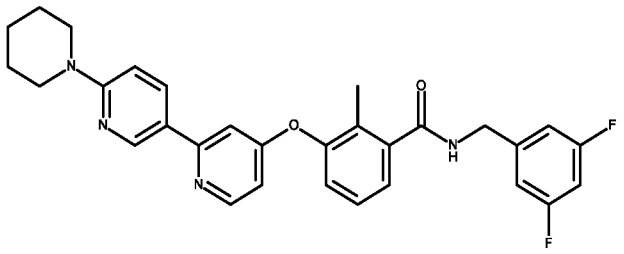

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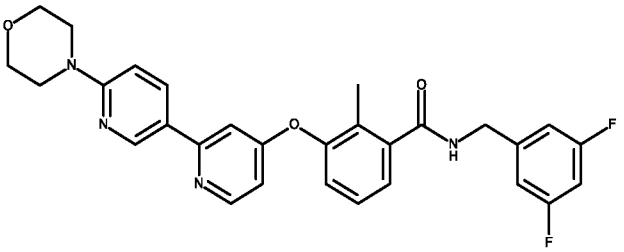

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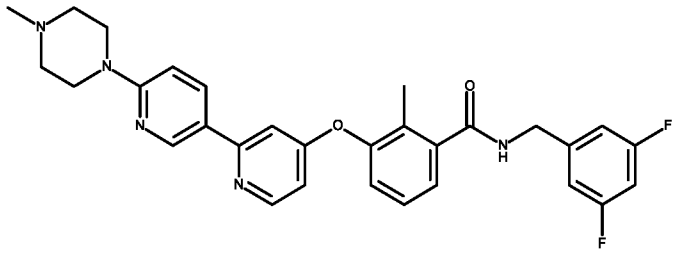

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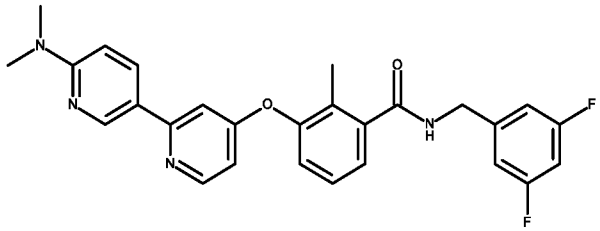

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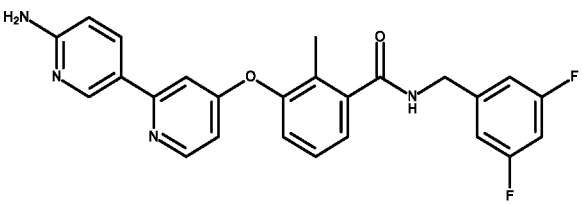

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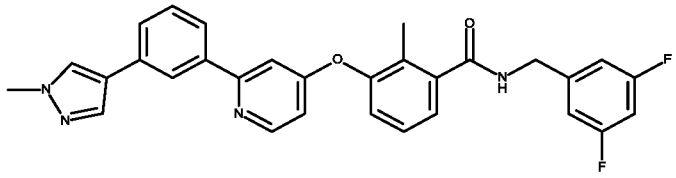

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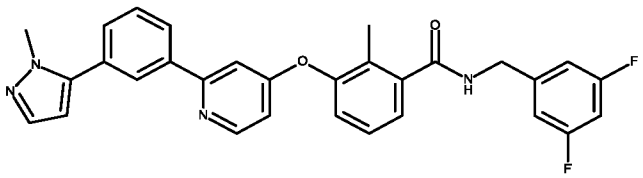
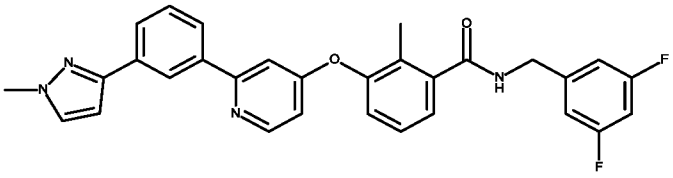
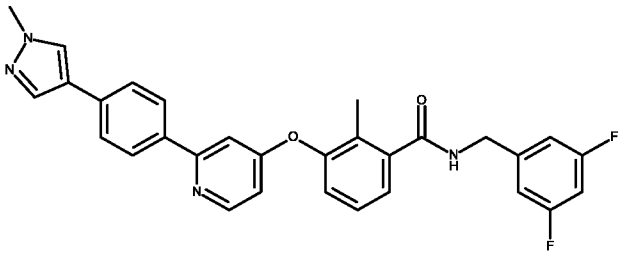


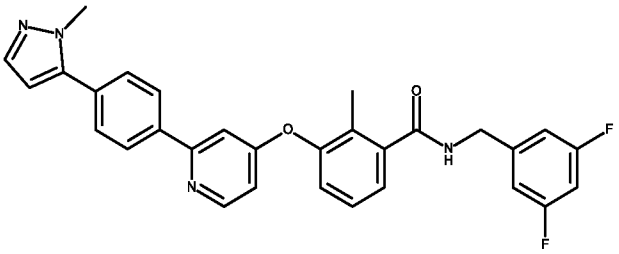
Formula (CCL)



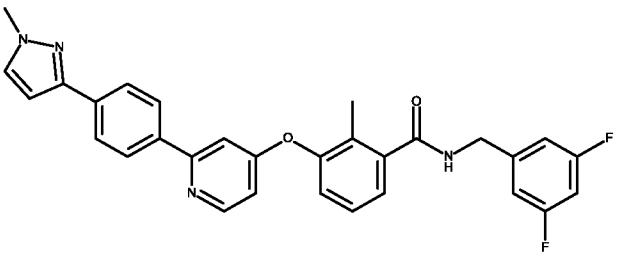
Formula (CCLI)



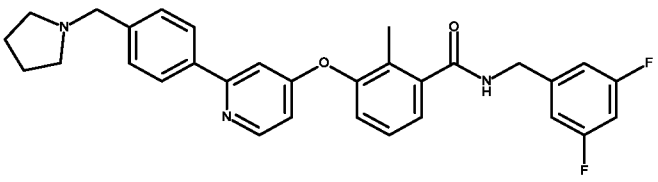
Formula (CCLII)



Formula (CCLIII)



Formula (CCLIV)



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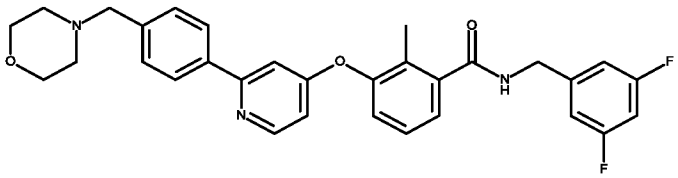
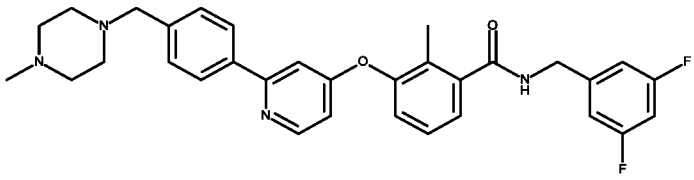
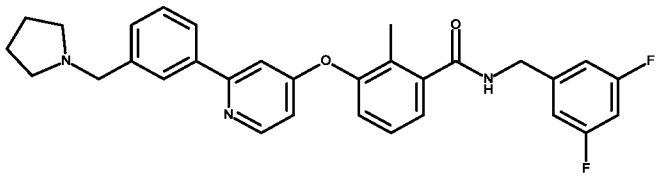


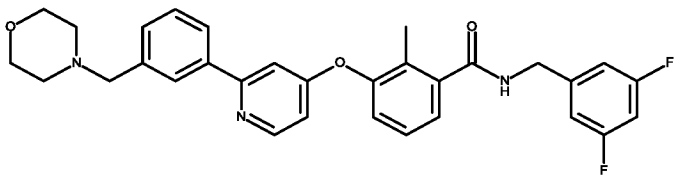
Formula (CCLVI)



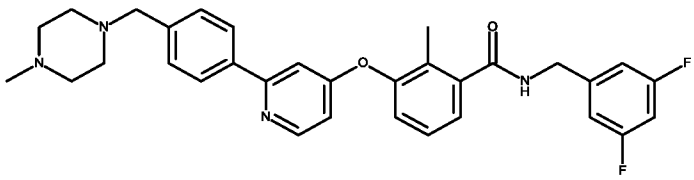
Formula (CCLVII)



Formula (CCLVIII)



Formula (CCLIX)



Formula (CCLX)

14. A pharmaceutical composition comprising a carrier, and as active ingredient the compound (C), as defined according to any one of claims 1 to 13.

15. A compound (C) as defined according to any one of claims 1 to 13, for use as a medicament.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/082907

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D213/68 C07D213/74 C07D213/89 C07D401/12
C07D405/14 C07D413/04 C07D471/04 A61P35/00 A61K31/4439
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/023888 A1 (B C I PHARMA [BE]) 11 February 2021 (2021-02-11) claim 1; table 1	1-3,6,9, 14,15
X	US 2013/065880 A1 (GUO XIALING [US] ET AL) 14 March 2013 (2013-03-14) paragraph [0012]; compounds 12-14, 16, 19, 20, 22, 23 paragraph [0044] - paragraph [0053]	1-4,6,7, 14,15
A	US 2007/142440 A1 (BURGDORF LARS [DE] ET AL) 21 June 2007 (2007-06-21) paragraph [0015] - paragraph [0016]; claim 1; compounds 1, 3, 6-29	1-8, 10-15
A	WO 2013/086397 A1 (ARRAY BIOPHARMA INC [US]; AMGEN INC [US]) 13 June 2013 (2013-06-13) claim 1; compounds 1696, 1707, 1716, 1729	1-8, 10-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 2024	07/05/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/082907

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 9
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-3, 6, 9, 14, 15(all partially)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 7, 8, 10-13(completely); 1-6, 9, 14, 15(partially)

Compound (C) in which z is 1, the A group is a cycloalkyl, heterocyclyl, aryl, heteroaryl group and R9 and R2 do not together form a saturated or unsaturated cyclic moiety, pharmaceutical compositions comprising them and said compounds for therapeutic use

---

2. claims: 1-3, 6, 9, 14, 15(all partially)

Compound (C) in which z is 1, the A group is a cycloalkyl, heterocyclyl, aryl, heteroaryl group, and R9 and R2 together form a saturated or unsaturated cyclic moiety, pharmaceutical compositions comprising them and said compounds for therapeutic use;

---

3. claims: 1-5, 14, 15(all partially)

Compound (C) in which z is 0, the A group is a cycloalkyl, heterocyclyl, aryl, heteroaryl group, pharmaceutical compositions comprising them and said compounds for therapeutic use

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4. claims: 1-5, 14, 15(all partially)

Compound (C) in which z is 2, pharmaceutical compositions comprising them and said compounds for therapeutic use

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 9

The part of Invention 1 that is defined in claim 9 is in contradiction to the part of Invention 1 that is defined in claim 1, on which it is dependent. It is stated in claim 1 that when x is 0 and y is 0 (which is the case in Formula (II-b-2) of claim 9) then R9 is different than hydrogen or alkyl. However, in claim 9 R9'', which corresponds to R9 in claim 1, is defined as being inter alia hydrogen or alkyl. This contradiction between independent and dependent claims leads to a lack of clarity and an uncertainty regarding the scope, and for this reason no opinion regarding the patentability of Invention 1, claim 9, will be given.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.3), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/082907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2021023888 A1	11-02-2021	AU 2020324561 A1	17-03-2022
		BR 112022002222 A2	07-06-2022
		CA 3149846 A1	11-02-2021
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		US 2022388979 A1	08-12-2022
		WO 2021023888 A1	11-02-2021
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		US 2007142440 A1	21-06-2007
		WO 2005085202 A1	15-09-2005
WO 2013086397 A1	13-06-2013	TW 201329067 A	16-07-2013
		WO 2013086397 A1	13-06-2013