(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 October 2014 (30.10.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/175832 A1

(51) International Patent Classification:

C07D 417/12 (2006.01)	*A61K 31/5377* (2006.01)
C07D 413/14 (2006.01)	*A61K 31/506* (2006.01)
C07D 413/12 (2006.01)	*A61K 31/501* (2006.01)
C07D 413/04 (2006.01)	*A61K 31/496* (2006.01)
C07D 409/12 (2006.01)	*A61K 31/444* (2006.01)
C07D 403/12 (2006.01)	*A61K 31/4439* (2006.01)
C07D 401/14 (2006.01)	*A61K 31/4409* (2006.01)
C07D 401/12 (2006.01)	*A61K 31/4406* (2006.01)
C07D 401/04 (2006.01)	*A61K 31/426* (2006.01)
C07D 277/24 (2006.01)	*A61K 31/421* (2006.01)
C07D 263/32 (2006.01)	*A61K 31/4196* (2006.01)
C07D 249/08 (2006.01)	*A61K 31/4184* (2006.01)
C07D 235/08 (2006.01)	*A61K 31/4178* (2006.01)
C07D 233/58 (2006.01)	*A61K 31/4164* (2006.01)
C07D 231/12 (2006.01)	*A61K 31/415* (2006.01)
C07D 213/30 (2006.01)	*A61K 31/402* (2006.01)
C07D 207/325 (2006.01)	*A61K 31/40* (2006.01)
C07D 207/323 (2006.01)	*A61P 35/00* (2006.01)
A61K 31/538 (2006.01)	*A61P 3/10* (2006.01)

(21) International Application Number:
PCT/SG2014/000183

(22) International Filing Date:
25 April 2014 (25.04.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1307564.3 26 April 2013 (26.04.2013) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/175832 A1

(54) Title: WNT PATHWAY MODULATORS

(57) Abstract: The invention provides a compound of structure Ar1-Ar2-X-C(R1R2)-C(=O)-N(R3)-Ar3-Ar4 for modulating WNT activity. In this structure, Ar1, Ar2, Ar3 and Ar4 are, independently, optionally substituted aryl or heteroaryl groups; R1 and R3 are, independently, H or optionally substituted alkyl groups; R2 is H or an optionally substituted alkyl group or an alkylene group which, together with the carbon atom to which it is attached and X, forms a non-aromatic ring or an alkylene group which, together with the carbon atom to which it is attached and X and two adjacent atoms of Ar2, forms a non-aromatic ring; X is O, CR4R5, N or NR4, wherein if X is N, it is bonded to R2; R4 is H, optionally substituted alkyl or an alkylene chain, optionally containing a heteroatom and/or a carbonyl group, which, together with the C or N to which it is attached and two adjacent atoms of Ar2, forms a non-aromatic ring; R5 is H, NH2 or an optionally substituted alkyl group.

WNT PATHWAY MODULATORS

Field

[0001] The invention relates to WNT pathway modulators, processes for making them and methods for using them.

Background

[0002] Wnt proteins are secreted glycoproteins acting as growth factors that regulate various cellular functions, including proliferation, differentiation, death, migration, and polarity, by activating multiple intracellular signaling cascades, including the β-catenin-dependent and -independent pathways. There are 19 Wnt members that have been found in humans and mice, and they exhibit unique expression patterns and distinct functions during development. In humans and mice, the 10 members of the Frizzled (Fz) family comprise a series of seven-pass transmembrane receptors that have been identified as Wnt receptors. In addition to Fz proteins, single-pass transmembrane proteins, such as low-density lipoprotein receptor-related protein 5 (LRP5), LRP6, receptor tyrosine kinase (RTK)-like orphan receptor 1(Ror1), Ror2, and receptor-like tyrosine kinase (Ryk), have been shown to function as co-receptors for Wnt signaling. Therefore, it has been assumed traditionally that the binding of different Wnts to their specific receptors selectively triggers different outcomes via distinct intracellular pathways.

[0003] In the absence of Wnt signaling, β-catenin is bound and phosphorylated by a "destruction complex" containing the adenomatous polyposis coli (APC) and Axin proteins, as well as glycogen synthase kinase 3 (GSK3) and casein kinase I (CKI). Phosphorylated β-catenin is bound by the F box protein Slimb/β-TrCP and polyubiquitinated, leading to proteosomal degradation. In addition, the complex acts to prevent nuclear localization of b-catenin. Upon Wnt binding to Frizzled (Fz) and low-density lipoprotein-related proteins 5 and 6 (LRP5/6), GSK3, Axin, and other destruction complex components are recruited to the receptor complex. The function of the destruction complex is inhibited, and unphosphorylated β-catenin accumulates in the cytoplasm and eventually translocates to the nucleus. There, it associates with TCF proteins, converting TCF from a repressor into an activator of Wnt-responsive gene transcription.

[0004] Deregulation of components of Wnt/β-catenin signaling is implicated in a wide spectrum of diseases including degenerative diseases, metabolic diseases, and a number of cancers such as cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreas adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor and medulloblastoma.

[0005] Wnt signaling plays a role both during development, and within stem cell niches in adults. This is best established in skin, hematopoietic stem cells, mammary gland and in intestinal proliferation. For example, high level expression of DKK1, an inhibitor of Wnt signaling, blocks normal stem cell proliferation in mouse intestine, suggesting there is an essential role for Wnt signaling in maintenance of stem cells in the digestive tract. The role of Wnt in self renewal and expansion of stem cells has also been demonstrated for embryonic and neural stem cells, suggesting that Wnt signaling may be a general requirement of stem cell maintenance. Inhibition of Wnt signaling, e.g., by overexpression of axin or an extracellular Wnt-binding protein, sFRP, reduces hematopoietic stem cell (HSC) growth *in vitro* and the ability to reconstitute HSCs *in vivo*. Notably, while overexpression of activated β-catenin can expand HSC populations in culture for extended periods, two groups have reported that β−catenin is not required for HSC survival and serial transplantation, supporting the proposal that there is more to Wnt signaling than stabilization of β-catenin in stem cell survival. Diverse Wnts can regulate stem cell proliferation: Wnts 1, 5a, and 10b are able to stimulate expansion of HSC populations and Wnt5a acts synergistically with stem cell factor (SCF) to expand and promote self renewal of HSCs. The demonstration of a role for Wnt5a in HSC self renewal and its ability to synergize with stem cell factor is particularly interesting because Wnt5a often acts in a β-catenin independent manner. While Wnt signaling is critical for stem cell maintenance, it may act via signaling pathways distinct from or in parallel to the β-catenin pathway.

[0006] The Wnt/β-catenin signaling pathway is essential to embryonic development and organ morphogenesis, and dysregulation of this pathway in adults has been linked to fibroblast biology and fibrosis. It has been demonstrated that Wnt/β-catenin signaling plays a role in severe fibrotic diseases, such as pulmonary fibrosis, liver fibrosis, skin fibrosis and renal fibrosis.

[0007] Dysregulation of Wnt/β-catenin signaling contributes also to the development of diabetic retinopathy by inducing retinal inflammation, vascular leakage, and neovascularization.

[0008] The binding of Wnt proteins to plasma membrane receptors on mesenchymal cells induces the differentiation of these cells into the osteoblast lineage and thereby supports bone formation. Wnts are also key signaling proteins in joint remodeling processes. Active Wnt signaling contributes to osteophyte formation and might have an essential role in the anabolic pattern of joint remodeling that is observed in ankylosing spondylitis and osteoarthritis. In contrast, blockage of Wnt signaling facilitates bone erosion and contributes to catabolic joint remodeling, a process that is observed in rheumatoid arthritis.

[0009] There is therefore a need for compounds that modulate and/or inhibit the WNT pathway so as to treat diseases associated with WNT activity.

Summary of Invention

[00010] In a first aspect of the invention there is provided a compound of structure I for modulating WNT activity:

$$Ar^1\text{-}Ar^2\text{-}X\text{-}C(R^1R^2)\text{-}C(=O)\text{-}N(R^3)\text{-}Ar^3\text{-}Ar^4$$

(I)

wherein:

Ar^1, Ar^2, Ar^3 and Ar^4 are, independently, optionally substituted aryl or heteroaryl groups;

R^1 and R^3 are, independently, H or optionally substituted alkyl groups;

R^2 is H or an optionally substituted alkyl group or an alkylene group which, together with the carbon atom to which it is attached and X, forms a non-aromatic ring or an alkylene group which, together with the carbon atom to which it is attached and X and two adjacent atoms of Ar^2, forms a non-aromatic ring;

X is O, CR^4R^5, CH_2O, N or NR^4, wherein if X is N, it is bonded to R^2;

R^4 is H, optionally substituted alkyl or an alkylene chain, optionally containing a heteroatom and/or a carbonyl group, which, together with the C or N to which it is attached and two adjacent atoms of Ar^2, forms a non-aromatic ring; and

R^5 is H, NH_2 or an optionally substituted alkyl group.

[00011] The following options may be used in conjunction with the first aspect, either individually or in any suitable combination.

[00012] R^1 and R^3 may both be H.

[00013] X may be O, NH or CH_2.

[00014] R^2 may be H or it may be methyl. In some embodiments X is a nitrogen atom and R^2 is $(CH_2)_3$ and is attached to said nitrogen atom so as to form a 5-membered ring.

[00015] Ar^1 may be a 5-membered heterocyclic ring or it may be a pyridyl ring. It may contain 1 or 2 ring nitrogen atoms. In some embodiments Ar^1 has no ring atoms that are not N or C.

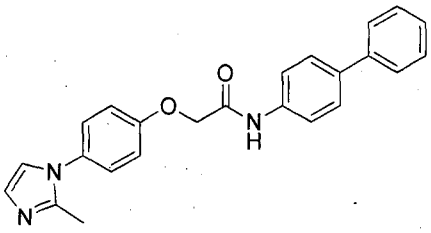
[00016] Ar^2 may be a 6-membered ring. Ar^1 and X may be in a 1,4-relationship on Ar^2, or may be in a 1,3-relationship or a 1,2-relationship thereon. Ar^2 may be a phenyl or may be pyridyl.

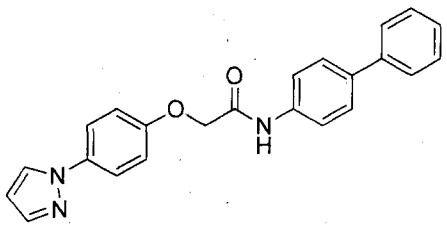
[00017] Ar^3 may be a 6-membered ring. Ar^4 and the nitrogen atom attached to Ar^3 may be in a 1,4-relationship on Ar^3. Ar^3 may be a phenyl ring or may contain 1 or 2 ring nitrogen atoms.

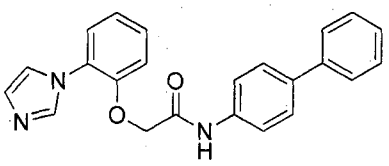
[00018] Ar^4 may be a 6-membered ring. Ar^4 may be a phenyl ring or may contain 1 or 2 ring nitrogen atoms.

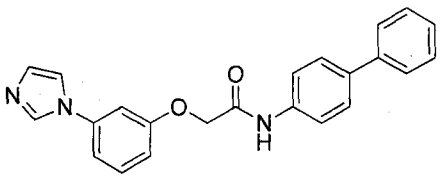
[00019] In some embodiments, X=O and R^1, R^2 and R^3 are all H. In other embodiments X=NH, R^1 and R^3 are H and R^2 is CH_3.

[00020] The compound may be any of the compounds from Examples 1 to 139 provided herein (not including intermediates described in the syntheses). The compound may be a racemate. It may be a single optical isomer. In the event that diastereomers are possible, it may be a single diastereomer or it may be a mixture of diastereomers. It may be any one of the following compounds:









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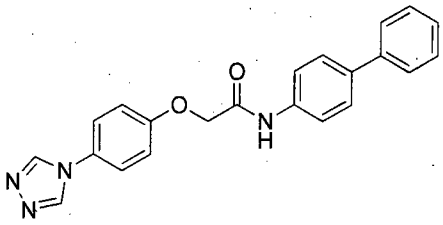

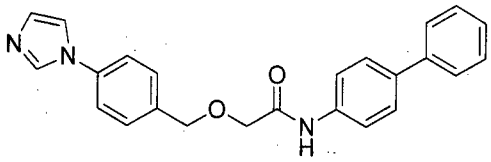

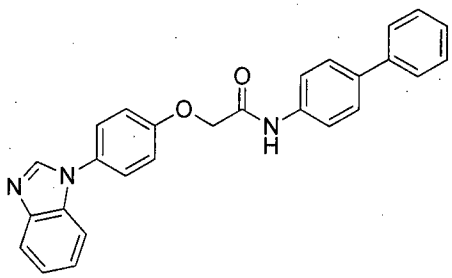

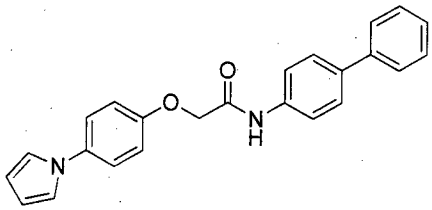

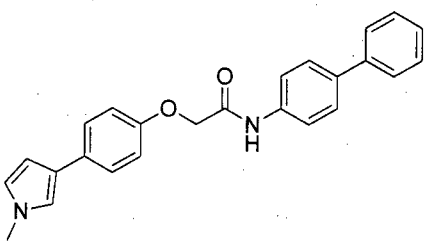

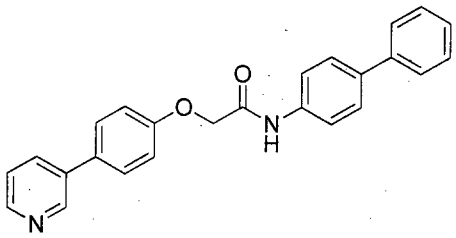

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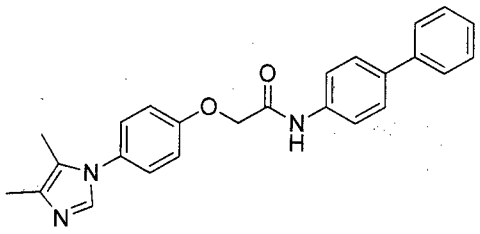

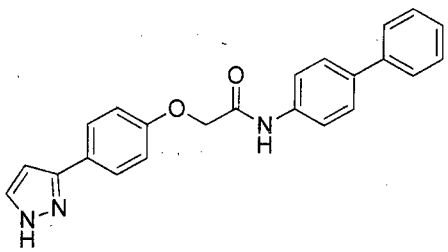

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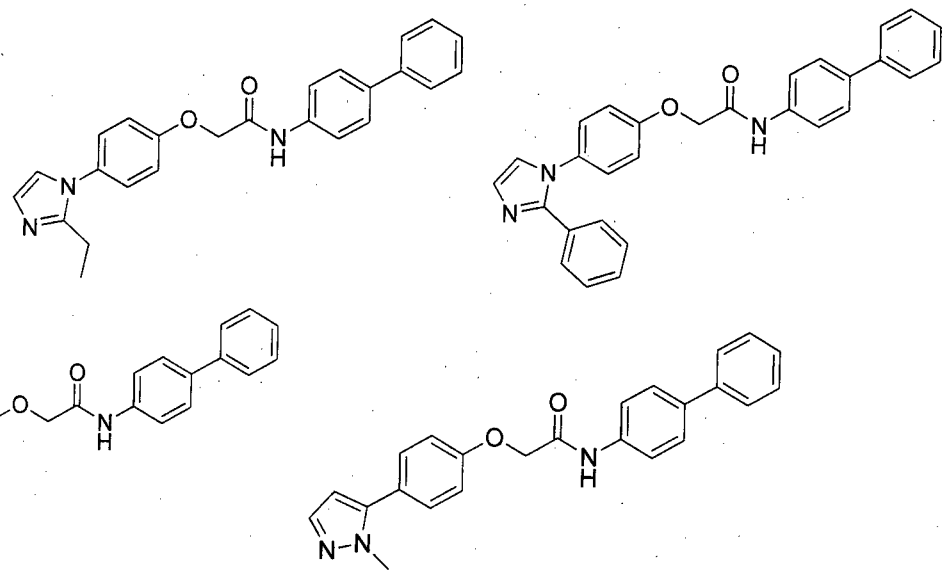

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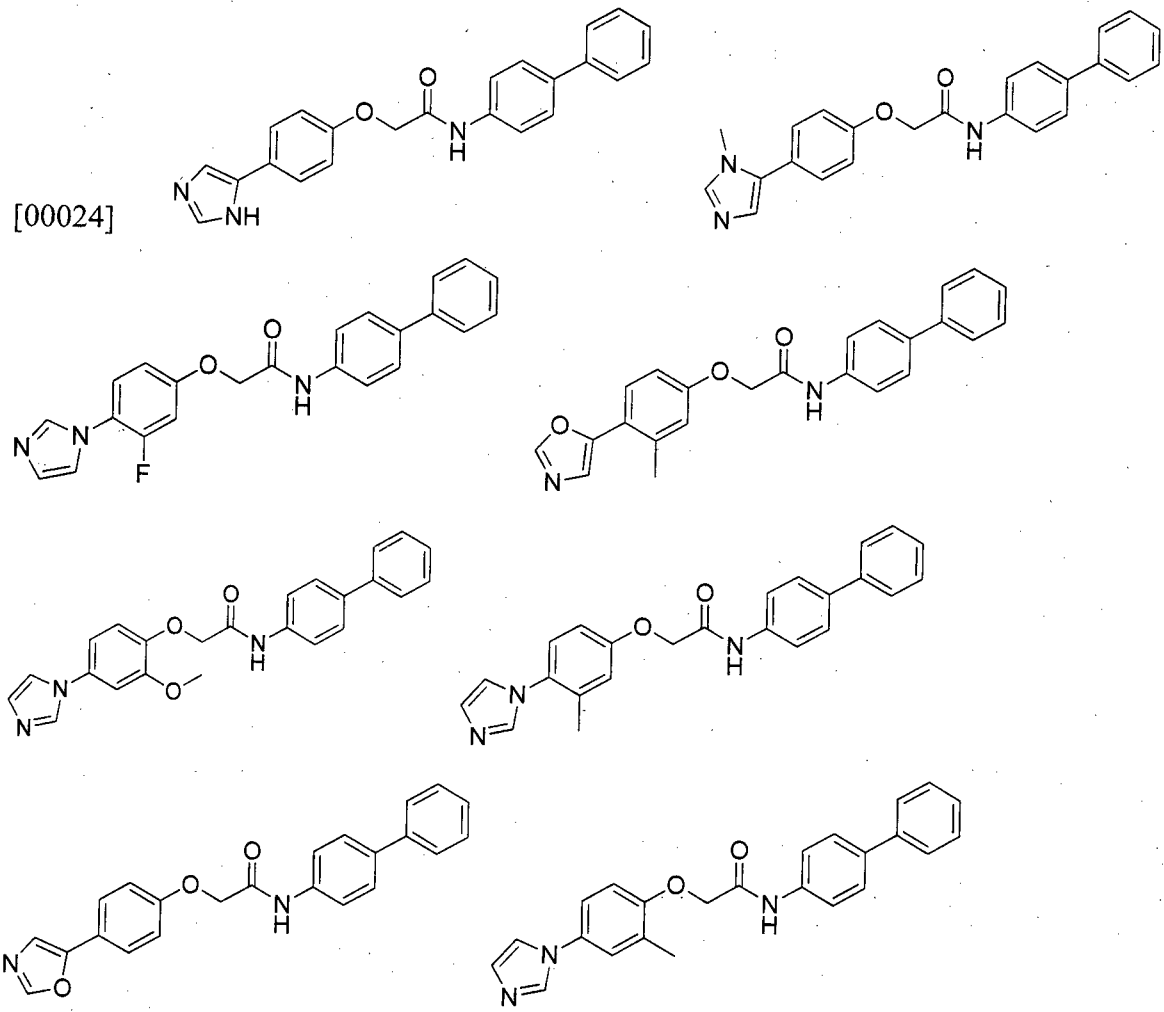
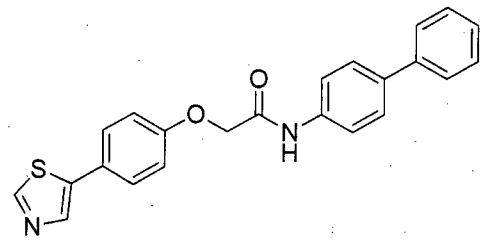
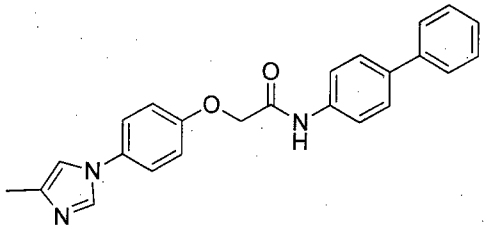
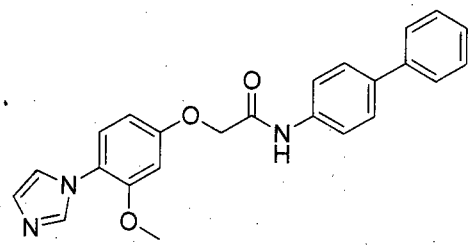
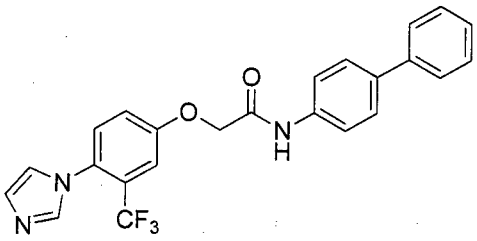
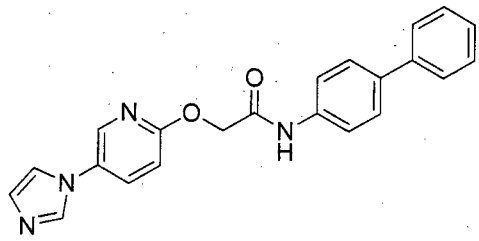
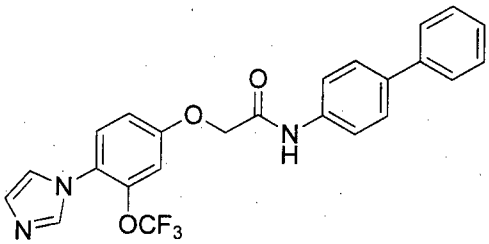
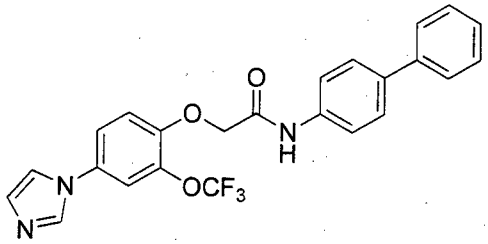
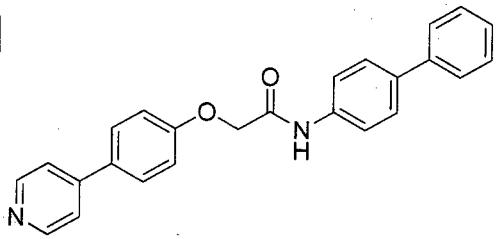
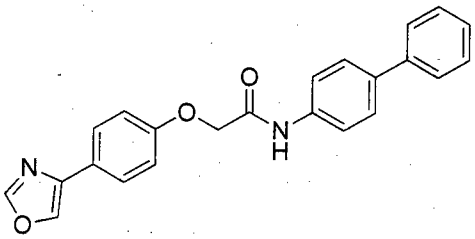
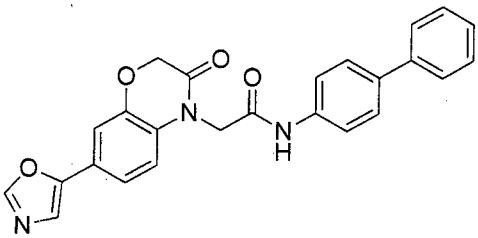
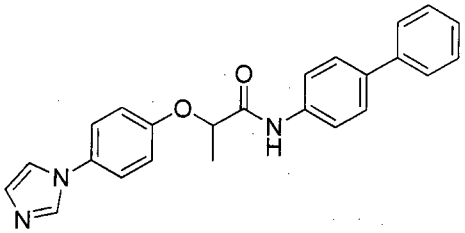
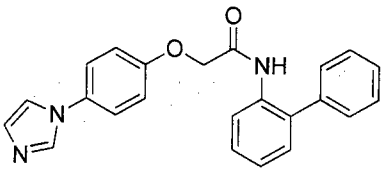
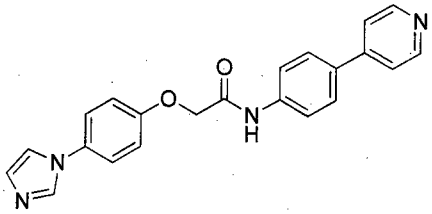
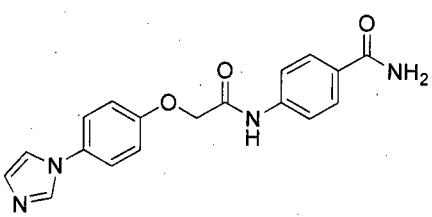
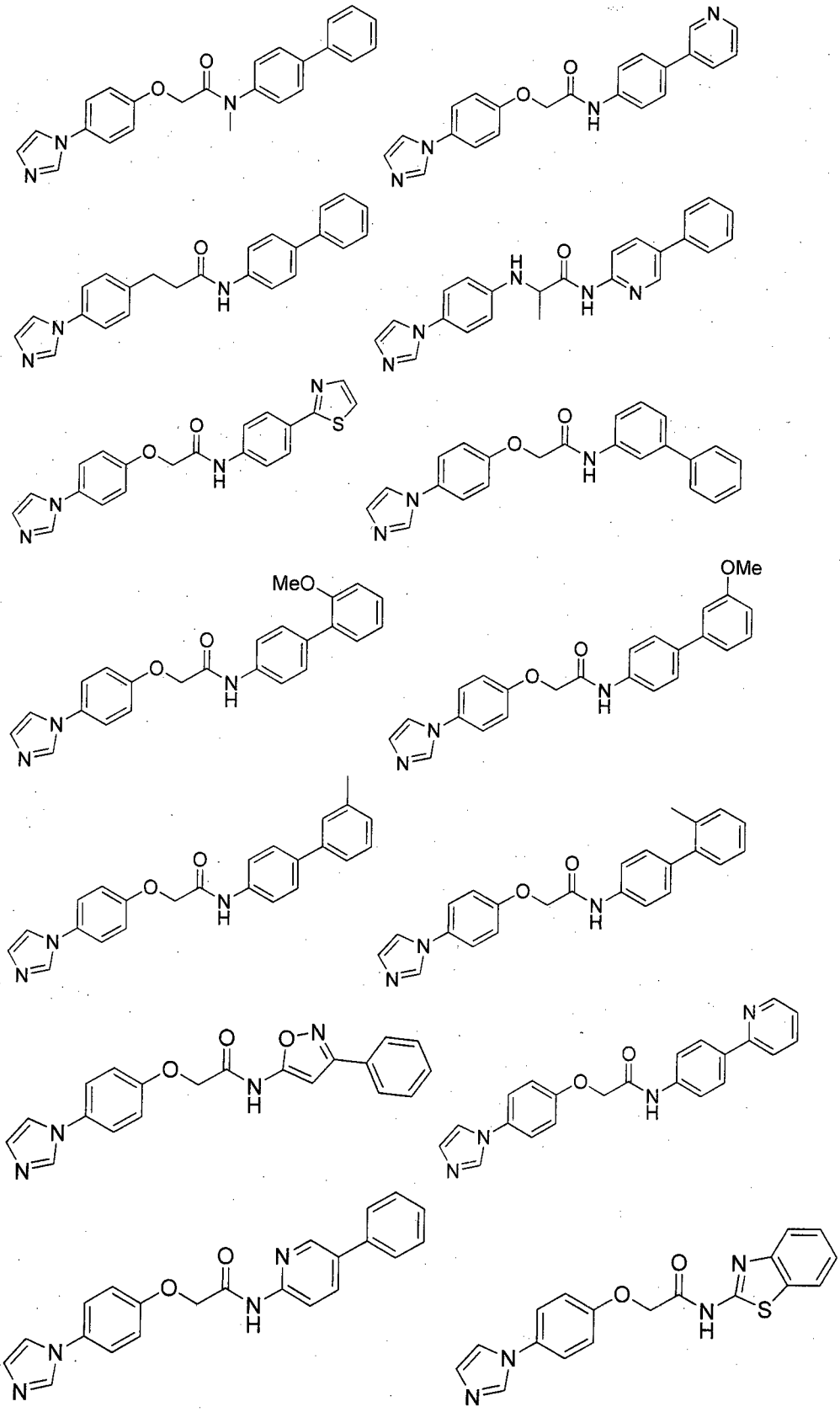
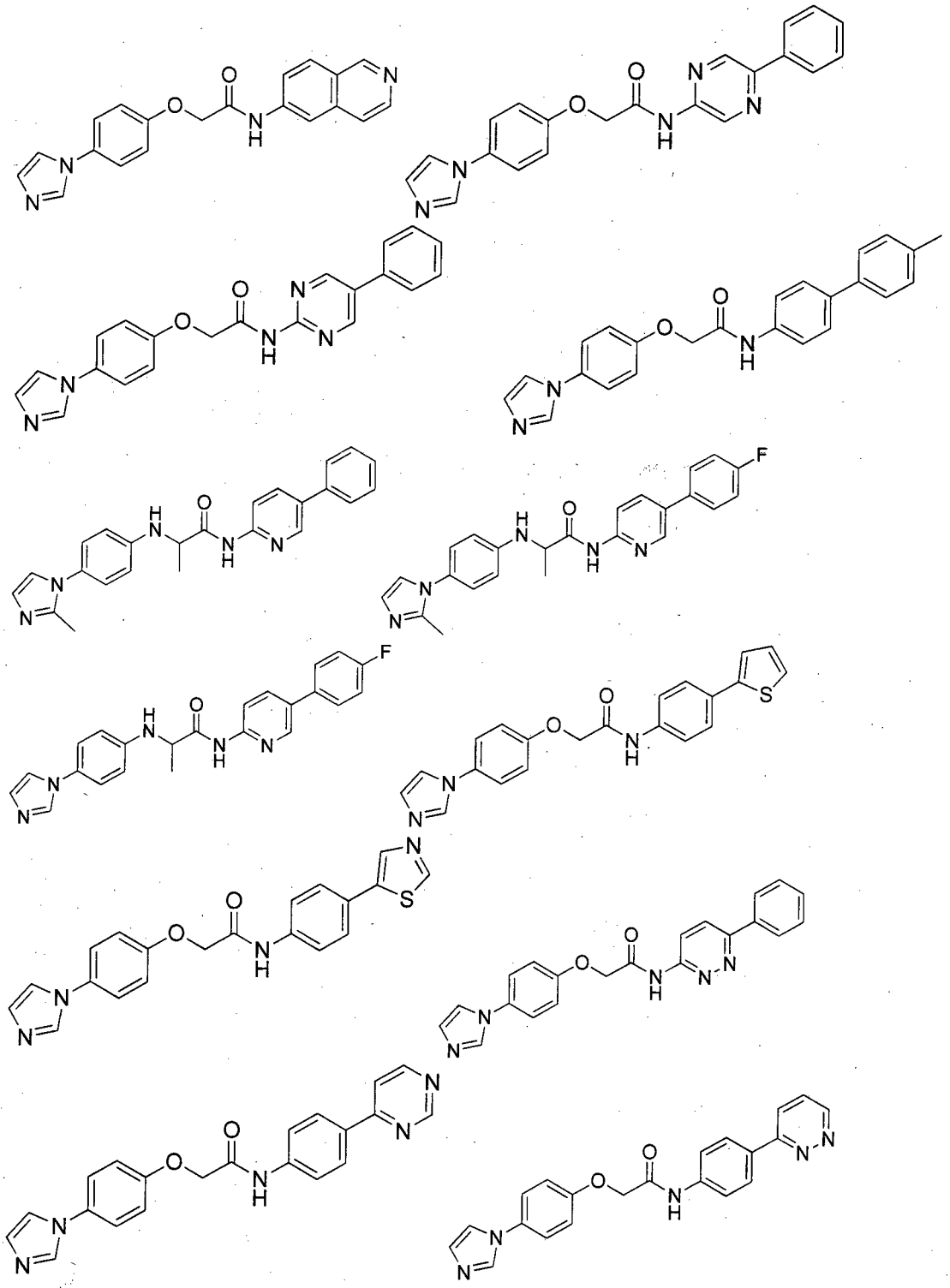
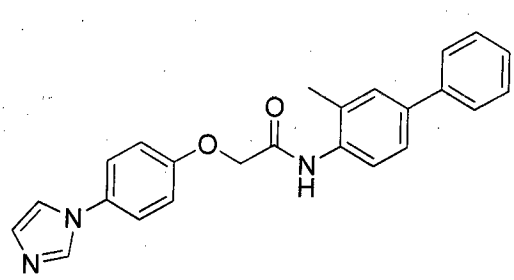
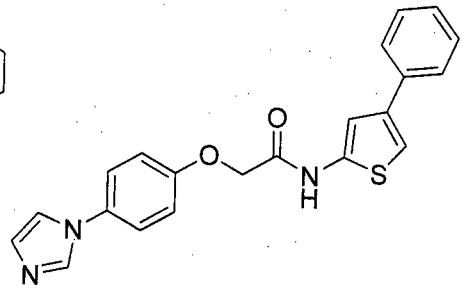


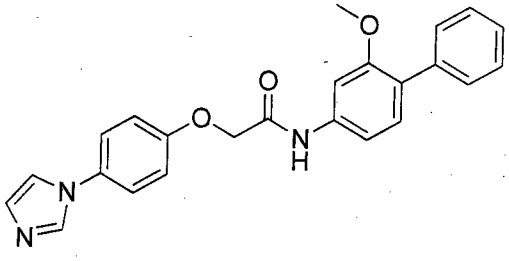















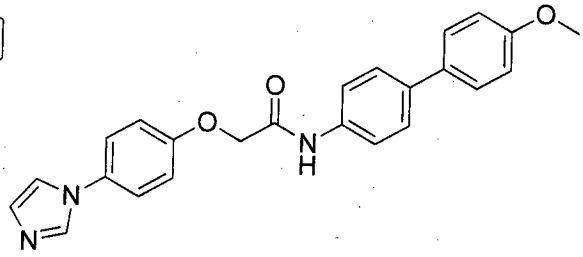


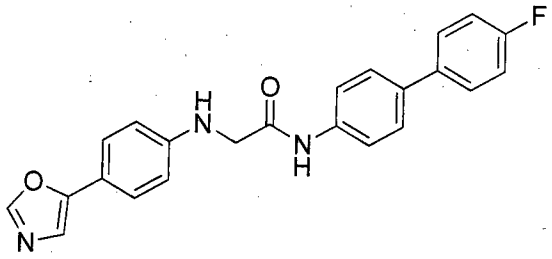


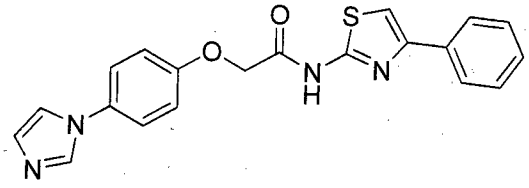


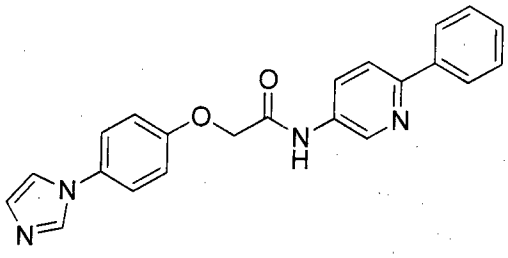


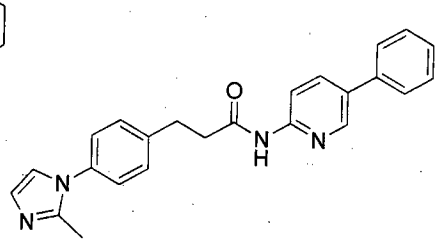


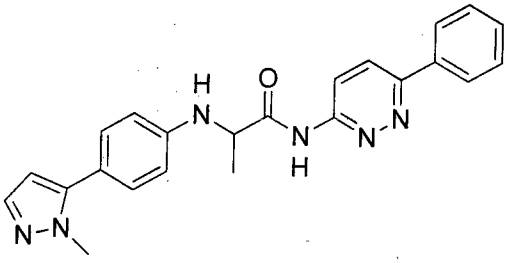


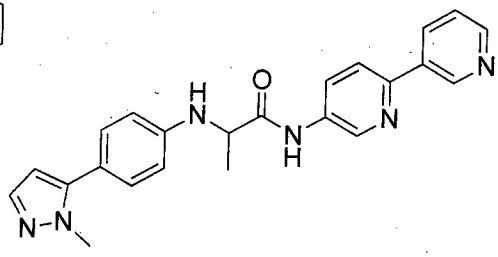


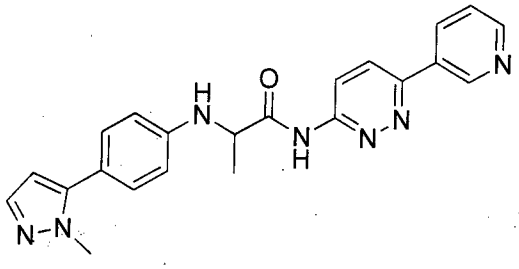


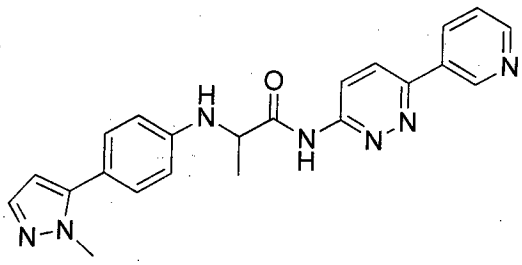


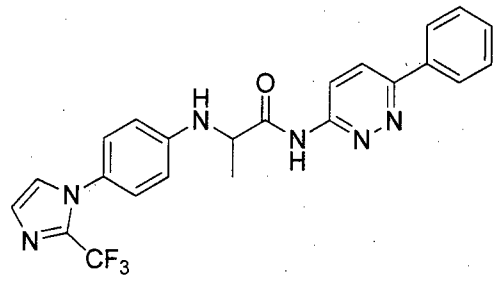


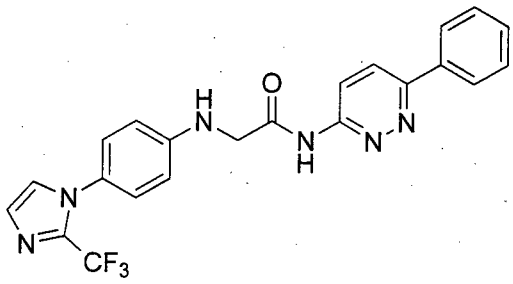


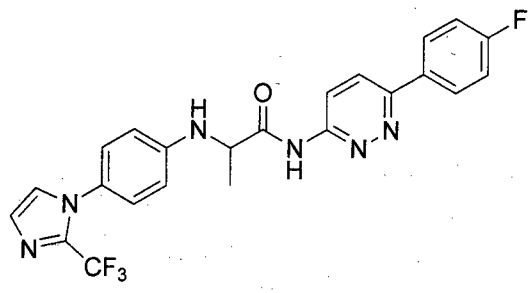


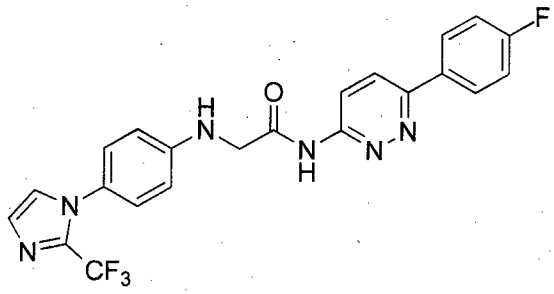


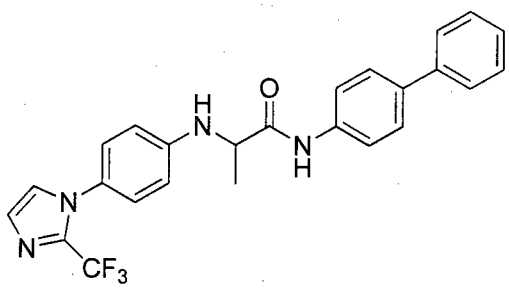


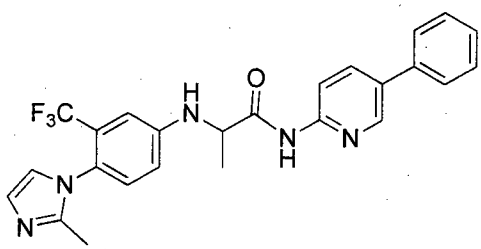


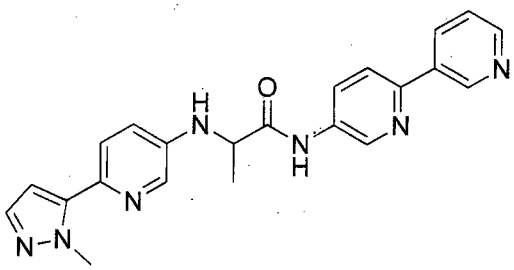


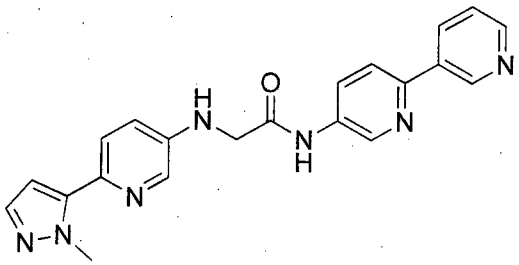


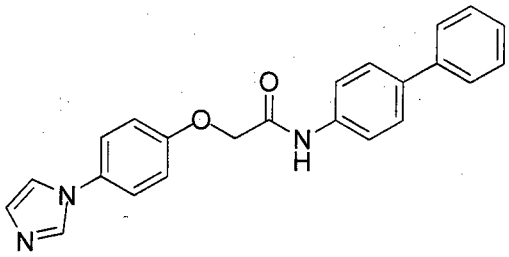


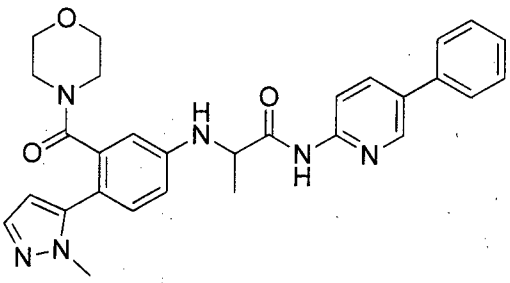


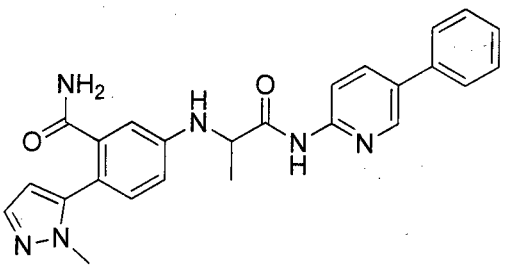


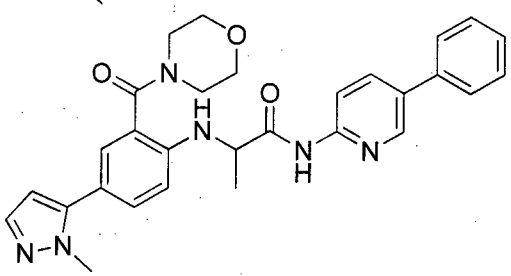


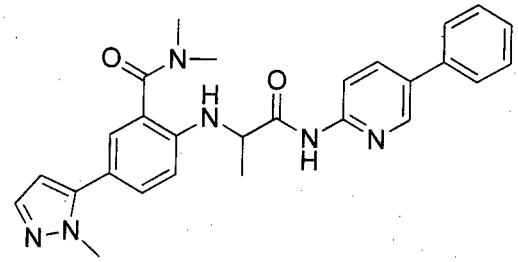


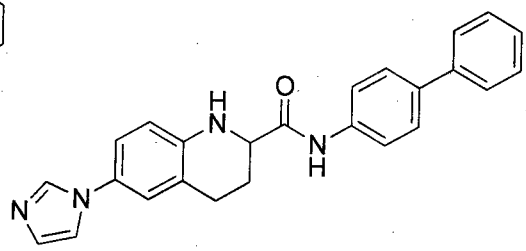


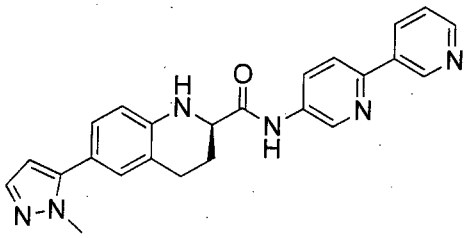


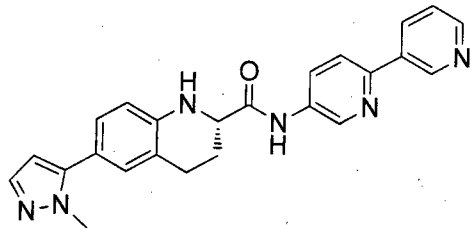


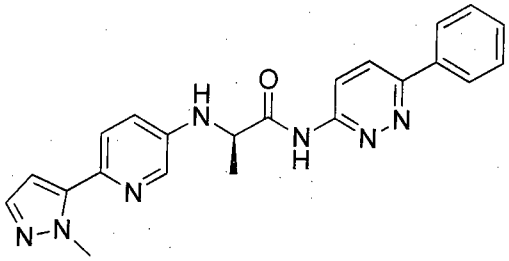


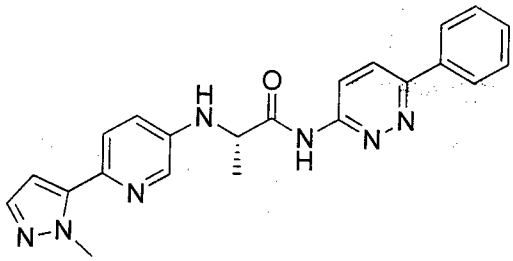


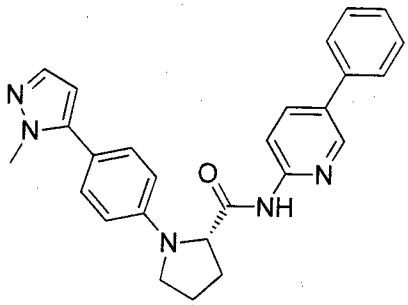


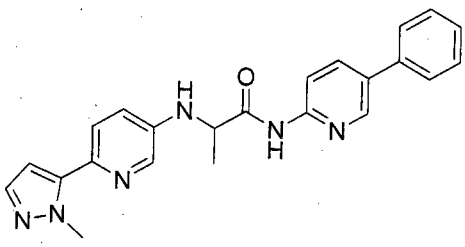


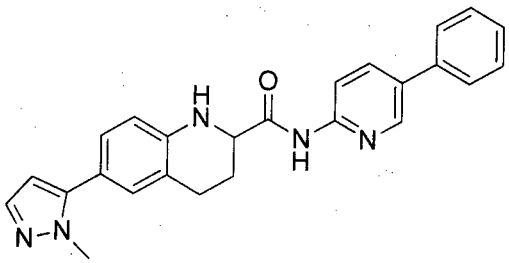


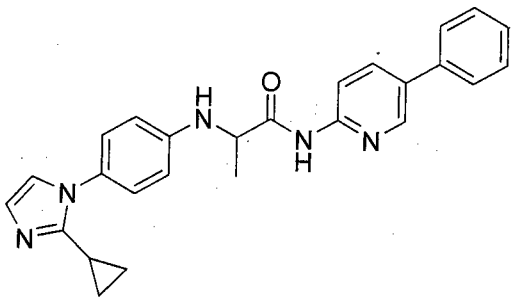


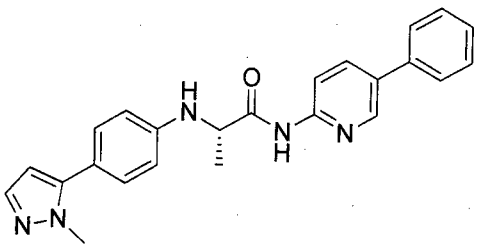


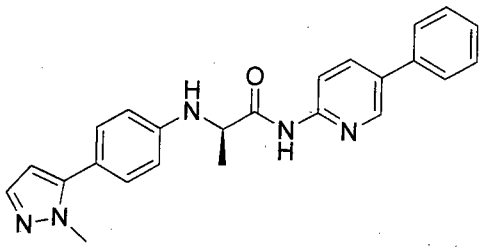


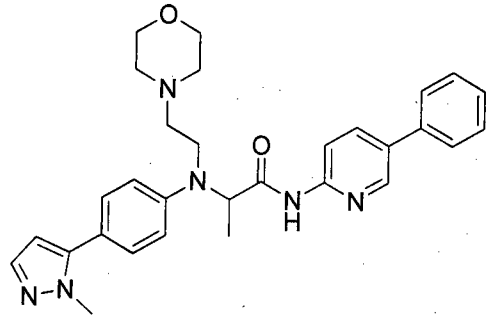


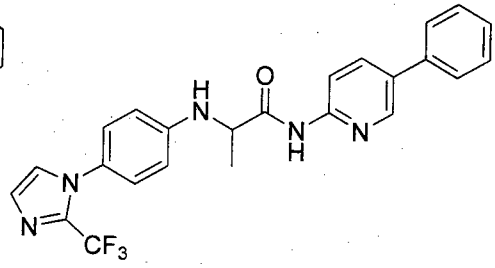


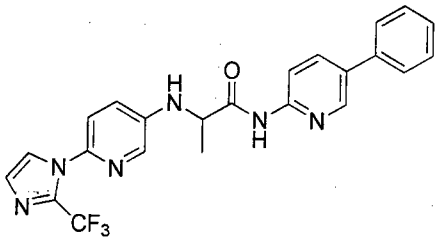


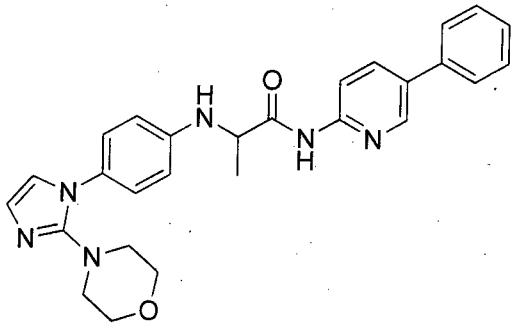


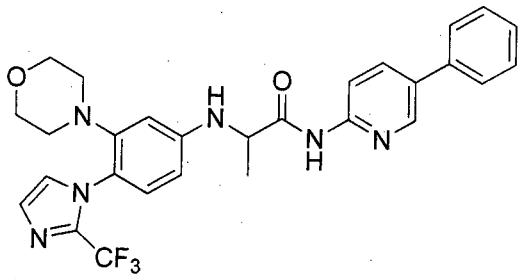


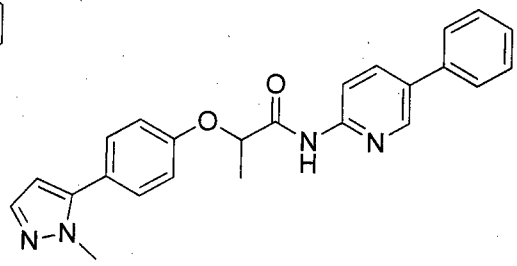


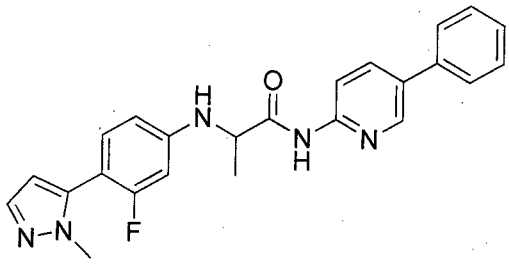


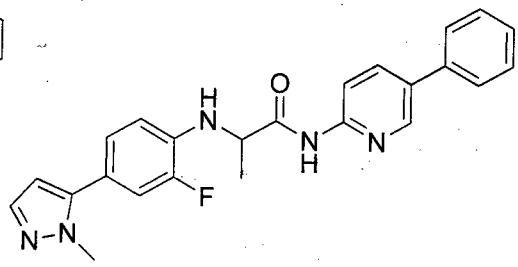


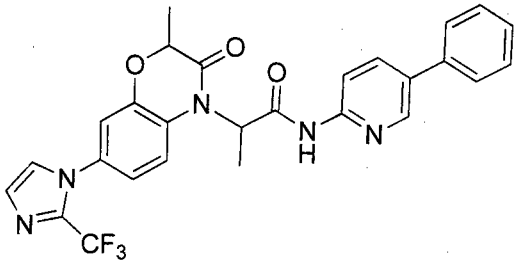


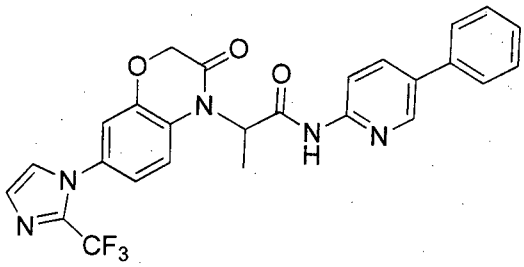


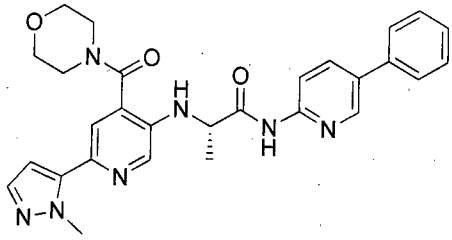


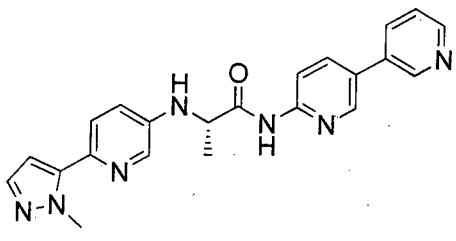


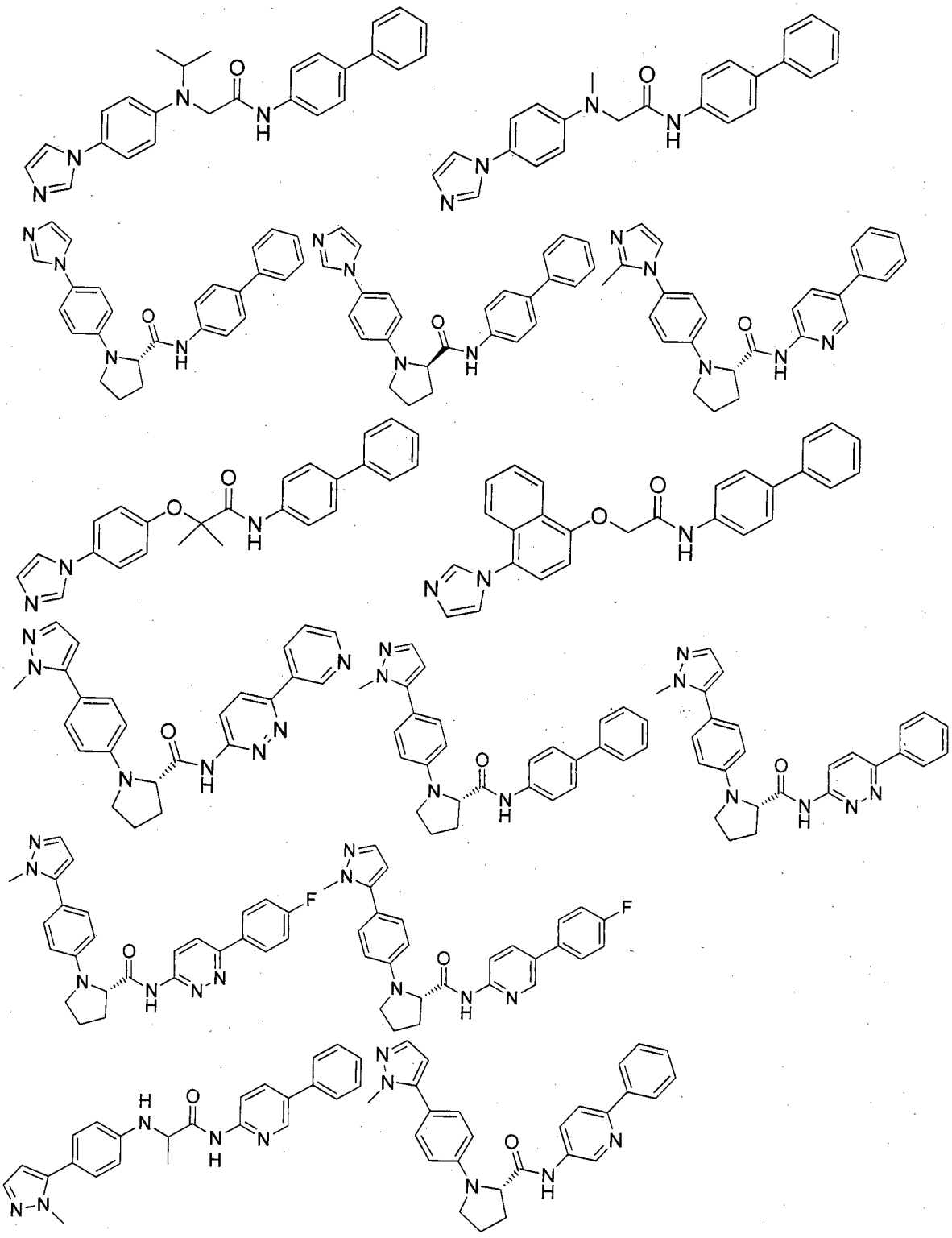


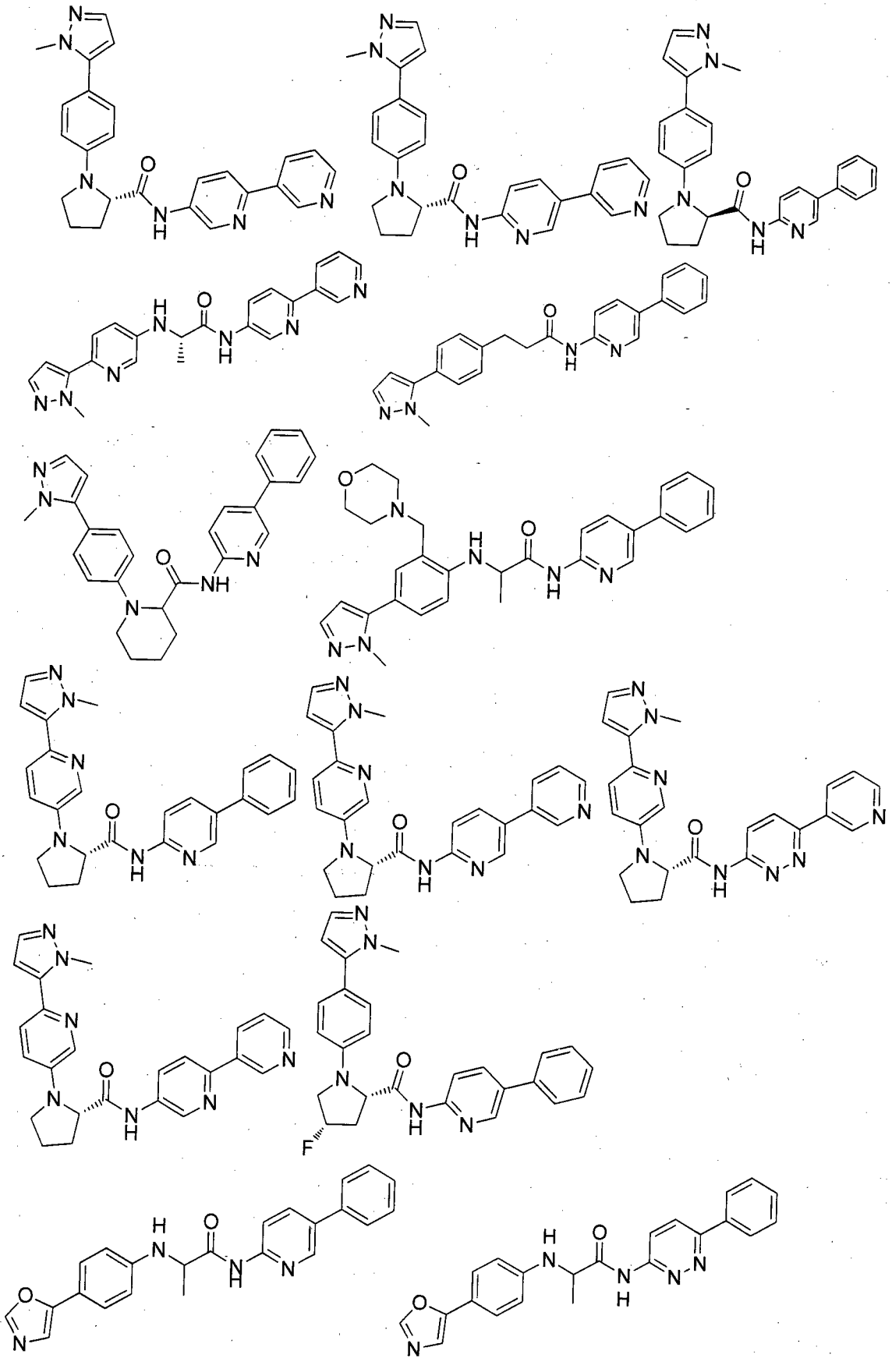












[00025] At each asymmetric centre in the molecule independently, the stereochemistry may be S or may be R.

[00026] The compound may have a IC_{50} against HEK293-STF3A cells of less than about 5μm, or less than about 1μm, or less than about 0.1μm, or less than about 0.01μm.

[00027] In an embodiment of this aspect there is provided a compound of structure (I):

$$Ar^1\text{-}Ar^2\text{-}X\text{-}C(HR^2)\text{-}C(=O)\text{-}N(H)\text{-}Ar^3\text{-}Ar^4$$

(I)

wherein:

Ar^1 is a 5-membered heterocyclic ring having either two or three heteroatoms independently selected from O and N provided that at least one is N;

Ar^2 is either a phenyl ring which is substituted in the 1 and 4 positions by Ar^1 and X, or a pyridine ring in which Ar^1 is in the 2 position and X is in the 5 position of said ring;

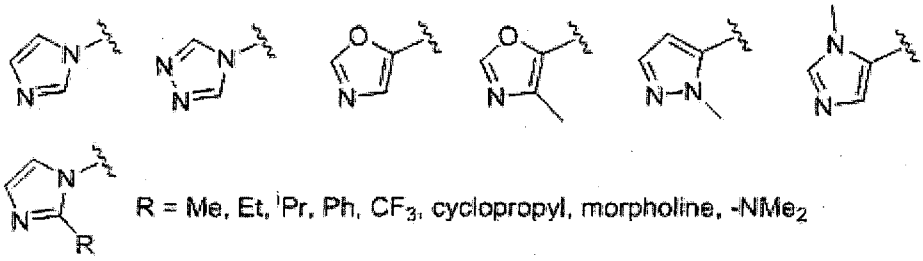
Ar^3 and Ar^4 are, independently, optionally substituted aryl or heteroaryl groups;

R^2 is H or methyl or $-(CH_2)_3-$ which, together with the carbon atom to which it is attached and X, forms a pyrrolidine ring, wherein if R^2 is $-(CH_2)_3-$, X is N; and

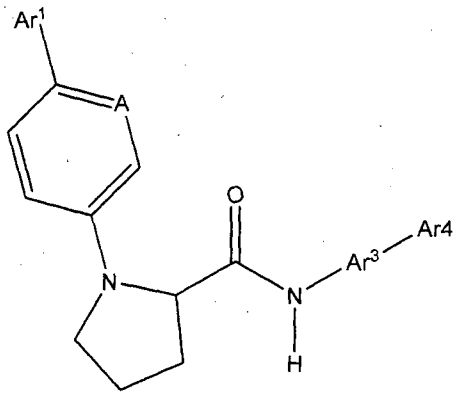
X is O, N or NH, wherein if X is N, it is bonded to R^2.

[00028] In this embodiment, Ar^1 may be unsubstituted or may have a single substituent, e.g. methyl, ethyl, isopropyl, phenyl, trifluoromethyl, morpholino or dimethylamino.

[00029] Specific examples of Ar^1 include:



[00030] In a further embodiment, there is provided a compound of structure (Ia):

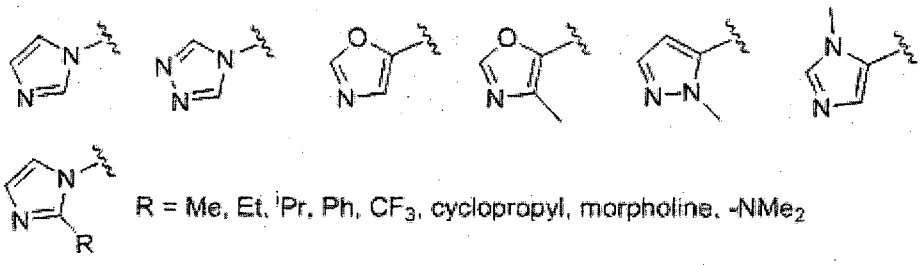


(Ia)

wherein:

A is CH or N;

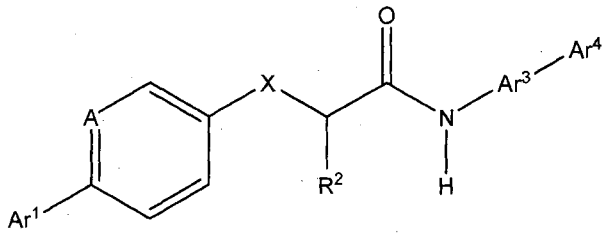
Ar^1 is selected from the following groups:



; and

Ar^3 and Ar^4 are, independently, optionally substituted aryl or heteroaryl groups.

[00031] In a further embodiment, there is provided a compound of structure (Ib):



(Ib)

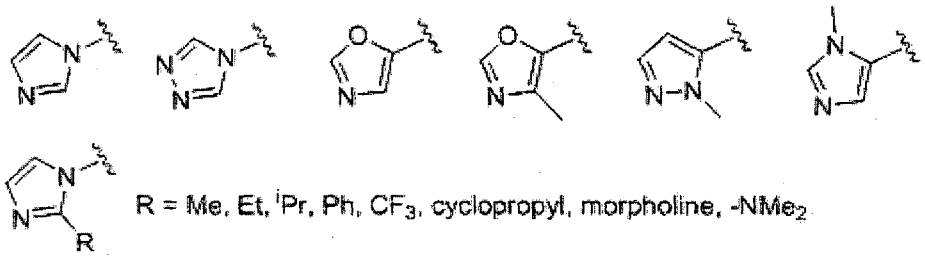
wherein:

A is CH or N;

X is O or NH;

R^2 is H or Me;

Ar^1 is selected from the following groups:



; and

Ar^3 and Ar^4 are, independently, optionally substituted aryl or heteroaryl groups.

[00032] The invention as described in the first aspect also encompasses all enantiomers and diastereomers of the compounds as well as salts of the compounds. The salt may be a pharmaceutically or veterinarially acceptable salt, for example a hydrochloride salt. Suitable salts include those listed in P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002.

[00033] In a second aspect of the invention there is provided a process for making a compound of structure I as described in the first aspect. There is also provided a compound when made by the process of the second aspect. This process may comprise coupling a compound of structure II with a compound of structure III

Ar^1-Ar^2-X-C(R^1R^2)-C(=O)-OH (II)

$HN(R^3)$-Ar^3-Ar^4 (III)

wherein R^1, R^2, R^3, X, Ar^1, Ar^2, Ar^3 and Ar^4 are as defined in the first aspect.

[00034] Alternatively the process may comprise coupling a compound of structure IV with a compound of structure V

(IV) (V)

wherein Hal is a halogen, e.g. Cl, Br or I and R^1, R^2, R^3, X, Ar^1, Ar^2, Ar^3 and Ar^4 are as defined in the first aspect.

[00035] It will be understood that other coupling reactions may lead to the compounds of the first aspect, e.g. coupling an Ar^1 derivative with an Ar^2-X-C(R^1R^2)-C(=O)-N(R^3)-Ar^3-Ar^4 derivative. These various coupling reactions will be readily apparent to a skilled person. In certain instances one or more functional groups may be protected during the coupling reaction. In this case, a subsequent reaction may be required in order to deprotect the protected functional group to generate the desired product.

[00036] In a third aspect of the invention there is provided a pharmaceutical composition comprising the compound of the first aspect, or a compound made by the process of the second aspect, and one or more pharmaceutically acceptable carriers, diluents and/or adjuvants.

[00037] In a fourth aspect of the invention there is provided use of a compound according to the first aspect, or of a compound made by the process of the second aspect, for the manufacture of a medicament for the treatment of a condition characterised by excessive WNT activity.

[00038] The condition may be a cancer, e.g. any one of cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreas adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma. The condition may be a severe fibrotic disease, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or

renal fibrosis. It may be a degenerative disease. It may be a metabolic disease such as diabetic retinopathy.

[00039] In a fifth aspect of the invention there is provided a compound according to the first aspect, or a compound made by the process of the second aspect, for use in therapy.

[00040] In a sixth aspect of the invention there is provided a method of treating a condition characterised by excessive WNT activity, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to the first aspect, or of a compound made by the process of the second aspect, or of a composition according to the third aspect. The disease or condition may be selected from the group consisting of cancer, fibrosis, stem cell and diabetic retinopathy. The cancer may be a cancer characterised by high WNT activity.

[00041] The condition may be a cancer, e.g. cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreas adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor or medulloblastoma.The condition may be a severe fibrotic diseases, such as pulmonary fibrosis, liver fibrosis, skin fibrosis or renal fibrosis. It may be a degenerative disease. It may be a metabolic disease such as diabetic retinopathy.

[00042] The subject may be a human subject or may be a non-human subject, e.g. a mammalian non-human subject or a non-human non-mammal.

Brief Description of Drawings

[00043] Fig. 1 shows a scheme of Wnts and signalling pathways.

[00044] Fig. 2 shows results of efficacy testing on compound 129.

[00045] Fig. 3 shows results of efficacy testing on compound 136.

Description of Embodiments

[00046] The invention relates to the preparation and the use of new compounds that modulate Wnt activity, to pharmaceutical compositions containing these compounds, to methods of using the compounds, either as a single agent or in combination, for treating diseases and conditions associated with Wnt pathway activity i.e. cancer, fibrosis, stem cell and diabetic retinopathy. Thus the invention relates to a class of compounds that act as inhibitors of the Wnt pathway and to pharmaceutical compositions comprising these compounds and to their use for the preparation of a medicament for the prophylaxis and treatment of diseases having a dysfunction linked to Wnt signaling pathway where Wnt plays a role in proliferation of cancer via multiple mechanisms, including a key role in stem cells maintenance. Suitable cancers that may be treated include, but are not limited, to cervical, colon, breast, bladder, head and neck, gastric, lung, ovarian, prostate, thyroid, non-small-cell lung, as well as chronic lymphocytic leukemia, mesothelioma, melanoma, pancreas adenocarcinoma, basal cell carcinoma, osteosarcoma, hepatocellular carcinoma, Wilm's tumor and medulloblastoma. The compounds may be used in the treatment other diseases with high Wnt expression such as fibrosis (including skin, idiopathic pulmonary, liver, renal interstitial, myocardial, infarct and liver) and diabetic retinopathy.

[00047] Figure 1 illustrates diverse Wnts, Wnt receptors and downstream pathways which all contribute to the role of Wnt. These pathways all play a role in development, stem cell maintenance, cancer and metastasis.

[00048] The compounds of the present invention are defined by structure (I):

$$Ar^1\text{-}Ar^2\text{-}X\text{-}C(R^1R^2)\text{-}C(=O)\text{-}N(R^3)\text{-}Ar^3\text{-}Ar^4$$

(I)

[00049] In the definition of the various components of this structure, the following apply:

[00050] Aryl (aromatic): this refers to homoaryl (i.e. carbocyclic) groups. They may be monocyclic (i.e. phenyl) or may be fused ring structures, optionally a 2 or 3 fused ring structures (e.g. naphthyl, anthracyl etc.).

[00051] Heteroaryl (heteroaromatic): this refers to aromatic structures comprising at least one ring heteroatom. These structures may have 1, 2 or 3 heteroatoms per ring. Each heteroatom may, independently, be nitrogen, oxygen or sulfur, or may be some other heteroatom. In many embodiments, the heteroatom or at least one of the heteroatoms, is nitrogen. Heteroaryl groups may comprise 5 membered rings or 6 membered rings. In some instances a heteroaryl group may be a fused ring structure, e.g. with 2 or 3 fused rings, at least one of which is heterocyclic. In some instances a heteroaryl group may comprise one or more fused aryl (i.e. homoaryl) rings. Examples of heteroaryl groups are pyridyl, oxazolyl, indolyl, imidazolyl, thiazolyl, pyrazolyl, pyridazinyl, furyl, thiophenyl, pyrazinyl, pyrimidinyl etc. In the case of imidazolyl and pyrazolyl groups, these may be attached through one of the nitrogen atoms or through a carbon atom. In the latter case, one of the nitrogen atoms may be substituted with an alkyl, aryl or heteroaryl group or some other group, or may bear a hydrogen atom.

[00052] For aryl or heteroaryl groups which have two substituents, the substituents may be in any suitable relationship, i.e. for 5 membered rings they may be in a 1,2 or 1,3 relationship and for 6 membered rings they may be in a 1,2, 1,3 or 1,4 relationship, provided (for heteroaryl rings) that such substitution is possible. Similarly if aryl or heteroaryl rings have more than 2 substituents, they may be in any suitable relationship. For example 3 substituents on a phenyl ring may be in a 1,2,3, 1,2,4, 1,3,5 or 1,3,5 relationship.

[00053] Alkyl: these groups may have from 1 to about 20 carbon atoms, or 1 to 16, 1 to 12, 1 to 8 or 1 to 6, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. They may be linear, branched or cyclic or may comprise two or more of these forms, provided that branched or cyclic alkyl groups have at least 3 carbon atoms. They may be optionally substituted. The term should be taken to encompass unsaturated equivalents of these groups (i.e. alkenyl and alkynyl groups). Examples include methyl, ethyl, propyl, butyl, cyclopropyl, cyclohexyl, cyclohexylmethyl, propenyl etc. Alkyl groups are bonded to one atom.

[00054] Alkylene: these may have from 1 to about 20 carbon atoms, or 1 to 16, 1 to 12, 1 to 8 or 1 to 6, e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 carbon atoms. They may be linear, branched or cyclic or may comprise two or more of these forms, provided that branched or cyclic alkylene groups have at least 3 carbon atoms. They may be

optionally substituted. The term should be taken to encompass unsaturated equivalents of these groups. Examples include $-(CH_2)-$, -CH=CH–, $-(CH_2)_2-$, $-(CH_2)_3-$ etc. Alkylene groups may be bonded to two atoms, or to the same atom through two bonds, each to a different atom in the alkylene group or to the same atom in the alkylene group. In some cases the alkylene group may be bonded through terminal atoms, i.e. may be α,ω-alkylene groups.

[00055] Optionally substituted: this indicates that there may or may not be substituents other than those specifically indicated. For example structure (I) contains a moiety $-Ar^3-Ar^4$, in which Ar^3 is optionally substituted. This should be taken to indicate that Ar^3 has at least substituent Ar^4 and may have other non-hydrogen substituents or may have no other non-hydrogen substituents. Possible substituents include alkyl groups, aryl groups and heteroaryl groups, as defined elsewhere herein and each of which may be optionally substituted. Other suitable substituents include hydroxy, alkoxy (i.e. –O-alkyl), aryloxy (i.e. –O-aryl), perhaloalkyl (e.g. trifluoromethyl), perhaloalkoxy (e.g. trifluoroalkoxy), halo (e.g. fluoro, chloro or bromo), ester (either –O-C(=O)R or –C(=O)-OR, where R is alkyl or aryl), amide (either –NR'-C(=O)R or –C(=O)-NRR', where R and R' are H, alkyl or aryl or, in the latter case, where R and R', together with the nitrogen atom to which they are attached, form an aliphatic ring for example an azetidine or aziridine ring), amine (i.e. NRR', where R and R' are H, alkyl or aryl or, together with the nitrogen atom to which they are attached, form an aliphatic ring for example an azetidine or aziridine ring), morpholino, etc.

[00056] It will be recognised that many of the compounds within the scope of the present invention may be present as different optical isomers and/or diastereomers. In such cases, the present invention contemplates all of the various alternatives with respect to asymmetric centres, either as pure substances or as mixtures of optical isomers and/or diastereomers. In particular, where optical isomers are possible, the invention encompasses (+), (-) and racemic forms. The degree of optical purity of (+) and (-) forms may be greater than about 50%, or greater than about 60, 70, 80, 90, 95 or 99%.

[00057] The compounds of the invention are amides. In certain embodiments, X is N and R^2 is $(CH_2)_3$, so that the $-X-C(R^1R^2)-$ of the molecule represents a pyrrolidine ring.

[00058] In many embodiments Ar^2 is a 6 membered ring. It may be fused with a second ring, optionally also 6-membered. It may be homoaromatic or it may be heteroaromatic. In some such embodiments, Ar^3 is also a 6-membered ring. In many examples, Ar^1 is a 5 membered ring however in other examples it is a 6 membered ring. In many examples Ar^4 is a 5 membered ring.

[00059] In summary, options contemplated by the invention are set out below. The code used is as follows:
5: 5 membered ring; 6: 6 membered ring; o: homoaromatic; e: heteroaromatic. For each option the combination is in the order $Ar^1Ar^2Ar^3Ar^4$. Thus, for example 5e6o6o6o represents a compound in which Ar^1 is a 5 membered heteroaromatic ring and Ar^2, Ar^3 and Ar^4 are all 6 membered homoaromatic rings. The contemplated options include:
5e5e5e5e, 5e5e5e6e, 5e5e5e6o, 5e5e6e5e, 5e5e6e6e, 5e5e6e6o, 5e5e6o5e, 5e5e6o6e, 5e5e6o6o, 5e6e5e5e, 5e6e5e6e, 5e6e5e6o, 5e6e6e5e, 5e6e6e6e, 5e6e6e6o, 5e6e6o5e, 5e6e6o6e, 5e6e6o6o, 5e6o5e5e, 5e6o5e6e, 5e6o5e6o, 5o6e6e5e, 5e6o6e6e, 5e6o6e6o, 5e6o6o5e, 5e6o6o6e, 5e6o6o6o, 6e5e5e5e, 6e5e5e6e, 6e5e5e6o, 6e5e6e5e, 6e5e6e6e, 6e5e6e6o, 6e5e6o5e, 6e5e6o6e, 6e5e6o6o, 6e6e5e5e, 6e6e5e6e, 6e6e5e6o, 6e6e6e5e, 6e6e6e6e, 6e6e6e6o, 6e6e6o5e, 6e6e6o6e, 6e6e6o6o, 6e6o5e5e, 6e6o5e6e, 6e6o5e6o, 6e6e6e5e, 6e6o6e6e, 6e6o6e6o, 6e6o6o5e, 6e6o6o6e, 6e6o6o6o, 6o5e5e5e, 6o5e5e6e, 6o5e5e6o, 6o5e6e5e, 6o5e6e6e, 6o5e6e6o, 6o5e6o5e, 6o5e6o6e, 6o5e6o6o, 6o6e5e5e, 6o6e5e6e, 6o6e5e6o, 6o6e6e5e, 6o6e6e6e, 6o6e6e6o, 6o6e6o5e, 6o6e6o6e, 6o6e6o6o, 6o6o5e5e, 6o6o5e6e, 6o6o5e6o, 6o6e6e5e, 6o6o6e6e, 6o6o6e6o, 6o6o6o5e, 6o6o6o6e, 6o6o6o6o.

[00060] In some embodiments Ar^2 has no more than 1 heteroatom. In others it has no more than 1 nitrogen atom. In some embodiments Ar^2 is a 6-membered ring (either homoaromatic or heteroaromatic). In other embodiments, when $-X-C(R^1R^2)-$ is $-CH_2-CH_2-$, Ar^1 is not a pyrazole ring linked to Ar^2 through a nitrogen atom in Ar^1. In some embodiments, Ar^1 has no more than 3 nitrogen atoms. Any two or more of these embodiments may be combined. Thus, for example in some embodiments, Ar^2 is a 6-membered ring (either homoaromatic or heteroaromatic), Ar^1 has no more than 3 nitrogen atoms, and, when $-X-C(R^1R^2)-$ is $-CH_2-CH_2-$, Ar^1 is not a pyrazole ring linked to Ar^2 through a nitrogen atom in Ar^1.

[00061] In some embodiments Ar^1 is a 1-methylpyrazole-5-yl group. Ar^1 may be a 1-methylpyrazole-5-yl group, X may be N or NH and Ar^2 may be a pyridine ring having the 1-methylpyrazole-5-yl group in the 2 position and the N or NH in the 5-position.

[00062] The compounds of the invention are commonly made by coupling a compound of structure II with a compound of structure III

Ar^1-Ar^2-X-C(R^1R^2)-C(=O)-OH (II)

$HN(R^3)$-Ar^3-Ar^4 (III)

so as to form an amide bond. Suitable conditions for this reaction are well known to those skilled in the art. Commonly a coupling agent, for example HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate), BOP ((benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate), DCC (N,N'-dicyclohexylcarbodiimide), DIPC (N,N'-diisopropylcarbodiimide), HOAt (3-hydroxytriazolo[4,5-*b*]pyridine) or similar will be used. Typically the reaction will be conducted under an inert atmosphere, e.g. nitrogen, argon, helium etc. The reaction may be conducted in any suitable solvent, commonly a dipolar aprotic solvent such as N-methyl morpholine, dioxane, THF, acetone, DMSO, DMF etc.

[00063] The synthesis of reagents II and III will depend on the details of the structure of these compounds. For example reagent II may be made by coupling a suitable Ar^1-containing compound with a suitable Ar^2-X- C(R^1R^2)-C(=O)-OA reagent (where -OA is a removable protecting group such as alkoxy). Coupling between aromatic/heteroaromatic groups may be conducted by well known methods such as a copper (I) catalysed coupling. Similarly reagent III may be made by coupling a suitable Ar^4-containing reagent with a suitable $HN(R^3)$-Ar^3-containing reagent (optionally protected to prevent unwanted reaction of the amine function) by a similar aryl and/or heteroaryl coupling reaction, followed if necessary by deprotection of the amine function.

[00064] Another route to making the compounds of the invention involves coupling a compound of structure IV with a compound of structure V

Ar^1-Ar^2-X-H (IV)

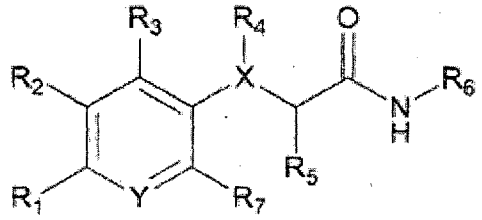
Hal-C(R^1R^2)-C(=O)N(R^3)- Ar^3-Ar^4 (V)

[00065] The skilled person will readily appreciate how to conduct such coupling reactions. For example if X is OH, the reaction may be accomplished under mild conditions in the presence of a mild base such as carbonate. Synthesis of reagents IV and V may be accomplished by commonly known methods. For example $HN(R^3)$-Ar^3-Ar^4 may be converted to reagent V by reaction with an appropriate haloacetyl halide. This may be a base catalysed reaction, e.g. using a tertiary amine catalyst such as triethylamine.

[00066] In some instances pyridine rings in reagents may be protected as their N-oxide and subsequently deprotected using a suitable reducing agent, e.g. iron powder in acetic acid.

[00067] In certain cases the coupling reactions such as described above may not be the final step in the synthesis. Thus the coupling may be effected before coupling Ar^1 to Ar^2, or before coupling Ar^4 to Ar^3. Suitable aryl-aryl coupling reactions that may be used to couple Ar^1 to Ar^2, or Ar^4 to Ar^3 (either before or after other coupling reactions used in the synthesis) include reaction of aryl halides (commonly bromides or iodides) with nitrogen heterocycles such as imidazole. This coupling may be catalysted by Cu(I) and base. Other suitable coupling reactions include reaction of palladium catalysed coupling of boronates or alkyl tin derivatives.

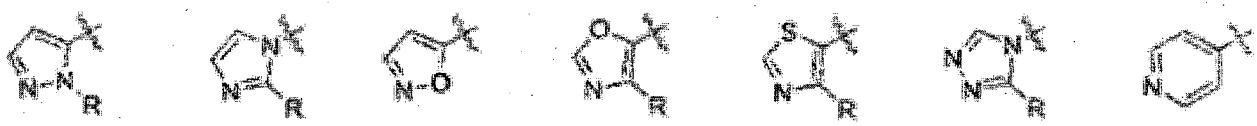
[00068] An alternative way to define certain of the compounds of the present invention is set out below. It should be noted that in this definition, X and R_1 to R_7 are not necessarily the same as for the earlier definition, although the general definitions of "alkyl", "aryl" etc. do apply.



X = O, N, C

Y = C, N

R_1 = substituted and unsubstituted 5 membered or 6 membered heterocycles including, but not limited to:



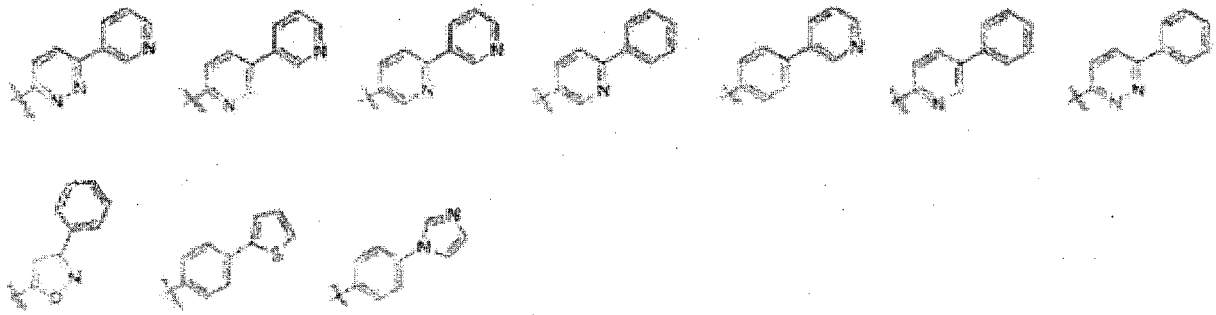
where R = H, alkyl, aryl, amine, amide

R_2, R_3 = (independently) alkyl, alkoxy, amine, carboxylic acid, carboxylic amide or fused bicycle

R_4 = alkyl or fused ring with aromatic ring at R_3

R_5 = smaller alkyl, cyclic amino acid fused with R_4 or R5 is fused with R_7

R_6 = biaryl, biaryl with heteroatom(s) or 5 membered and 6 membered heterocycles including, but not limited to:



R_7 = F, O, CO_2H, CONHalkyl or CONHaryl, CONdialkyl or cyclic amide

[00069] As discussed earlier, the compounds of the present invention may be used in therapy. They may be used for manufacture of medicaments for use in therapy.

[00070] The compounds of the present invention may be administered as compositions either therapeutically or preventively. In a therapeutic application, compositions are administered to a patient already suffering from a disease, in an amount sufficient to cure or at least partially arrest the disease and its complications. The composition should provide a quantity of the compound or agent sufficient to effectively treat the patient.

[00071] The therapeutically effective dose level for any particular patient will depend upon a variety of factors including: the disorder being treated and the severity of the disorder; activity of the compound or agent employed; the composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of sequestration of the agent or compound; the duration of the treatment; drugs used in

combination or coincidental with the treatment, together with other related factors well known in medicine.

[00072] One skilled in the art would be able, by routine experimentation, to determine an effective, non-toxic amount of agent or compound which would be required to treat applicable diseases.

[00073] Generally, an effective dosage is expected to be in the range of about 0.0001mg to about 1000mg per kg body weight per 24 hours; typically, about 0.001mg to about 750mg per kg body weight per 24 hours; about 0.01mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 500mg per kg body weight per 24 hours; about 0.1mg to about 250mg per kg body weight per 24 hours; about 1.0mg to about 250mg per kg body weight per 24 hours. More typically, an effective dose range is expected to be in the range about 1.0mg to about 200mg per kg body weight per 24 hours; about 1.0mg to about 100mg per kg body weight per 24 hours; about 1.0mg to about 50mg per kg body weight per 24 hours; about 1.0mg to about 25mg per kg body weight per 24 hours; about 5.0mg to about 50mg per kg body weight per 24 hours; about 5.0mg to about 20mg per kg body weight per 24 hours; about 5.0mg to about 15mg per kg body weight per 24 hours.

[00074] Typically, in therapeutic applications, the treatment would be for the duration of the disease state.

[00075] Further, it will be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the disease state being treated, the form, route and site of administration, and the nature of the particular individual being treated. Also, such optimum conditions can be determined by conventional techniques.

[00076] It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the composition given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

[00077] In general, suitable compositions may be prepared according to methods which are known to those of ordinary skill in the art and accordingly may include a pharmaceutically acceptable carrier, diluent and/or adjuvant.

[00078] These compositions can be administered by standard routes. In general, the compositions may be administered by the parenteral (e.g., intravenous, intraspinal, subcutaneous or intramuscular), or oral, or by direct injection to the affected site.

[00079] The carriers, diluents and adjuvants must be "acceptable" in terms of being compatible with the other ingredients of the composition, and not deleterious to the recipient thereof.

[00080] Examples of pharmaceutically acceptable carriers or diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysolpoxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrridone; agar; carrageenan; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 10% to 99.9% by weight of the compositions.

[00081] The compositions of the invention may be in a form suitable for administration by injection, in the form of a formulation suitable for oral ingestion (such as capsules, tablets, caplets, elixirs, for example), in an aerosol form suitable for administration by inhalation, such as by intranasal inhalation or oral inhalation, in a form suitable for parenteral administration, that is, subcutaneous, intramuscular or intravenous injection.

[00082] For administration as an injectable solution or suspension, non-toxic parenterally acceptable diluents or carriers can include, Ringer's solution, isotonic saline, phosphate buffered saline, ethanol and 1,2 propylene glycol.

[00083] Some examples of suitable carriers, diluents, excipients and adjuvants for oral use include peanut oil, liquid paraffin, sodium carboxymethylcellulose, methylcellulose, sodium alginate, gum acacia, gum tragacanth, dextrose, sucrose, sorbitol, mannitol, gelatine and lecithin. In addition these oral formulations may contain suitable flavouring and colourings agents. When used in capsule form the capsules may be coated with compounds such as glyceryl monostearate or glyceryl distearate which delay disintegration.

[00084] Adjuvants typically include emollients, emulsifiers, thickening agents, preservatives, bactericides and buffering agents.

[00085] Solid forms for oral administration may contain binders acceptable in human and veterinary pharmaceutical practice, sweeteners, disintegrating agents, diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatine, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, guar gum, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

[00086] Liquid forms for oral administration may contain, in addition to the above agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame

oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

[00087] Suspensions for oral administration may further comprise dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or acetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

[00088] The emulsions for oral administration may further comprise one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as guar gum, gum acacia or gum tragacanth.

[00089] Methods for preparing parenterally administrable compositions are apparent to those skilled in the art, and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa., hereby incorporated by reference herein.

[00090] The composition may incorporate any suitable surfactant such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

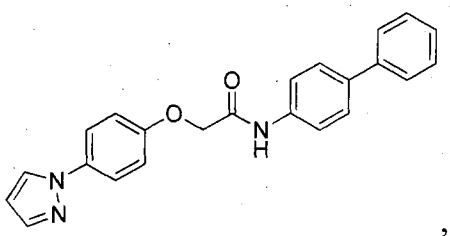
[00091] The compositions may also be administered in the form of liposomes. Liposomes are generally derived from phospholipids or other lipid substances, and are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The compositions in liposome form may contain stabilisers, preservatives, excipients and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art, and in relation to this

specific reference is made to: Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, the contents of which is incorporated herein by reference.

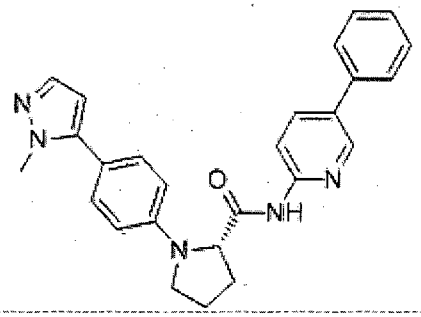
[00092] The oral formulation may be formulated with pharmacologically acceptable ingredients to make a tablet or capsule etc with an enteric coating. Methods for such formulations are well known to those skilled in the art (see e.g., Remington: The Science and Practice of Pharmacy, 19th ed. (1995) Mack Publishing Company, Easton, Pa.; herein incorporated by reference). The enteric coating may be an enteric coating which enhances delivery of the composition or active(s) drugs to specific regions of the gastrointestinal tract for enhanced bioavailability, such as are described in United States of America Patent Application Publication No. 20040162263 entitled "Pharmaceutical formulations targeting specific regions of the gastrointesinal tract" to Sands *et al* and published 19 August 2004.

Examples

[00093] The following examples provide compounds according to the present invention together with a number of general synthetic schemes for preparing the compounds. Each synthetic scheme has been illustrated with a specific example, and the examples following that may be made by the same general process. The person skilled in the art will readily appreciate the variations required to the illustrated example of each synthetic scheme in order to prepare other related compounds. With reference to the following examples, reference in this specification to a compound number will refer to the product described in, or finally produced by, the example of the same number. Thus, for example, Compound 2 is

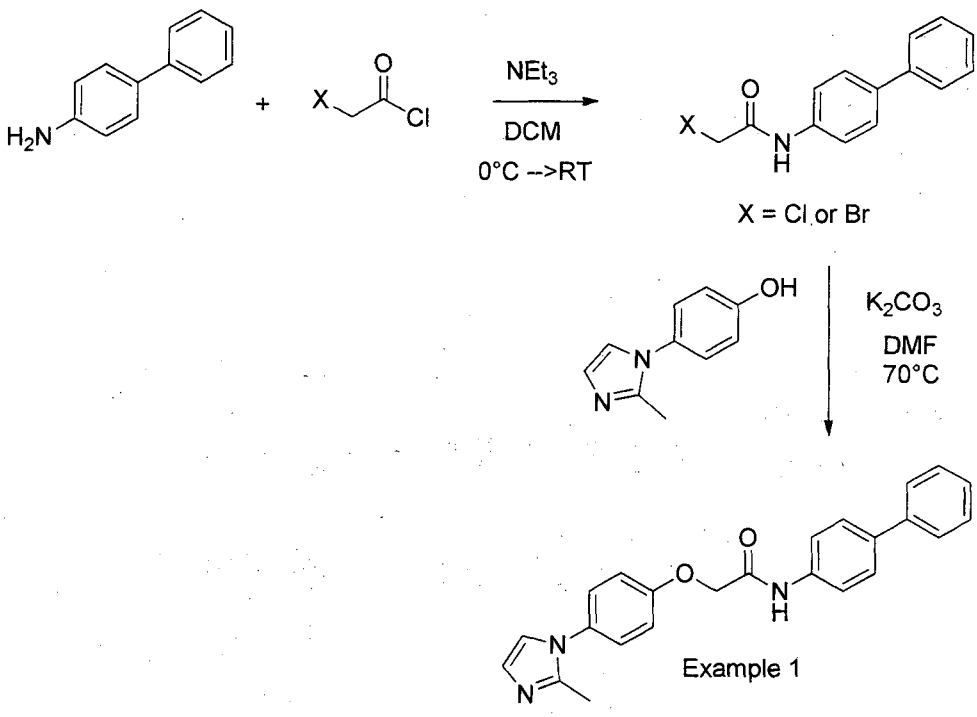


, described in Example 2 and Compound 94 is



----------, produced in Example 94. It should be noted that Compound 35 is the compound finally produced in Example 35 in which X=O, however all three compounds (i.e. in which X=NH, O or CH_2) are contemplated in the invention).

[00094] Example 1: N-(biphenyl-4-yl)-2-(4-(2-methyl-1H-imidazol-1-yl)phenoxy)acetamide



General Procedure 1:

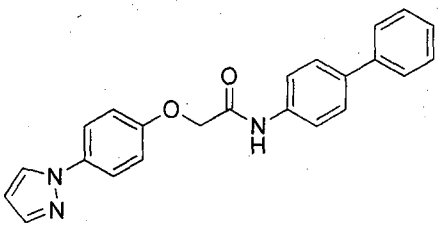
[00095] To biphenyl-4-amine (500 mg, 2.95 mmol) in anhydrous DCM (15 ml) at 0°C was added triethylamine (495 µl, 3.54 mmol) and 2-chloroacetyl chloride (282 µl, 1.418 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and.stirred for 2h, then it was diluted with H_2O (30 mL) and extracted with DCM (3x15 mL). The combined

organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude product N-(biphenyl-4-yl)-2-bromoacetamide (600 mg, brown solid) was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.70-7.63 (m, 6H), 7.46-7.42 (m, 2H), 7.35-7.31 (m, 1H), 4.27 (s, 2H).

[00096] To a solution of N-(biphenyl-4-yl)-2-bromoacetamide (92 mg, 0.316 mmol) and 4-(2-methyl-1H-imidazol-1-yl)phenol (55 mg, 0.316 mmol) in DMF (2 ml) was added K_2CO_3 (153 mg, 1.105 mmol). The solution was heated at 70°C for 16 h, then it was diluted with H_2O (25 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was purified by preparative HPLC (C18, eluent ACN, water, formic acid 0.1%) to afford N-(biphenyl-4-yl)-2-(4-(2-methyl-1H-imidazol-1-yl)phenoxy)acetamide (17 mg, 14%, HPLC 96%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 4H), 7.46-7.31 (m, 5H), 7.20 (d, *J*=1.6Hz, 1H), 7.15-7.13 (m, 2H), 6.87 (d, *J*=1.6Hz, 1H), 4.80 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.28, 157.19, 143.64, 139.52, 137.73, 135.31, 131.05, 128.80, 127.00, 126.87, 126.84, 126.51, 126.18, 120.93, 119.95, 115.30, 67.27, 13.31; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[00097] In some cases NaH is used as a base (instead of K_2CO_3) under an inert gas, e.g. nitrogen. 2-bromoacetyl chloride may be used instead of 2-chloroacetyl chloride.

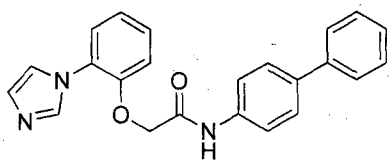
[00098] Example 2: 2-(4-(1H-pyrazol-1-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



73mg, 61%, HPLC 98%, light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.38 (d, *J*=2.4Hz, 1H), 7.78-7.64 (m, 9H), 7.44 (t, *J*=7.2Hz, 2H), 7.33 (t, *J*=7.6Hz, 1H), 7.14 (t, *J*=9.2Hz, 2H), 6.50 (t, *J*=2.0Hz, 1H), 4.77 (s, 2H) ; ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.45,

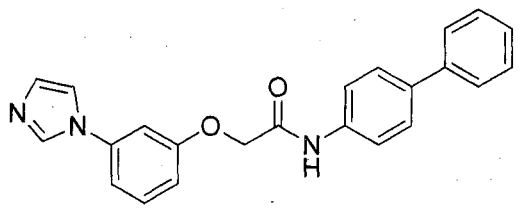
156.09, 140.41, 139.61, 137.79, 135.39, 134.00, 128.87, 127.48, 127.06, 126.90, 126.26, 120.08, 119.92, 115.47, 107.38, 67.51; MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[00099] Example 3: 2-(2-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



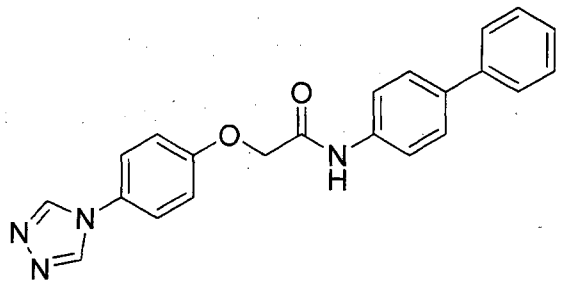
29 mg, 19%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.10 (s, 1H), 7.70-7.61 (m, 7H), 7.48-7.33 (m, 5H), 7.23-7.21 (m, 1H), 7.14-7.08 (m, 2H), 4.86 (s, 2H) ; ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.09, 150.52, 139.55, 137.70, 135.38, 128.87, 128.67, 128.33, 127.08, 126.99, 126.30, 126.25, 125.43, 121.75, 120.49, 119.76, 113.85, 67.46; MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[000100] Example 4: 2-(3-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



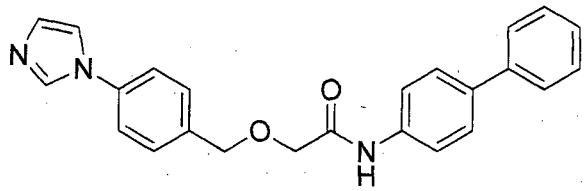
112 mg, 49%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.28 (s, 1H), 7.78-7.72 (m, 3H), 7.65 (d, J = 8.8 Hz, 4H), 7.48-7.42 (m, 3H), 7.37-7.26 (m, 3H), 7.11 (s, 1H), 7.03-6.99 (m, 1H), 4.83 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): 166.28, 158.88,139.60, 137.96, 137.78, 135.57, 135.40, 130.80, 129.86, 128.89, 127.09, 126.93, 126.27, 120.06, 118.01, 112.96, 112.91, 109.18, 67.35; MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

Example5: 2-(4-(4H-1,2,4-triazol-4-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



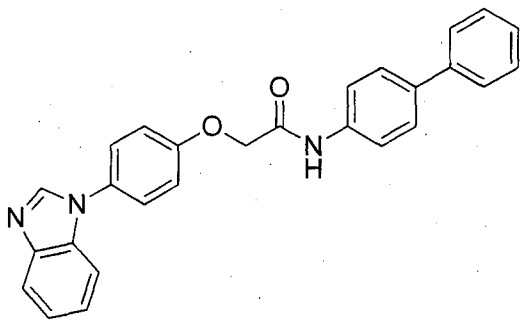
36 mg, 34%, HPLC 98%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.02 (s, 2H), 7.77-7.72 (m, 2H), 7.67-7.61 (m, 6H), 7.47-7.41 (m, 2H), 7.36-7.30 (m, 1H), 7.21-7.16 (m, 2H), 4.82 (s, 2H); MS (ESI) *m/z* 371 $[C_{22}H_{18}N_4O_2 + H]^+$.

[000101] Example6: 2-(4-(1H-imidazol-1-yl)benzyloxy)-N-(biphenyl-4-yl)acetamide



6.8 mg, 6%, HPLC 97%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.26 (s, 1H), 7.78-7.72 (m, 3H), 7.69-7.60 (m, 6H), 7.59-7.54 (m, 2H), 7.47-7.41 (m, 2H), 7.36-7.30 (m, 1H), 7.11 (s, 1H), 4.68 (s, 2H), 4.15 (s, 2H); MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

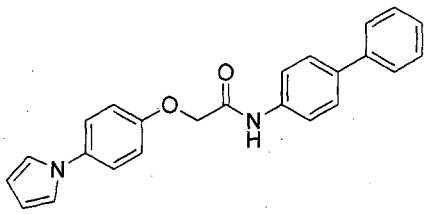
[000102] Example 7: 2-(4-(1H-benzo[d]imidazol-1-yl)phenoxy)-N-(biphenyl-4-



yl)acetamide

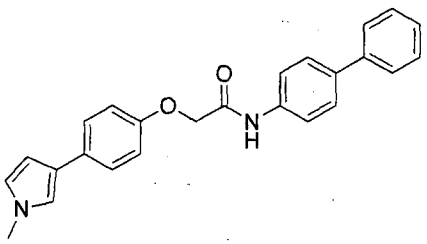
23 mg, 19%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.46 (s, 1H), 7.79-7.73 (m, 3H), 7.69-7.59 (m, 6H), 7.55-7.51 (m, 1H), 7.48-7.41 (m, 2H), 7.36-7.23 (m, 5H), 4.84 (s, 2H); MS (ESI) *m/z* 420 $[C_{27}H_{21}N_3O_2 + H]^+$.

[000103] Example 8: 2-(4-(1H-pyrrol-1-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



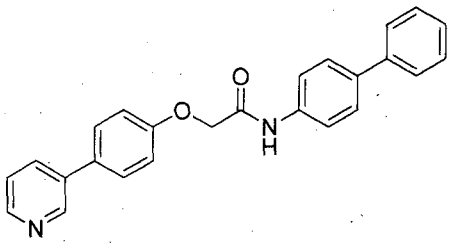
49mg, 65%, HPLC 97%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 4H), 7.52-7.42 (m, 4H), 7.35-7.31 (m, 1H), 7.25 (t, *J*=2.0 Hz, 2H), 7.11-7.08 (m, 2H), 6.22 (t, *J*=2.0 Hz, 2H), 4.75 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.53, 155.45, 139.59, 137.80, 135.36, 134.14, 128.87, 127.06, 126.90, 126.25, 120.84, 120.04, 119.06, 115.62, 109.93, 67.48; MS (ESI) *m/z* 369 $[C_{24}H_{20}N_2O_2 + H]^+$.

[000104] Example 9: N-(biphenyl-4-yl)-2-(4-(1-methyl-1H-pyrrol-3-yl)phenoxy)acetamide



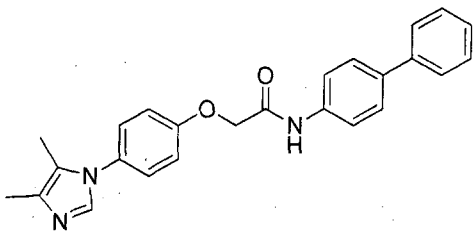
32mg, 28%, HPLC 96%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 4H), 7.46-7.31 (m, 5H), 7.06-7.04 (m, 2H), 6.78 (t, *J*=2.0Hz, 1H), 6.07-6.01 (m, 2H), 4.75 (s, 2H), 3.60 (s, 3H) ; ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.60, 156.66, 139.60, 137.83, 135.35, 133.10, 129.30, 128.87, 127.06, 126.90, 126.25, 123.55, 120.03, 114.71, 107.76, 107.13, 67.24, 34.69 ; MS (ESI) *m/z* 383 $[C_{25}H_{22}N_2O_2 + H]^+$.

[000105] Example 10: N-(biphenyl-4-yl)-2-(4-(pyridin-3-yl)phenoxy)acetamide



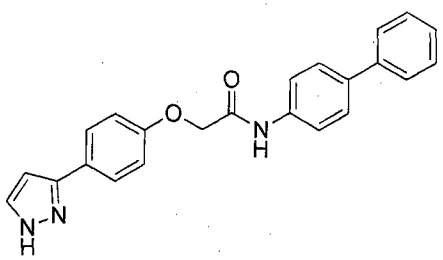
8mg, 16%, HPLC 97%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.85 (d, *J*= 2.0Hz, 1H), 8.51 (d, *J*= 4.4Hz, 1H), 8.02 (d, *J*= 8.0Hz, 1H), 7.76-7.63 (m, 8H), 7.44 (t, *J*= 7.2Hz, 3H), 7.33 (t, *J*= 7.2Hz, 1H), 7.15 (d, *J*= 8.8Hz, 2H), 4.79 (s, 2H) ; MS (ESI) *m/z* 381 $[C_{25}H_{20}N_2O_2 + H]^+$.

[000106] Example 11: N-(biphenyl-4-yl)-2-(4-(4,5-dimethyl-1H-imidazol-1-yl)phenoxy)acetamide



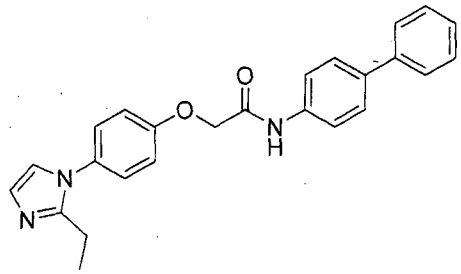
32 mg, 30%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 4H), 7.56 (s,1H), 7.44 (t, *J*=7.6 Hz, 5H), 7.35-7.31 (m, 3H), 7.14-7.12 (m, 2H), 4.80 (s, 2H), 2.09 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.20, 162.93, 157.11, 139.42, 137.62, 135.21, 135.06, 132.96, 129.92, 128.69, 126.89, 126.74, 126.44, 126.08, 122.20, 119.85, 115.23, 67.17, 12.50, 8.56; MS (ESI) *m/z* 398 $[C_{25}H_{23}N_3O_2 + H]^+$.

[000107] Example 12: 2-(4-(1H-pyrazol-3-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



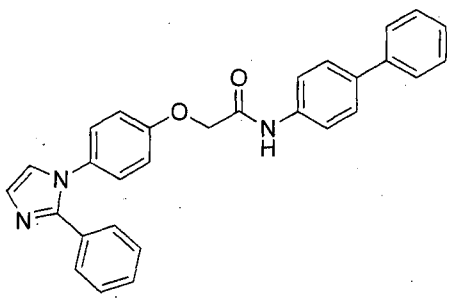
31 mg, 24%, HPLC 98%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 9.44 (s, 1H), 7.76 (d, *J*=2.4 Hz, 1H), 7.71-7.58 (m, 8H), 7.44 (t, *J*=7.6 Hz, 2H), 7.32 (t, *J*=7.6 Hz, 1H), 6.78-6.76 (m, 2H), 6.59 (d, *J*=2.4 Hz, 1H), 5.04 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 165.54, 156.87, 150.67, 139.50, 137.99, 135.17, 133.07, 128.79, 126.97, 126.94, 126.33, 126.16, 124.39, 119.48, 115.25, 101.75, 54.55; MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[000108] Example 13: N-(biphenyl-4-yl)-2-(4-(2-ethyl-1H-imidazol-1-yl)phenoxy)acetamide



43 mg, 81%, HPLC 95%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.76-7.64 (m, 6H), 7.46-7.31 (m, 5H), 7.18-7.12 (m, 3H), 6.89 (s, 1H), 4.80 (s, 2H), 2.58-2.49 (m, 2H), 1.11 (t, *J*=7.6Hz, 3H); MS (ESI) *m/z* 398 $[C_{25}H_{23}N_3O_2 + H]^+$.

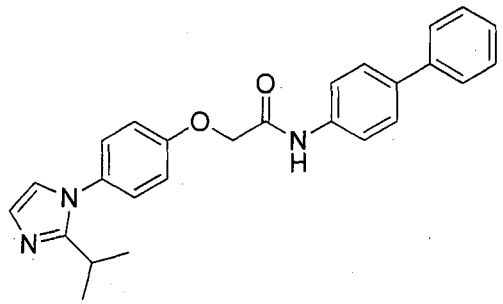
[000109] Example 14: N-(biphenyl-4-yl)-2-(4-(2-phenyl-1H-imidazol-1-yl)phenoxy)acetamide



41 mg, 73%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.75-7.73 (m, 2H), 7.66-7.64 (m, 4H), 7.44-7.41 (m, 3H), 7.33-7.25 (m, 8H), 7.15-7.08 (m, 3H), 4.78 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.26, 157.41, 145.70, 139.59, 137.79, 135.39, 131.63,

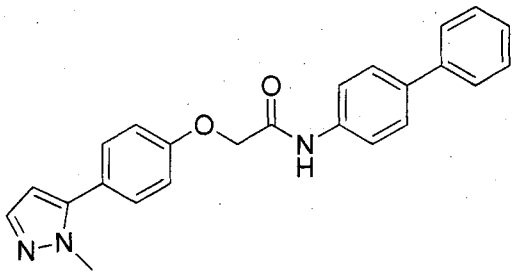
130.47, 128.88, 128.43, 128.16, 128.09, 128.03, 127.29, 127.08, 126.91, 126.26, 123.95, 120.03, 115.44, 67.34; MS (ESI) *m/z* 446 $[C_{29}H_{23}N_3O_2 + H]^+$.

[000110] Example 15: N-(biphenyl-4-yl)-2-(4-(2-isopropyl-1H-imidazol-1-yl)phenoxy)acetamide



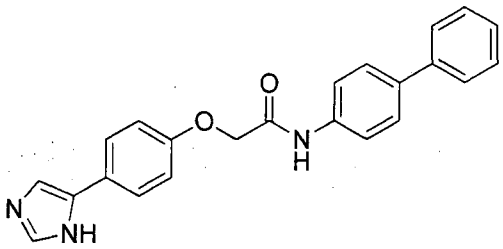
7 mg, 6%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (bs, 1H), 7.78-7.72 (m, 2H), 7.69-7.61 (m, 4H), 7.48-7.41 (m, 2H), 7.38-7.30 (m, 3H), 7.18-7.10 (m, 3H), 6.89 (d, J = 1.2Hz, 1H), 4.81 (s, 2H), 2.95-2.80 (m, 1H), 1.19 (d, J = 6.8Hz, 6H); MS (ESI) *m/z* 412 $[C_{26}H_{25}N_3O_2 + H]^+$.

[000111] Example 16: N-(biphenyl-4-yl)-2-(4-(1-methyl-1H-pyrazol-5-yl)phenoxy)acetamide



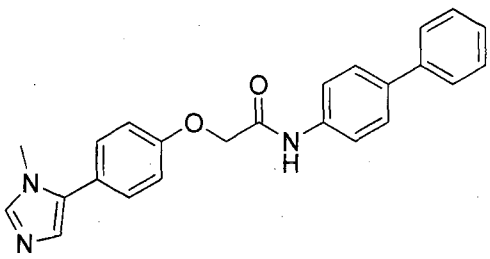
100 mg, 91%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (bs, 1H), 7.78-7.73 (m, 2H), 7.68-7.62 (m, 4H), 7.52-7.41 (m, 5H), 7.37-7.30 (m, 1H), 7.15-7.10 (m, 2H), 6.33 (d, J = 1.6Hz, 1H), 4.80 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): 166.39, 157.83, 142.32, 139.58, 137.80, 137.71, 135.34, 129.75, 128.84, 127.04, 126.88, 126.23, 123.22, 120.00, 114.93, 105.36, 67.17, 37.33; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000112] Example 17: 2-(4-(1H-imidazol-5-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



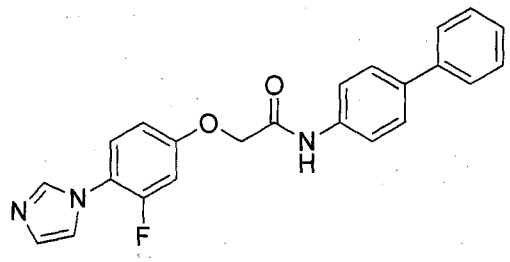
8 mg, 8%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (bs, 1H), 7.78-7.72 (m, 2H), 7.72-7.67 (m, 2H), 7.67-7.62 (m, 6H), 7.48-7.41 (m, 3H), 7.36-7.30 (m, 1H), 7.05-6.98 (m, 2H), 4.72 (s, 2H); MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[000113] Example 18: N-(biphenyl-4-yl)-2-(4-(1-methyl-1H-imidazol-5-yl)phenoxy)acetamide



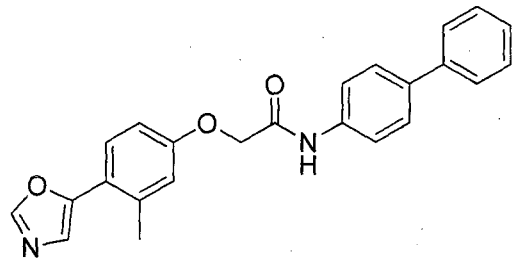
83 mg, 76%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (bs, 1H), 7.79-7.72 (m, 2H), 7.69-7.61 (m, 5H), 7.49-7.41 (m, 4H), 7.37-7.30 (m, 1H), 7.13-7.06 (m, 2H), 6.99-6.94 (m, 1H), 4.78 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.50, 157.35, 139.60, 139.22, 137.82, 135.35, 132.27, 129.26, 128.87, 127.06, 126.91, 126.88, 126.25, 122.83, 120.01, 114.98, 67.19, 32.15; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000114] Example 19: N-(biphenyl-4-yl)-2-(3-fluoro-4-(1H-imidazol-1-yl)phenoxy)acetamide



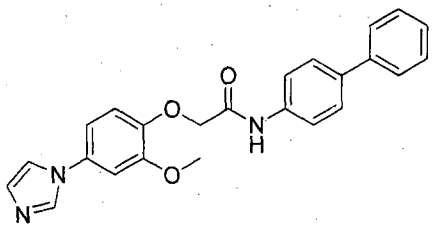
80 mg, 72%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (bs, 1H), 7.94 (s, 1H), 7.78-7.70 (m, 2H), 7.70-7.61 (m, 4H), 7.61-7.53 (m, 1H), 7.50-7.40 (m, 3H), 7.37-7.30 (m, 1H), 7.24-7.17 (m, 1H), 7.10 (s, 1H), 7.04-6.97 (m, 1H), 4.85 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 165.95, 158.21, 158.11, 156.30, 153.83, 139.58, 137.75, 137.44, 135.41, 128.96, 128.88, 127.09, 126.94, 126.76, 126.26, 120.43, 119.99, 118.60, 118.48, 111.47, 103.84, 103.60, 67.49; MS (ESI) *m/z* 388 $[C_{23}H_{18}FN_3O_2 + H]^+$.

[000115] Example 20: N-(biphenyl-4-yl)-2-(3-methyl-4-(oxazol-5-yl)phenoxy)acetamide



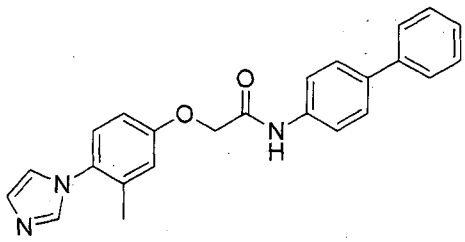
102 mg, 92%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (bs, 1H), 8.42 (s, 1H), 7.78-7.71 (m, 2H), 7.69-7.57 (m, 5H), 7.48-7.41 (m, 2H), 7.38-7.29 (m, 2H), 7.05-7.00 (m, 1H), 7.00-6.95 (m, 1H), 4.78 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 166.32, 157.81, 151.02, 149.71, 139.58, 137.77, 136.53, 135.35, 128.83, 128.29, 127.03, 126.87, 126.22, 123.05, 120.14, 120.02, 117.30, 112.47, 67.09, 21.32; MS (ESI) *m/z* 385 $[C_{24}H_{20}N_2O_3 + H]^+$.

[000116] Example 21: 2-(4-(1H-imidazol-1-yl)-2-methoxyphenoxy)-N-(biphenyl-4-yl)acetamide



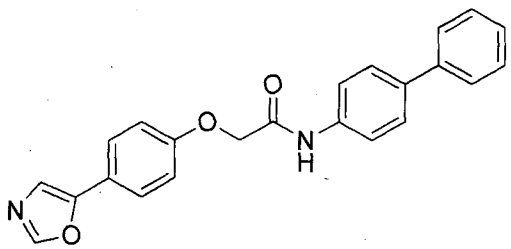
29 mg, 26%, HPLC 97%, white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.09 (s, 1H), 7.74-7.69 (m, 2H), 7.65-7.58 (m, 4H), 7.56-7.53 (m, 1H), 7.46-7.39 (m, 2H), 7.34-7.29 (m, 1H), 7.26 (d, J = 2.4Hz, 1H), 7.23-7.19 (m, 1H), 7.15-7.09 (m, 2H), 4.74 (s, 2H), 4.01 (s, 3H); MS (ESI) *m/z* 400 $[C_{24}H_{21}N_3O_3 + H]^+$.

[000117] Example 22: 2-(4-(1H-imidazol-1-yl)-3-methylphenoxy)-N-(biphenyl-4-yl)acetamide



40 mg, 37%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.40 (s, 1H), 7.74-7.69 (m, 2H), 7.64-7.58 (m, 4H), 7.45-7.39 (m, 2H), 7.34-7.29 (m, 1H), 7.28-7.22 (m, 2H), 7.16-7.09 (m, 2H), 7.05-7.00 (m, 1H), 4.76 (s, 2H), 2.16 (s, 3H); MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

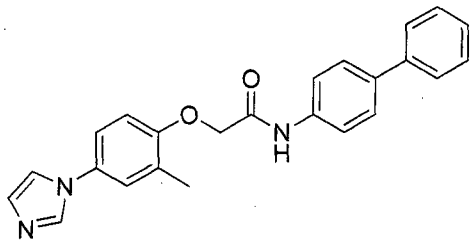
[000118] Example 23: N-(biphenyl-4-yl)-2-(4-(oxazol-5-yl)phenoxy)acetamide



71 mg, 66%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.38 (s, 1H), 7.77-7.72 (m, 2H), 7.72-7.67 (m, 2H), 7.67-7.62 (m, 4H), 7.55 (s, 1H), 7.48-7.41

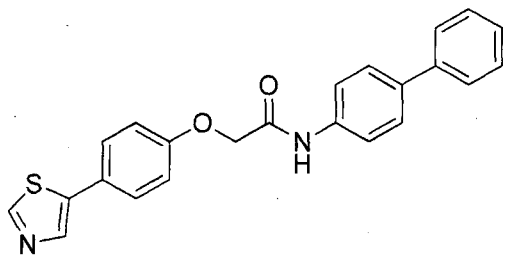
(m, 2H), 7.36-7.30 (m, 1H), 7.16-7.10 (m, 2H), 4.79 (s, 2H); MS (ESI) *m/z* 371 [$C_{23}H_{18}N_2O_3$ + H]$^+$.

[000119] Example 24: 2-(4-(1H-imidazol-1-yl)-2-methylphenoxy)-N-(biphenyl-4-yl)acetamide



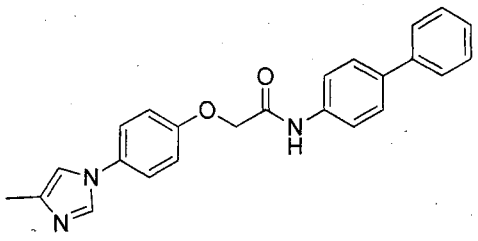
23 mg, 21%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.01 (s, 1H), 7.72-7.66 (m, 2H), 7.63-7.57 (m, 4H), 7.49-7.45 (m, 1H), 7.44-7.37 (m, 3H), 7.37-7.27 (m, 2H), 7.10 (s, 1H), 7.08-7.02 (m, 1H), 4.82 (s, 2H), 2.42 (s, 3H); MS (ESI) *m/z* 384 [$C_{24}H_{21}N_3O_2$ + H]$^+$.

[000120] Example 25: N-(biphenyl-4-yl)-2-(4-(thiazol-5-yl)phenoxy)acetamide



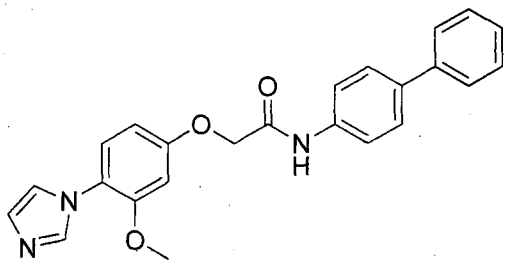
71 mg, 66%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (bs, 1H), 9.02 (s, 1H), 8.20 (s, 1H), 7.78-7.70 (m, 2H), 7.70-7.60 (m, 6H), 7.49-7.40 (m, 2H), 7.38-7.30 (m, 1H), 7.10 (d, J = 8.8 Hz, 2H), 4.79 (s, 2H); MS (ESI) *m/z* 387 [$C_{23}H_{18}N_2O_2$ + H]$^+$.

[000121] Example 26: N-(biphenyl-4-yl)-2-(4-(4-methyl-1H-imidazol-1-yl)phenoxy)acetamide



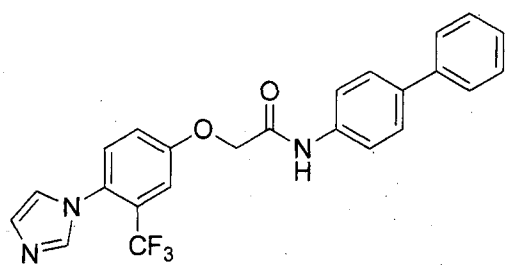
23 mg, 11%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.00 (d, *J*=1.2Hz, 1H), 7.76-7.74 (m, 2H), 7.66-7.64 (m, 4H), 7.55-7.51 (m, 2H), 7.45 (t, *J*=7.6Hz, 2H), 7.34 (t, *J*=7.6Hz, 2H), 7.14-7.12 (m, 2H), 4.78 (s, 2H), 2.15 (s, 3H); MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000122] Example 27: 2-(4-(1H-imidazol-1-yl)-3-methoxyphenoxy)-N-(biphenyl-4-yl)acetamide



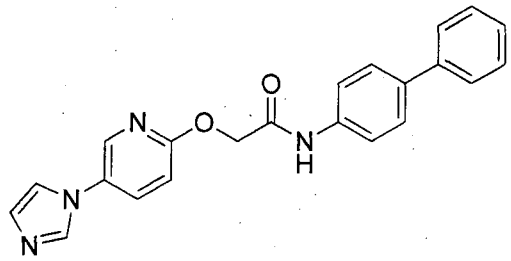
30 mg, LC-MS 99%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 8.24 (br. s, 1H), 7.71-7.57 (m, 7H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 12.0 Hz, 2H), 6.72 (d, *J* = 4.0 Hz, 1H), 6.64-6.62 (dd, *J* = 4.0, *J* = 4.0 Hz, 1H), 4.68 (s, 2H), 3.87 (s, 3H); MS (ESI) *m/z* 400 [M+1].

[000123] Example 28: 2-(4-(1H-imidazol-1-yl)-3-(trifluoromethyl)phenoxy)-N-(biphenyl-4-yl)acetamide



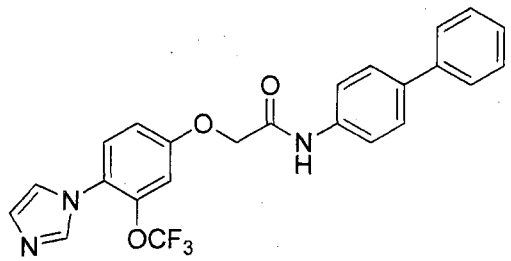
50 mg, LC-MS 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.70-7.58 (m, 7H), 7.47-7.33 (m, 5H), 7.26 (s, 1H), 7.08 (s, 1H), 4.68 (s, 2H); MS (ESI) *m/z* 438 [M+1].

[000124] Example 29: 2-(5-(1H-imidazol-1-yl)pyridin-2-yloxy)-N-(biphenyl-4-yl)acetamide



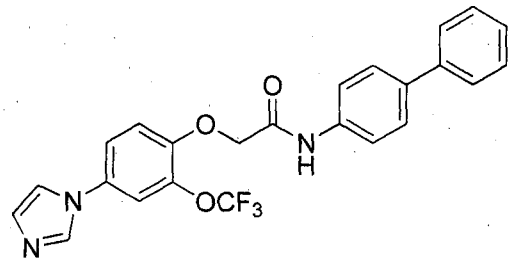
30 mg, 6%, LC-MS 99%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.5 (s, 1H), 9.1 (bs, 1H), 8.3 (s, 1H), 7.90-7.87 (m, 2H), 7.70-7.63 (m, 7H), 7.44 (t, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 6.66 (d, J = 12.0 Hz, 1H), 4.8 (s, 2H); MS (ESI) *m/z* 371.05 $[C_{22}H_{18}N_4O_2+H]^+$.

[000125] Example 30: 2-(4-(1H-imidazol-1-yl)-3-(trifluoromethoxy)phenoxy)-N-(biphenyl-4-yl)acetamide



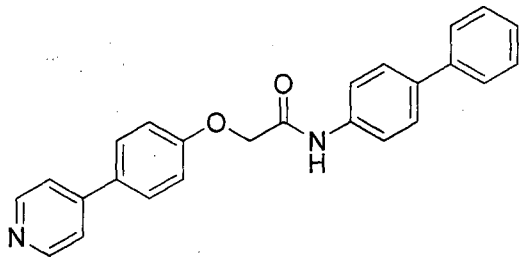
60 mg, LC-MS 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H),7.70-7.68 (m, 3H), 7.63-7.58 (m, 4H),7.46-7.41 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (bs, 1H), 7.14-7.13 (bs, 2H), 7.06 (dd, J = 4.0 Hz, 1H), 4.70 (s, 2H); MS (ESI) *m/z* 453 [M+1].

[000126] Example 31: 2-(4-(1H-imidazol-1-yl)-2-(trifluoromethoxy)phenoxy)-N-(biphenyl-4-yl)acetamide



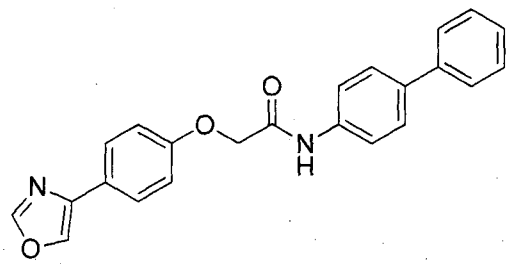
40 mg, LC-MS 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.41 (bs, 1H), 7.81 (s, 1H), 7.68-7.58 (m, 6H), 7.47-7.43 (t, J = 8.0 Hz, 2H),7.38-7.35 (m, 3H), 7.24 (bs, 2H), 7.17 (d, J = 8.0 Hz, 1H), 4.73 (s, 2H); MS (ESI) *m/z* 453 [M+1].

[000127] Example 32: N-(biphenyl-4-yl)-2-(4-(pyridin-4-yl)phenoxy)acetamide



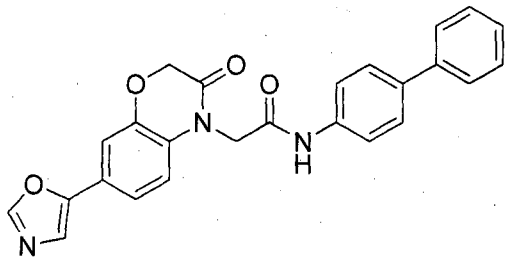
100 mg, 45%, LC-MS 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.27 (s, 1H), 8.59 (d, J = 5.7 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.7-7.6 (m, 6H), 7.45 (t, J = 7.9 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 4.82 (s, 2H); MS (ESI) *m/z* 381.20 $[C_{25}H_{20}N_2O_2+ H]^+$.

[000128] Example 33: N-(biphenyl-4-yl)-2-(4-(oxazol-4-yl)phenoxy)acetamide



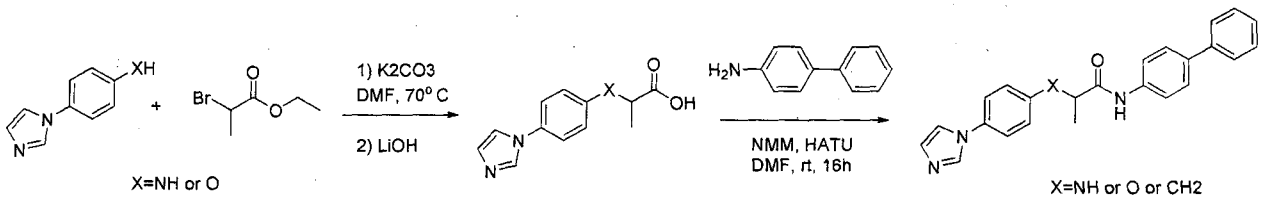
150 mg, 33%, LC-MS 98 %. ^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.21 (s, 1H), 8.52 (s, 1H), 8.42 (s, 1H), 7.75 (d, J = 8.4 Hz, 4H), 7.65 (d, J = 8.8 Hz, 4H), 7.45 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 4.76 (s, 2H); MS (ESI) m/z 371 [M+1].

[000129] Example 34: N-(biphenyl-4-yl)-2-(7-(oxazol-5-yl)-3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)acetamide



28 mg, 56%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (bs, 1H), 8.41 (s, 1H), 7.71-7.61 (m, 7H), 7.48-7.38 (m, 4H), 7.36-7.29 (m, 1H), 7.23-7.17 (m, 1H), 4.85-4.75 (m, 4H); MS (ESI) m/z 426 $[C_{25}H_{19}N_3O_4 + H]^+$.

[000130] Example 35: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)propanamide



General procedure 2:

[000131] To a solution of 4-(1H-imidazol-1-yl)phenol (300 mg, 1.873 mmol) and ethyl 2-bromopropanoate (243µl, 1.873mmol) in DMF (4 ml) was added K_2CO_3 (906 mg, 6.555 mmol). The solution was heated at 70°C for 16 h, then it was diluted with H_2O (25 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent Hexane/EtOAc 50:50) to afford ethyl 2-(4-(1H-imidazol-1-

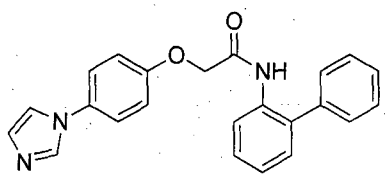
yl)phenoxy)propanoate as a yellow oil (325 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.29-7.26 (m, 2H), 7.18-7.17 (m, 2H), 6.97-6.95 (m, 2H), 4.76 (q, *J*= 6.8Hz, 1H), 4.23 (q, *J*= 7.2Hz, 2H), 1.644 (d, *J*= 6.8Hz, 3H), 1.26 (t, *J*= 7.2Hz, 3H).

[000132] Methyl ethyl 2-(4-(1H-imidazol-1-yl)phenoxy)propanoate obtained from the above reaction (163 mg, 0.625 mmol) was added to a solution of LiOH (30 mg, 1.250 mmol) in THF (1 mL) and H_2O (1 mL) and stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and the residue was acidifed to pH 1 using 1M HCl. It was then concentrated and the residue dried at 50°C under vacuum to yield 2-(4-(1H-imidazol-1-yl)phenoxy)propanoic acid. The crude product (140 mg) was used without further purification.

[000133] To a solution of 2-(4-(1H-imidazol-1-yl)phenoxy)propanoic acid (140 mg, 0.603 mmol) in DMF (3 mL) was added HATU (344 mg, 0.905 mmol) and *N*-methyl morpholine (265 µl, 2.412 mmol). The reaction mixture was stirred at room temperature under inert atmosphere for 1 h, followed by the addition of biphenyl-4-amine (102 mg, 0.603 mmol). The reaction mixture was left to stir for 16 h, then it was diluted with H_2O (25 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent Hexane/EtOAc 30:70) to afford 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)propanamide (146 mg, 63%, HPLC 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.09 (s, 1H), 7.74-7.71 (m, 2H), 7.63-7.54 (m, 7H), 7.43 (t, *J*= 7.6Hz, 2H), 7.32 (t, *J*= 7.6Hz, 1H), 7.11 (d, *J*= 8.8Hz, 2H), 7.05 (s, 1H), 4.96 (q, *J*= 6.8Hz, 1H), 1.59 (d, *J*= 6.4Hz, 3H) ; ^{13}C NMR (400 MHz, DMSO-d_6) δ 169.82, 155.97, 139.59, 137.84, 135.51, 135.45, 130.86, 129.53, 128.87, 127.07, 126.87, 126.25, 122.05, 120.07, 118.26, 116.18, 74.17, 18.56; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

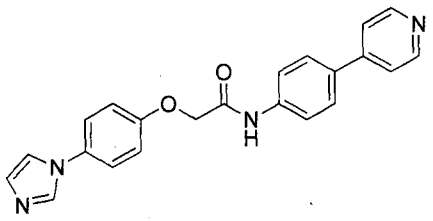
[000134] In some cases when X = NH, NH was protected as its NBoc derivative in order to achieve good amide coupling.

[000135] Example 36: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-2-yl)acetamide



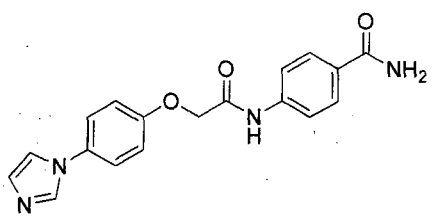
80 mg, 47%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.14 (s, 1H), 7.88 (d, *J*=8.0 Hz, 1H), 7.65 (s, 1H), 7.55-7.27 (m, 10H), 7.08 (s, 1H), 6.91 (d, *J*=8.8 Hz, 2H), 4.61 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.33, 155.90, 138.12, 135.49, 134.88, 134.00, 130.99, 130.19, 129.59, 128.86, 128.71, 128.04, 127.57, 125.54, 124.00, 121.86, 118.24, 115.59, 67.22; MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[000136] Example 37: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(pyridin-4-yl)phenyl)acetamide



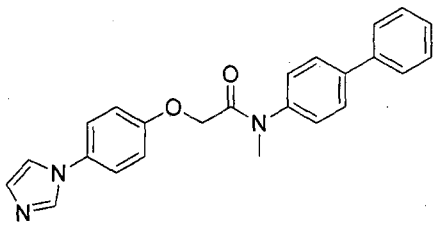
110 mg, 69%, HPLC 99%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.60 (d, *J*=6.0 Hz, 2H), 8.13 (s, 1H), 7.81 (s, 4H), 7.70-7.57 (m, 5H), 7.15 (d, *J*=9.2 Hz, 2H), 7.07 (s, 1H), 4.80 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.63, 156.52, 150.16, 146.28, 139.43, 135.51, 132.01, 130.87, 129.55, 127.23, 121.96, 120.63, 120.00, 118.28, 115.73, 67.38; MS (ESI) *m/z* 371 $[C_{22}H_{18}N_4O_2 + H]^+$.

[000137] Example 38: 4-(2-(4-(1H-imidazol-1-yl)phenoxy)acetamido)benzamide



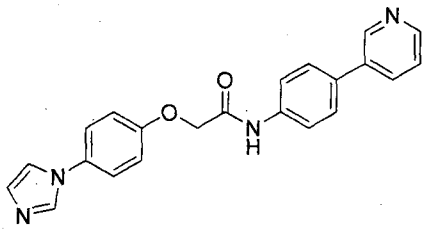
16mg, 13%, HPLC 98%, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.13 (s, 1H), 7.85 (d, *J*=8.8 Hz, 3H), 7.71 (d, *J*=8.8 Hz, 2H), 7.64 (s, 1H), 7.57 (d, *J*=8.8 Hz, 2H), 7.24 (br s, 1H), 7.13 (d, *J*=8.8 Hz, 2H), 7.07 (s, 1H), 4.79 (s, 2H); MS (ESI) *m/z* 337 $[C_{18}H_{16}N_4O_3 + H]^+$.

[000138] Example 39: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)-N-methylacetamide



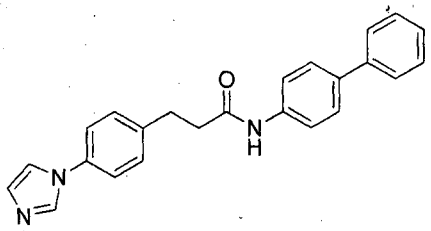
14mg, 10%, HPLC 98%, light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.31 (m, 11H), 7.25-7.16 (m, 3H), 6.90 (br s, 2H), 4.53 (s, 2H), 3.36 (s, 3H); MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000139] Example 40: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(pyridin-3-yl)phenyl)acetamide



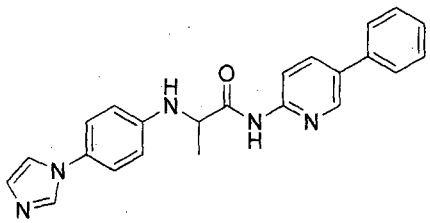
81 mg, 60%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.88 (d, *J*=2.0 Hz, 1H), 8.54-8.52 (m, 1H), 8.11-8.03 (m, 2H), 7.79-7.56 (m, 7H), 7.47-7.44 (m, 1H), 7.15 (d, *J*=8.8 Hz, 2H), 7.07 (s, 1H), 4.79 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 167.00, 157.09, 148.59, 147.80, 138.93, 136.02, 135.51, 134.07, 132.72, 131.42, 130.05, 127.65, 124.27, 122.50, 120.69, 118.78, 116.30, 68.02; MS (ESI) *m/z* 371 $[C_{22}H_{18}N_4O_2 + H]^+$.

[000140] Example 41: 3-(4-(1H-imidazol-1-yl)phenyl)-N-(biphenyl-4-yl)propanamide



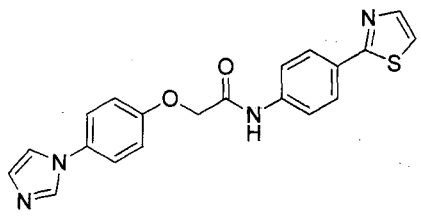
85 mg, 34%, HPLC 98%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 8.20 (s, 1H), 7.70-7.55 (m, 9H), 7.45-7.39 (m, 4H)), 7.31 (t, *J*= 7.6 Hz, 1H), 7.08 (s, 1H), 2.98 (t, *J*= 7.6Hz, 2H), 2.68 (t, *J*= 7.6Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 170.21, 139.90, 139.64, 138.57, 135.33, 134.96, 134.65, 129.64, 129.52, 128.77, 126.86, 126.78, 126.11, 120.23, 119.34, 117.89, 37.66, 30.03; MS (ESI) *m/z* 368 $[C_{24}H_{21}N_3O + H]^+$.

[000141] Example 42: 2-(4-(1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



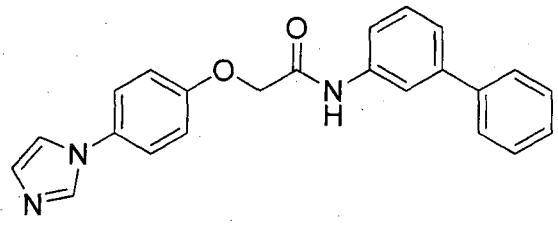
15 mg, 8%, HPLC 96%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.64 (d, *J*=2.0 Hz, 1H), 8.17-8.15 (m, 1H), 8.10-8.07 (m, 1H), 7.97 (s, 1H), 7.70-7.68 (m, 2H), 7.50-7.45 (m, 3H), 7.40-7.31 (m, 3H), 7.00 (s, 1H), 6.73 (d, *J*=8.8 Hz, 2H), 6.25 (d, *J*=8.4 Hz, 1H), 4.31-4.23 (m, 1H), 1.44 (d, *J*=6.8 Hz, 3H); MS (ESI) *m/z* 384 $[C_{23}H_{21}N_5O + H]^+$.

[000142] Example 43: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(thiazol-2-yl)phenyl)acetamide



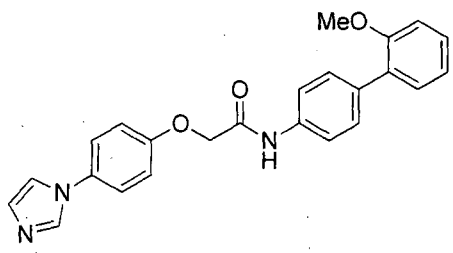
75 mg, 54%, HPLC 98%, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.13 (s, 1H), 7.94-7.93 (m, 2H), 7.89-7.88 (m, 1H), 7.80-7.78 (m, 2H), 7.73 (m, 1H), 7.64 (t, *J*= 1.2Hz, 1H), 7.59-7.57 (m, 2H), 7.15-7.13 (m, 2H), 7.07 (s, 1H), 4.80 (s, 2H) ; MS (ESI) *m/z* 377 $[C_{20}H_{16}N_4O_2S + H]^+$.

[000143] Example 44: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-3-yl)acetamide



15 mg, 18%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.91 (s, 1H), 7.64-7.58 (m, 3H), 7.55-7.48 (m, 3H), 7.47-7.38 (m, 5H), 7.37-7.31 (m, 1H), 7.25-7.19 (m, 2H), 7.13 (s, 1H), 4.77 (s, 2H); MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

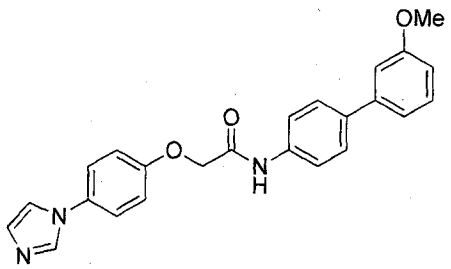
[000144] Example 45: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(2'-methoxybiphenyl-4-yl)acetamide



23 mg, 18%, HPLC 98%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 8.13 (s, 1H), 7.68-7.64 (m, 3H), 7.59-7.57 (m, 2H), 7.45-7.42 (m,2H), 7.34-7.26 (m, 2H), 7.15-6.99 (m,

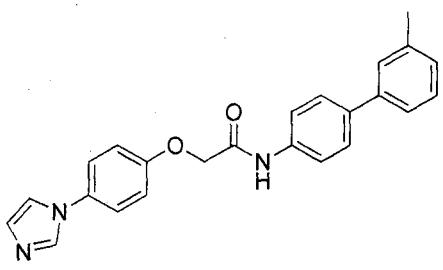
5H), 4.78 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.34, 156.57, 156.11, 137.08, 135.52, 133.52, 130.86, 130.15, 129.55, 129.52, 129.33, 128.60, 121.98, 120.75, 119.28, 118.29, 115.74, 111.76, 67.44, 55.47; MS (ESI) *m/z* 400 $[C_{24}H_{21}N_3O_3 + H]^+$.

[000145] Example 46: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(3'-methoxybiphenyl-4-yl)acetamide



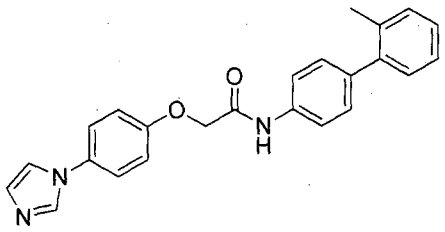
11 mg, 7%, HPLC 98%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.13 (s, 1H), 7.75-7.57 (m, 7H), 7.35 (t, *J*=7.6 Hz, 1H), 7.22-7.13 (m, 4H), 7.07 (s, 1H), 6.90 (d, *J*=6.4 Hz, 1H), 4.78 (s, 2H), 3.81 (s, 3H); MS (ESI) *m/z* 400 $[C_{24}H_{21}N_3O_3 + H]^+$.

[000146] Example 47: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(3'-methylbiphenyl-4-yl)acetamide



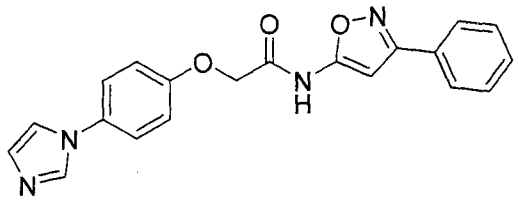
95 mg, 68%, HPLC 97%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 8.13 (s, 1H), 7.74-7.72 (m, 2H), 7.65-7.57 (m, 5H), 7.46-7.42 (m, 2H), 7.32 (t, *J*=7.6 Hz, 1H), 7.16-7.13 (m, 3H), 7.07 (s, 1H), 4.78 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.37, 156.56, 139.55, 137.98, 137.71, 135.52, 135.50, 130.86, 129.56, 128.76, 127.72, 126.92, 126.88, 123.39, 121.97, 119.99, 118.28, 115.73, 67.41, 21.09; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000147] Example 48: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(2'-methylbiphenyl-4-yl)acetamide



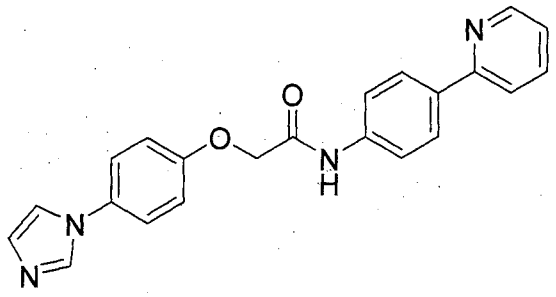
80 mg, 65%, HPLC 96%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.13 (s, 1H), 7.72-7.57 (m, 5H), 7.31-7.23 (m, 5H), 7.19-7.14 (m, 3H), 7.07 (s, 1H), 4.79 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.39, 156.58, 140.83, 137.17, 136.63, 135.52, 134.69, 130.87, 130.30, 129.56, 129.45, 129.28, 127.12, 125.89, 121.99, 119.44, 118.29, 115.74, 67.45, 20.17; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000148] Example 49: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(3-phenylisoxazol-5-yl)acetamide



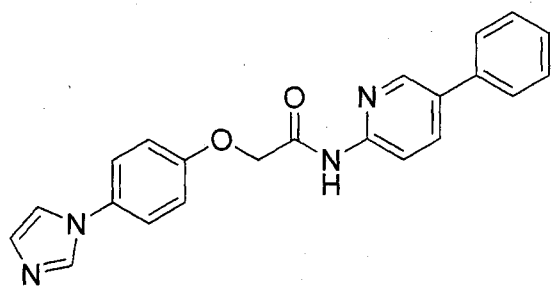
25 mg, 19%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 8.13 (s, 1H), 7.86-7.84 (m, 2H), 7.64 (s, 1H), 7.58-7.56 (m, 2H), 7.51-7.49 (m, 3H), 7.14-7.12 (m, 2H), 7.07 (s, 1H), 6.78 (s, 1H), 4.90 (s, 2H); MS (ESI) *m/z* 361 $[C_{20}H_{16}N_4O_3 + H]^+$.

[000149] Example 50: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(pyridin-2-yl)phenyl)acetamide



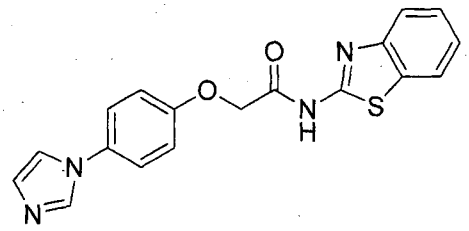
40 mg, 30%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.64 (d, J=4.4 Hz, 1H), 8.12 (s, 1H), 8.10-8.04 (m, 2H), 7.94-7.89 (m, 1H), 7.88-7.81 (m, 1H), 7.80-7.74 (m, 2H), 7.63 (s, 1H), 7.61-7.55 (m, 2H), 7.33-7.27 (m, 1H), 7.19-7.13 (m, 2H), 7.07 (s, 1H), 4.80 (s, 2H); MS (ESI) *m/z* 371 $[C_{22}H_{19}N_4O_2 + H]^+$.

[000150] Example 51: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(5-phenylpyridin-2-yl)acetamide



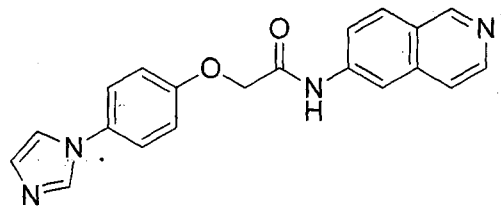
29 mg, 21%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 8.68 (s, 1H), 8.17-8.09 (m, 3H), 7.74-7.68 (m, 2H), 7.62 (s, 1H), 7.60-7.53 (m, 2H), 7.52-7.45 (m, 2H), 7.43-7.36 (m, 1H), 7.16-7.09 (m, 2H), 7.08 (s, 1H), 4.89 (s, 2H); MS (ESI) *m/z* 371 $[C_{22}H_{19}N_4O_2 + H]^+$.

[000151] Example 52: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(benzo[d]thiazol-2-yl)acetamide



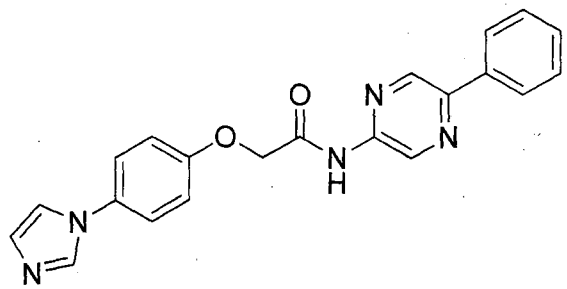
16 mg, 14%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 8.26 (s, 1H), 8.00 (d, J = 7.2Hz, 1H), 7.78 (d, J = 8.0Hz, 1H), 7.72-7.67 (m, 1H), 7.63-7.55 (m, 2H), 7.49-7.42 (m, 1H), 7.36-7.29 (m, 1H), 7.18-7.11 (m, 3H), 5.00 (s, 2H); MS (ESI) *m/z* 351 $[C_{18}H_{14}N_4O_2S + H]^+$.

[000152] Example 53: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(isoquinolin-6-yl)acetamide



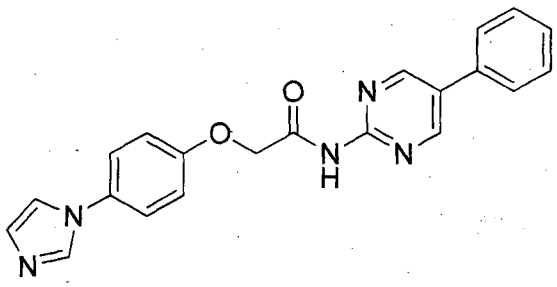
16 mg, 15%, HPLC 98%, off-white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 9.57 (s, 1H), 9.34 (s, 1H), 8.88-8.80 (m, 1H), 8.50-8.42 (m, 2H), 8.34 (d, J = 6.8Hz, 1H), 8.19-8.12 (m, 1H), 8.02-7.97 (m, 1H), 7.78-7.68 (m, 3H), 7.38-7.30 (m, 2H), 4.95 (s, 2H); MS (ESI) *m/z* 345 $[C_{20}H_{16}N_4O_2 + H]^+$.

[000153] Example 54: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(5-phenylpyrazin-2-yl)acetamide



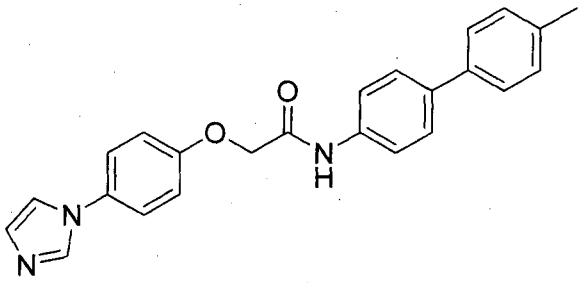
14 mg, 12%, HPLC 97%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 9.40-9.34 (m, 1H), 9.08-9.02 (m, 1H), 8.51 (s, 1H), 8.15-8.08 (m, 2H), 7.79 (s, 1H), 7.67-7.59 (m, 2H), 7.57-7.42 (m, 3H), 7.29 (s, 1H), 7.30-7.22 (m, 2H), 4.95 (s, 2H); MS (ESI) *m/z* 372 $[C_{21}H_{17}N_5O_2 + H]^+$.

[000154] Example 55: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(5-phenylpyrimidin-2-yl)acetamide



7 mg, 13%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 9.03 (s, 2H), 8.49 (bs, 1H), 7.82-7.75 (m, 3H), 7.63-7.56 (m, 2H), 7.56-7.49 (m, 2H), 7.49-7.41 (m, 1H), 7.28 (s, 1H), 7.15-7.09 (m, 2H), 5.10 (s, 2H); MS (ESI) *m/z* 372 $[C_{21}H_{17}N_5O_2 + H]^+$.

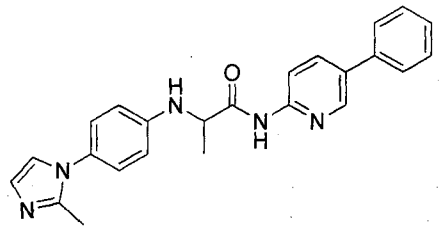
[000155] Example 56: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4'-methylbiphenyl-4-yl)acetamide



44 mg, 36%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.14 (s, 1H), 7.77-7.69 (m, 2H), 7.67-7.51 (m, 7H), 7.29-7.21 (m, 2H), 7.18-7.11 (m, 2H), 7.07 (s, 1H), 4.78 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 166.30, 156.54, 137.48, 136.70,

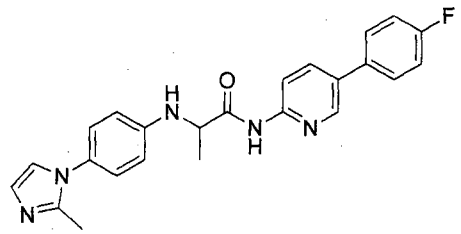
136.29, 135.49, 135.32, 130.84, 129.53, 129.43, 126.58, 126.05, 121.94, 120.00, 118.25, 115.72, 67.42, 20.58; MS (ESI) *m/z* 384 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000156] Example 57: 2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



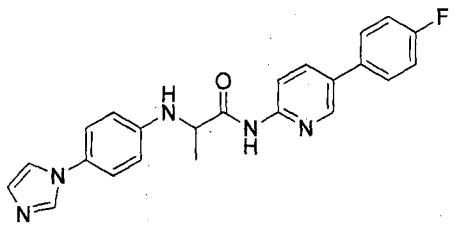
8 mg, 12%, HPLC 98%, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.65-8.64 (m, 1H), 8.18-8.16 (m, 1H), 8.11-8.08 (m, 1H), 7.70-7.68 (m, 2H), 7.48 (t, *J*=7.2 Hz ,2H), 7.40-7.36 (m, 1H), 7.13-7.09 (m, 3H), 6.81-6.80 (m, 1H), 6.72-6.70 (m, 2H), 6.35-6.34 (d, *J*=7.6 Hz ,1H), 4.31-4.23 (m, 1H), 2.18 (s, 3H), 1.45 (d, *J*=6.8 Hz ,3H) ; MS (ESI) *m/z* 398 $[C_{24}H_{23}N_5O + H]^+$.

[000157] Example 58: N-(5-(4-fluorophenyl)pyridin-2-yl)-2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)propanamide



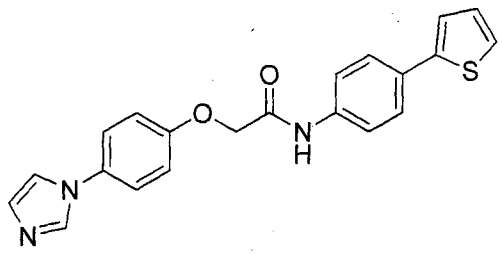
10 mg, 14%, HPLC 99%, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.63 (d, *J*=2.0 Hz, 1H), 8.18-8.06 (m, 2H), 7.76-7.72 (m, 2H), 7.30 (t, *J*=8.8 Hz, 2H), 7.11 (t, *J*=8.8 Hz, 3H), 6.81 (d, *J*=0.8 Hz, 1H), 6.71 (d, *J*=8.8 Hz, 2H), 6.34 (d, *J*=8.0 Hz, 1H), 4.30-4.23 (m, 1H), 2.18 (s, 3H), 1.44 (d, *J*=6.8 Hz, 3H); MS (ESI) *m/z* 416 $[C_{24}H_{22}FN_5O + H]^+$.

[000158] Example 59: 2-(4-(1H-imidazol-1-yl)phenylamino)-N-(5-(4-fluorophenyl)pyridin-2-yl)propanamide



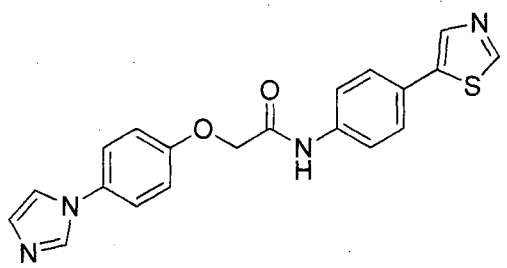
12 mg, 7%, HPLC 97%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.62 (d, *J*=2.4 Hz, 1H), 8.16-8.14 (m, 1H), 8.09-8.06 (m, 1H), 7.97 (s, 1H), 7.75-7.72 (m, 2H), 7.49 (s, 1H), 7.33-7.28 (m, 4H), 7.00 (s, 1H), 6.73 (d, *J*=8.8 Hz, 2H), 6.25 (d, *J*=8.4 Hz, 1H), 4.30-4.23 (m, 1H), 1.44 (d, *J*=6.8 Hz, 3H); MS (ESI) *m/z* 402 $[C_{23}H_{20}FN_5O + H]^+$.

[000159] Example 60: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(thiophen-2-yl)phenyl)acetamide



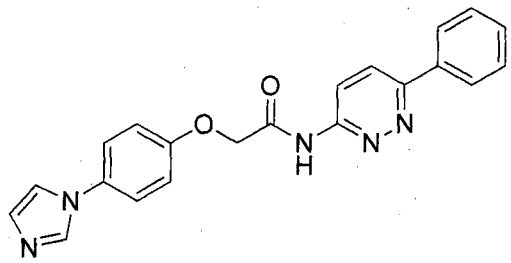
150 mg, 70%, LC-MS 95%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 10.22 (s, 1H), 8.13 (s, 1H), 7.85-7.52 (m, 7H), 7.40 (dd, *J* = 4.8 Hz, 2H), 7.20-7.11 (m, 4H), 4.78 (s, 2H); MS (ESI) *m/z* 376.08 $[C_{21}H_{17}N_3O_2S+H]^+$.

[000160] Example 61: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(thiazol-5-yl)phenyl)acetamide



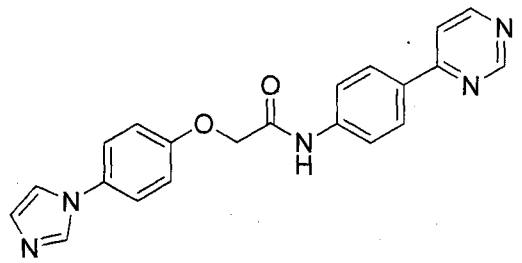
170 mg, 52%, LC-MS 96%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.28 (bs, 1H), 9.05 (bs, 1H), 8.25 (s, 1H), 8.14 (bs, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.75-7.54 (m, 7H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H) 4.79 (s, 2H); MS (ESI) m/z 377.11 [C20H16N4O2S+H]+.

[000161] Example 62: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(6-phenylpyridazin-3-yl)acetamide



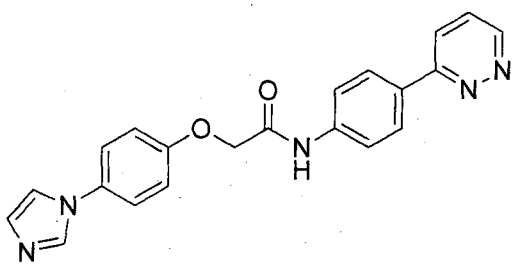
60 mg, 25%, LC-MS 95%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.37 (s, 1H), 8.38 (dd, J = 9.6 Hz, 2H), 8.11 (d, J = 7.2 Hz, 3H), 7.65-7.52 (m, 6H), 7.13 (d, J = 8.8 Hz, 3H), 4.96 (s, 2H); MS (ESI) *m/z* 372.06 $[C_{21}H_{17}N_5O_2+H]^+$.

[000162] Example 63: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(pyrimidin-4-yl)phenyl)acetamide



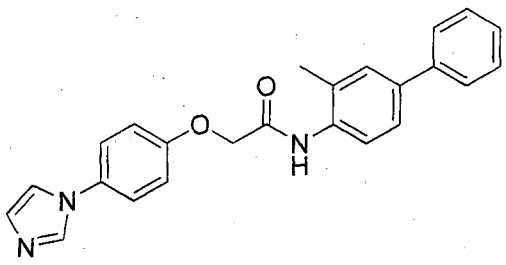
100 mg, 54%, LC-MS 90%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.40 (s, 1H), 9.20 (s, 1H), 8.81 (d, J = 5.3 Hz, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.81 (s, 1H), 8.04 (t, J = 2.8 Hz, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.65 (s, 1H), 7.58 (d, J = 7.8 Hz, 2H), 7.15 (d, J = 9.2 Hz, 2H), 7.07 (s, 2H), 4.82 (s, 2H); MS (ESI) m/z 372.12 [C21H17N5O2+H] +.

[000163] Example 64: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-(pyridazin-3-yl)phenyl)acetamide



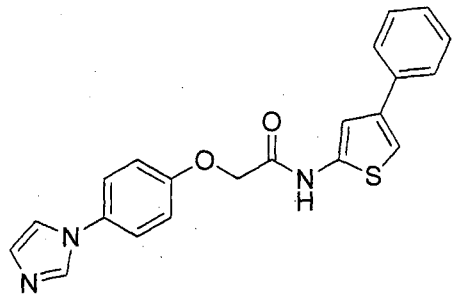
150 mg, 80%, LC-MS 97%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.36 (s, 1H), 9.17 (d, J = 4.0 Hz, 1H), 8.20-8.13 (m, 4H), 7.87-7.73 (m, 3H), 7.66-7.57 (m, 3H), 7.15 (d, J = 8.8 Hz, 1H), 7.08 (s, 2H); MS (ESI) *m/z* 372.06 $[C_{21}H_{17}N_5O_2+H]^+$.

[000164] Example 65: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(3-methylbiphenyl-4-yl)acetamide



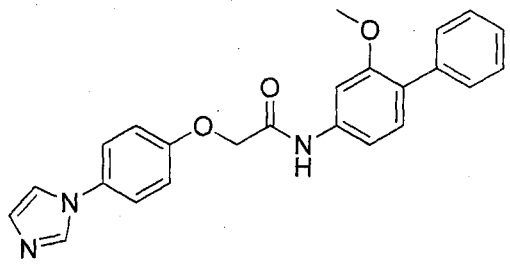
140 mg, 33%, LC-MS 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.57 (s, 1H), 8.15 (s, 1H), 7.7-7.58 (dd, 4H), 7.56-7.42 (m, 5H), 7.34 (t, J = 7.5 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.08 (s, 1H), 4.82 (s, 2H), 2.26 (s, 3H); MS (ESI) *m/z* 384.14 $[C_{24}H_{21}N_3O_2 + H]^+$.

[000165] Example 66: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-phenylthiophen-2-yl)acetamide



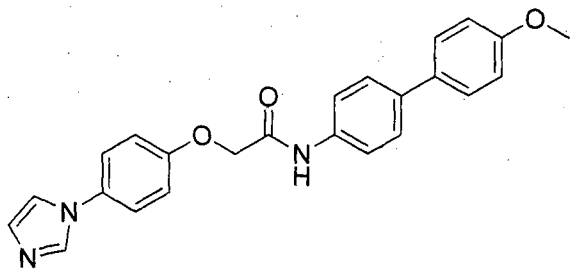
4 mg, 7%, LC-MS 95%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.4 (s, 1H), 8.1 (s, 1H), 7.66-7.42 (m, 5H), 7.39 (t, J = 8.0 Hz, 2H), 7.3 (s, 1H), 7.21-7.11 (m, 3 H), 6.90 (s, 1H), 4.8 (s, 2H); MS (ESI) *m/z* 376.02 $[C_{21}H_{17}N_3O_2S + H]^+$.

[000166] Example 67: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(2-methoxybiphenyl-4-yl)acetamide



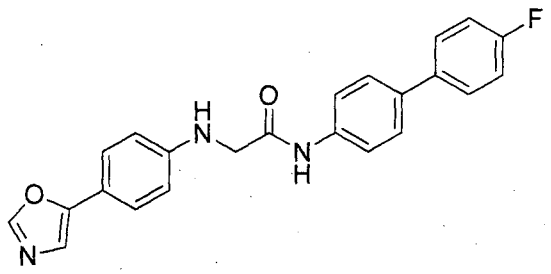
100 mg, 25%, LC-MS 99%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.23 (s, 1H), 8.15 (s, 1H), 7.66 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.51 (s, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.42-7.22 (m, 5H), 7.15 (d, J = 8.3 Hz, 2H), 7.08 (s, 1H), 7.79 (s, 2H), 3.74 (s, 3H); MS (ESI) *m/z* 400.13 $[C_{24}H_{21}N_3O_3 + H]^+$.

[000167] Example 68: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4'-methoxybiphenyl-4-yl)acetamide



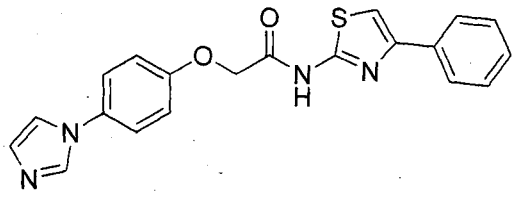
30 mg, 16%, HPLC 98%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 10.19 (s, 1H), 8.14 (s, 1H), 7.71 (m, 3H), 7.59 (d, J = 8.4 Hz, 6H), 7.14 (m, 3H), 7.0 (d, J = 8.4 Hz, 2H), 4.78 (s, 2H), 3.78 (s, 3H); MS (ESI) *m/z* 400.06 $[C_{24}H_{21}N_3O_3 + H]^+$.

[000168] Example 69: N-(4'-fluorobiphenyl-4-yl)-2-(4-(oxazol-5-yl)phenylamino)acetamide



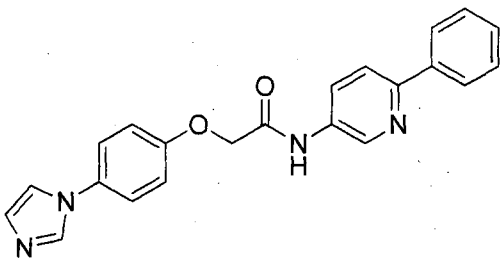
8 mg, 10%, LC-MS 97%), off- white solid. ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 8.42 (s, 1H), 7.81 (s, 1H), 7.64-7.56 (m, 8H), 7.2 (s, 1H), 7.1 (t, J = 8.0 Hz, 2H), 6.76 (d, J = 7.8 Hz, 2H), 4.58 (s, 1H), 3.99 (d, J = 8.0 Hz, 2H); MS (ESI) *m/z* 388.17 $[C_{23}H_{18}FN_3O_2 + H]^+$.

[000169] Example 70: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(4-phenylthiazol-2-yl)acetamide



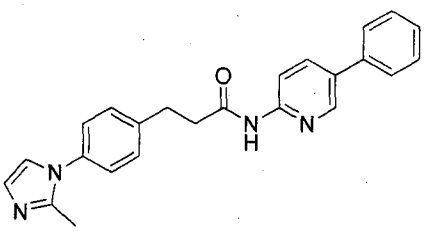
80 mg, 25%, LC-MS 97%. 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 12.54 (s, 1H), 8.13 (s, 1H), 7.9 (d, J = 7.1 Hz, 2H), 7.65 (d, J = 11.4 Hz, 2H),7.65 (d, J = 8.8 Hz, 2H),7.44 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 6.75 Hz, 1H), 7.12 (d, J = 5.2 Hz, 2H), 7.07 (s, 1H), 4.95 (s, 2H); MS (ESI) m/z 377.09 $[C20H16N4O2S+H]^+$.

[000170] Example 71: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(6-phenylpyridin-3-yl)acetamide



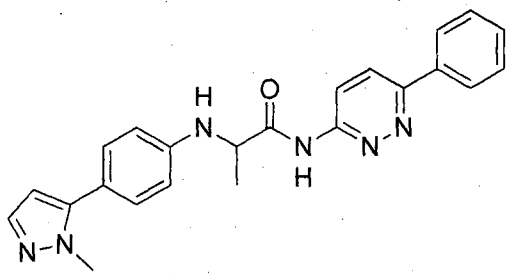
110 mg, 50%, HPLC 97%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* (ppm): 10.47 (s, 1H), 8.89 (s, 1H), 8.20-8.15 (m, 2H), 8.06-7.95 (m, 3H), 7.66-7.58 (m, 3H), 7.50-7.98 (m, 3H), 7.17-7.08 (m, 3H), 4.83 (bs, 2H); MS (ESI) *m/z* 371.17 $[C_{22}H_{18}N_4O_2+H]^+$.

[000171] Example 72: 3-(4-(2-methyl-1H-imidazol-1-yl)phenyl)-N-(5-phenylpyridin-2-yl)propanamide



9 mg, 8%, HPLC 96%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.63 (d, *J*=2.4 Hz, 1H), 8.20-8.17 (m, 1H), 8.10-8.08 (m, 1H), 7.71-7.69 (m, 2H), 7.50-7.34 (m, 7H), 7.23 (s, 1H), 6.88 (s, 1H), 2.99 (t, *J*=7.6 Hz, 2H), 2.79 (t, *J*=7.6 Hz, 2H), 2.25 (s, 3H) ; MS (ESI) *m/z* 383 $[C_{24}H_{22}N_4O + H]^+$.

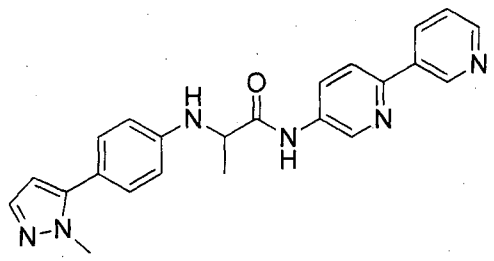
[000172] Example 73: 2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(6-phenylpyridazin-3-yl)propanamide



70 mg, 15%, LC-MS 96%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.35 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 7.56-7.48 (m, 3H), 7.36 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.39 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 4.37 (q, J = 6.8 Hz, 1H), 3.77 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 399.24 $[C_{23}H_{22}N_6O+H]^+$.

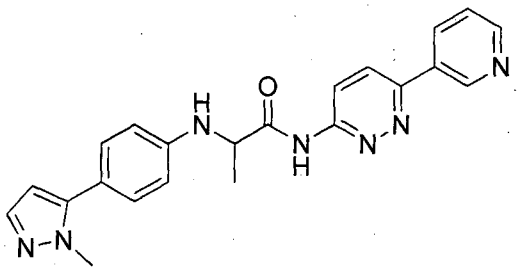
[000173] The racemates may be separated by either chiral preparative HPLC or may be chirally synthesized by using the method reported for the preparation of intermediate 5.

[000174] Example 74: N-(2,3'-bipyridin-5-yl)-2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanamide



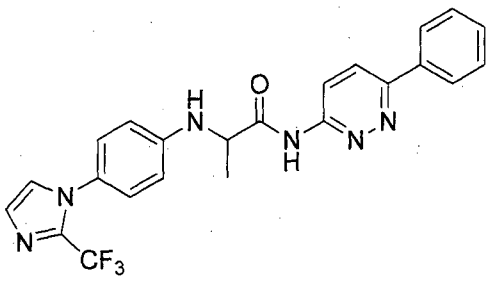
65 mg, 20 %, LC-MS 96 %, off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 9.16 (s, 1H), 8.79 (s, 1H), 8.64 (d, J = 2.2 Hz, 1H), 8.62 (s, 1H) 8.37-8.34 (dd, J = 2.4 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 1.8 Hz, 1H), 7.41-7.38 (q, J = 4.8 Hz, 1H), 7.3 (d, J = 8.3 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.23 (d, J = 1.8 Hz, 1H), 4.17 (bs, 1H), 3.99 (q, J = 7.0 Hz, 1H), 3.86 (s, 3H), 1.68 (d, J = 7.1 Hz, 3H); MS (ESI) *m/z* 399.24 $[C_{23}H_{22}N_6O + H]^+$.

[000175] Example 75: 2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(6-(pyridin-3-yl)pyridazin-3-yl)propanamide



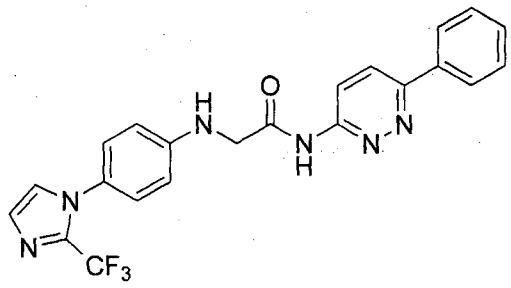
12 mg, 4%, LC-MS 99%, pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.43 (s, 1H), 9.26 (s, 1H), 8.69 (d, J = 4.0 Hz, 1H), 8.55-8.28 (m, 3H), 7.65-7.52 (m, 1H), 7.36 (s, 1H), 7.25 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.40 (d, J = 8.3 Hz, 1H), 6.21 (s, 1H), 4.45-4.32 (m, 1H), 3.78 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H); MS (ESI) *m/z* 400.25 $[C_{22}H_{21}N_7O + H]^+$.

[000176] Example 76: N-(6-phenylpyridazin-3-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl) phenylamino) propanamide



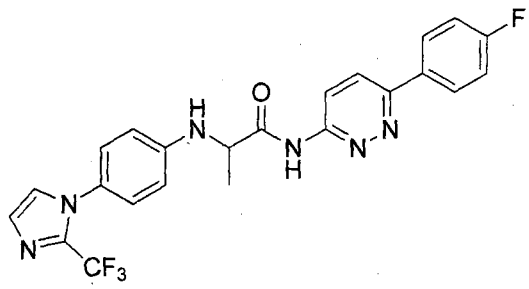
56 mg, 30%, LC-MS 96%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.39 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.6 Hz, 1H), 8.08 (d, J = 6.6 Hz, 2H), 7.56-7.48 (m, 4H), 7.19-7.17 (m, 3H), 6.72 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 7.9 Hz, 1H), 4.38 (t, J = 7.5 Hz, 1H), 1.49 (d, J = 7.1 Hz, 3H); MS (ESI) *m/z* 453.22 $[C_{23}H_{19}F_3N_6O + H]^+$.

[000177] Example 77: N-(6-phenylpyridazin-3-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenylamino)acetamide



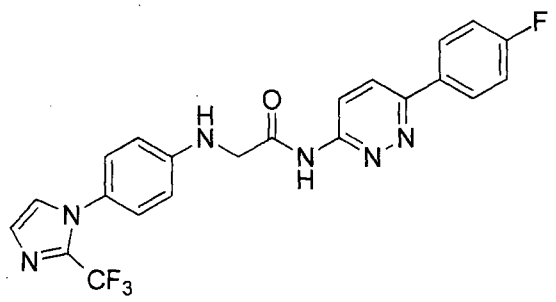
70 mg, 10%, LC-MS 97 %, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.16 (s, 1H), 8.67 (d, J = 9.6 Hz, 1H), 8.03-7.93 (m, 3H), 7.54-7.48 (m, 3H), 7.21-7.14 (m, 3H), 7.16 (d, J = 8.8 Hz, 3H), 7.08 (s, 1H), 6.72 (d, J = 8.8 Hz, 2H), 5.1 (bs, 1H), 4.19 (d, J = 5.2 Hz, 2H); MS (ESI) *m/z* 439.15 $[C_{22}H_{17}F_3N_6O+H]^+$.

[000178] Example 78: N-(6-(4-fluorophenyl)pyridazin-3-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenylamino)propanamide



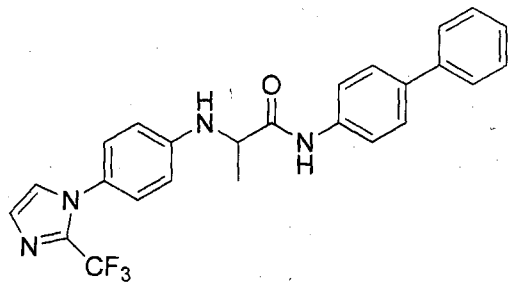
50 mg, 30%, LC-MS 99%, white solid. ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 11.39 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.7 Hz, 1H), 8.15 (q, J = 5.5 Hz, 2H), 7.55 (s, 1H), 7.38 (t, J = 8.8, 2H), 7.19-7.17 (m, 3H), 6.72 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 7.5 Hz, 1H), 4.38 (t, J = 7.3 Hz, 1H), 1.49 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 471.19 $[C_{23}H_{18}F_4N_6O + H]^+$.

[000179] Example 79: N-(6-(4-fluorophenyl)pyridazin-3-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenylamino)acetamide



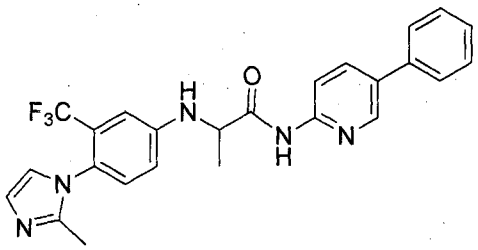
70 mg, 70%, LC-MS 95%, off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 11.30 (s, 1H), 8.39 (d, J = 10.0 Hz, 1H), 8.26 (d, J = 10.0 Hz, 1H), 8.16 (t, J = 8.8 Hz, 2H), 7.56 (s, 1H), 7.38 (t, J = 8.8 Hz, 2H), 7.18 (d, J = 9.2 Hz, 3H), 6.71 (d, J = 8.8 Hz, 2H), 6.59 (s, 1H), 4.13 (d, J = 6.0 Hz, 2H); MS (ESI) *m/z* 457.18 $[C_{22}H_{16}F_4N_6O + H]^+$.

[000180] Example 80: N-(biphenyl-4-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenylamino)propanamide



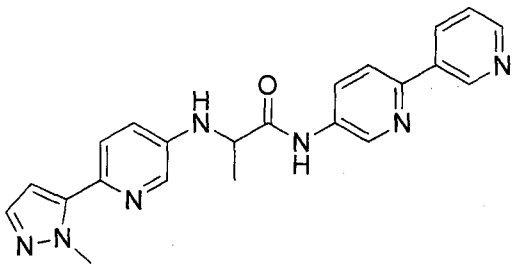
27 mg, 27%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.76-7.68 (m, 2H), 7.67-7.59 (m, 4H), 7.56-7.51 (m, 1H), 7.48-7.40 (m, 2H), 7.36-7.29 (m, 1H), 7.20-7.13 (m, 3H), 6.73-6.67 (m, 2H), 6.46 (d, J = 7.2Hz, 1H), 4.20-4.05 (m, 1H), 1.46 (d, J = 6.8Hz, 3H); MS (ESI) *m/z* 398 $[C_{25}H_{21}F_3N_4O + H]^+$.

[000181] Example 81: 2-(4-(2-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



16 mg, 7%, LC-MS 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.99 (s, 1H), 8.49 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 1.8 Hz, 8.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 7 Hz, 2H), 7.43 – 7.35 (m, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.07 (q, J = 2.6 Hz, 1H), 6.99 (s, 1H), 6.87 (s. 1H), 6.86 – 6.78 (m, 1H), 4.67 (s, 1H), 4.12 – 3.98 (m, 1H), 2.15 (s, 3H), 1.70 (d, J = 7 Hz, 3H); MS (ESI) *m/z* 464.2 $[C_{25}H_{22}F_3N_5O\text{-}H]^+$.

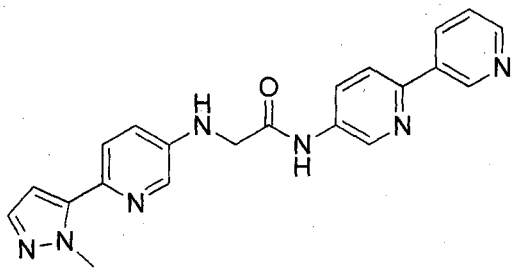
[000182] Example 82: N-(2,3'-bipyridin-5-yl)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)propanamide



60 mg, 18%, LC-MS 96%. ^{1}H NMR(400 MHz, $CDCl_3$) δ (ppm): 10.52 (s, 1H), 9.21 (d, J = 1.8 Hz, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.59 (dd, J = 1.3 Hz, 4.8 Hz, 1H), 8.37 (dt, J = 1.7, 8.0 Hz, 1H), 8.22 (dd, J = 2.6, 8.6 Hz, 1H), 8.11 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.55-7.45 (m, 2H), 7.37 (d, J = 1.7 Hz, 1H), 7.04 (dd. J = 2.6, 8.30 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.50 (d, J = 1.8 Hz, 1H), 4.22 (t, J = 7.0 Hz, 1H), 4.03 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 400.25 $[C_{22}H_{21}N_7O + H]^+$.

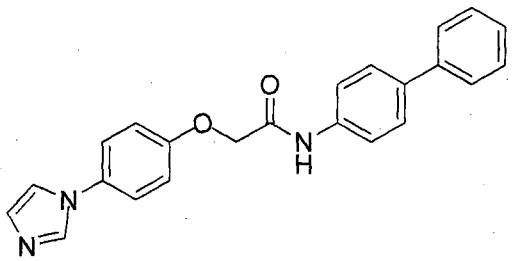
[000183] The racemates may be separated by either chiral preparaive HPLC or may be synthesized by using method reported for the preparation of intermediate 5.

[000184] Example 83: N-(2,3'-bipyridin-5-yl)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)acetamide



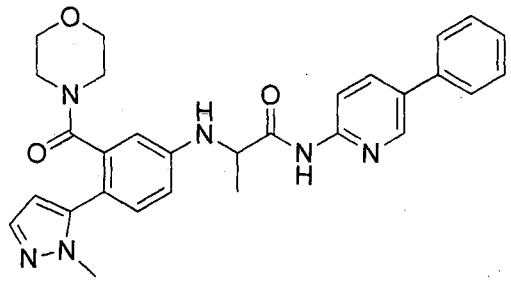
30 mg, 10%, LC-MS 98%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.5 (s, 1H), 9.23 (s, 1H), 8.90 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 9.6 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.12-8.04 (m, 2H), 7.52-7.48 (m, 2H), 7.38 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.30 (t, J = 5.6 Hz, 1H), 6.51 (s, 1H), 4.07 (d, J = 6.0 Hz, 2H), 4.05 (s, 3H); MS (ESI) *m/z* 386.1 $[C_{21}H_{19}N_7O + H]^+$.

[000185] Example 84: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)acetamide



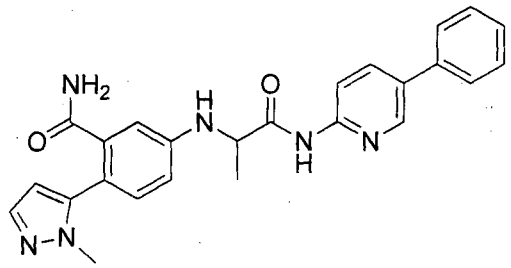
26 mg, 31%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.13 (s, 1H), 7.77-7.72 (m, 2H), 7.68-7.61 (m, 5H), 7.61-7.55 (m, 2H), 7.48-7.41 (m, 2H), 7.36-7.30 (m, 1H), 7.18-7.12 (m, 2H), 7.08 (s, 1H), 4.79 (s, 2H); MS (ESI) *m/z* 370 $[C_{23}H_{19}N_3O_2 + H]^+$.

[000186] Example 85: 2-(4-(1-methyl-1H-pyrazol-5-yl)-3-(morpholine-4-carbonyl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



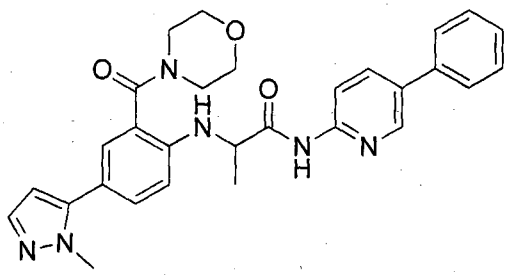
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.05 (m, 1H). 8.40 (s, 1H), 8.36 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.45-7.37 (m, 4H), 7.19 (d, J = 8.4 Hz, 1H), 6.77-6.66 (m, 2H), 6.20 (s, 1H), 4.33-4.28 (m, 1H), 3.98-3.75 (m, 1H), 3.75 (s, 3H), 3.63-3.41 (m, 5H), 3.12-2.8 (m, 3H), 1.67 (d, J = 8.0 Hz, 3H); MS (ESI) *m/z* 511.30 [M+1].

[000187] Example 86: 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzamide



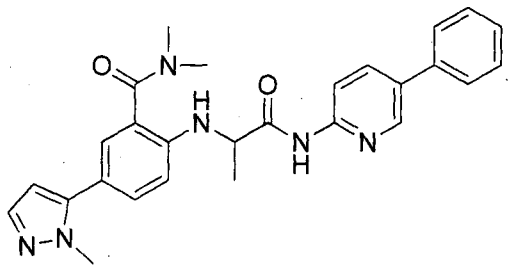
100 mg, 77%, LC-MS 99%. ^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 10.70 (s, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.17-8.11 (m, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.50-7.41 (m, 4H), 7.32 (d, J = 2.0 Hz, 1H), 7.15 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.79-6.41 (m, 2H), 6.50 (d, J = 8.0 Hz, 1H), 6.09 (s, 1H), 4.70-4.30 (m, 1H), 3.60 (s, 1H), 1.45 (d, J = 6.4 Hz, 3H); MS (ESI) *m/z* 441 [M+1].

[000188] Example 87: 2-(4-(1-methyl-1H-pyrazol-5-yl)-2-(morpholine-4-carbonyl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



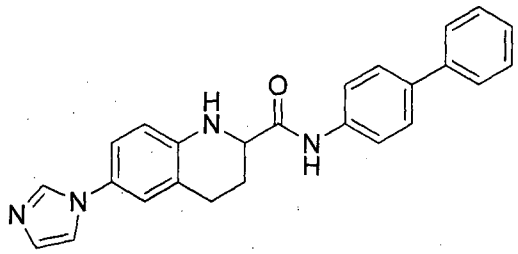
15 mg, 24%, LC-MS 96%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.04 (s, 1H), 8.47 (d, J = 3.2 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.93 (dd, J = 2.7, 8.8 Hz, 1H), 7.54-7.52 (m, 2H), 7.48-7.44 (m, 3H), 7.40-7.30 (m, 3H), 7.18 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.20 (s, 1H), 5.93 (d, J = 3.1 Hz, 1H), 4.02-4.00 (m, 1H), 3.64-3.70 (m, 1H), 1.68 (d, J = 7.0 Hz, 3H); MS (ESI) *m/z* 511.24 $[C_{29}H_{30}N_6O_3+H]^+$.

[000189] Example 88: 2-(7-(1-methyl-1H-pyrazol-5-yl)-3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)-N-(5-phenylpyridin-2-yl)propanamide



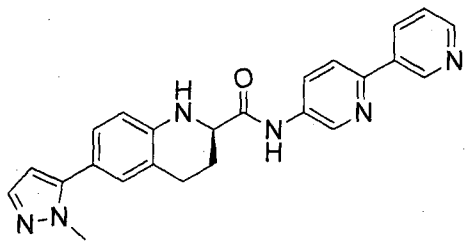
15 mg, 22%, LC-MS 99%, pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.97 (s, 1H), 8.66 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 7.1 Hz, 1H), 7.50-7.38 (m, 5H), 7.24 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.26 (d, J = 2.2 Hz, 1H), 5.67 (d, J = 8.4 Hz, 1H), 4.40-4.37 (m, 1H), 3.80 (s, 3H), 3.00 (bs, 6H), 1.46 (d, J = 7.1 Hz, 3H); MS (ESI) *m/z* 469.44 $[C_{27}H_{28}N_6O_2+H]^+$.

[000190] Example 89: N-(biphenyl-4-yl)-6-(1H-imidazol-1-yl)-1,2,3,4-tetrahydroquinoline-2-carboxamide



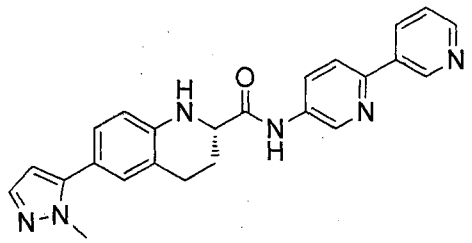
43 mg, 44%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.98 (bs, 1H), 7.78-7.72 (m, 2H), 7.70-7.60 (m, 4H), 7.51 (bs, 1H), 7.48-7.40 (m, 2H), 7.36-7.30 (m, 1H), 7.18-7.10 (m, 2H), 7.04 (bs, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 2.8 Hz, 1H), 4.15-4.05 (m, 1H), 2.85-2.60 (m, 2H), 2.15-1.95 (m, 2H); MS (ESI) *m/z* 395 $[C_{25}H_{22}N_4O + H]^+$.

[000191] Example 90: (R)-N-(2,3'-bipyridin-5-yl)-6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxamide



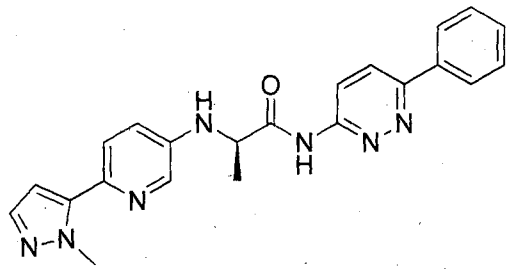
HPLC 98%, $[\alpha]_D$ +11.0°. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.28 (s, 1H), 9.23 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.7 Hz, 1H), 8.60-8.41 (m, 1H), 8.41-8.38 (m, 1H), 8.25-8.23 (dd, J = 2.6 Hz, J = 2.2 Hz, 1H), 8.06-8.04 (d, J = 8.3 Hz, 1H), 7.51-7.48 (m, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.10-7.07 (m, 1H), 7.04 (s, 1H), 6.72-6.70 (d, J = 7.9 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.20 (d, J = 1.7 Hz, 1H), 4.14 (s, 1H), 3.80 (s, 3H), 2.80-2.67 (m, 2H), 2.12-2.04 (m, 2H); MS (ESI) m/z 411.2 [C24H22N6O]+.

[000192] Example 91: (S)-N-(2,3'-bipyridin-5-yl)-6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxamide



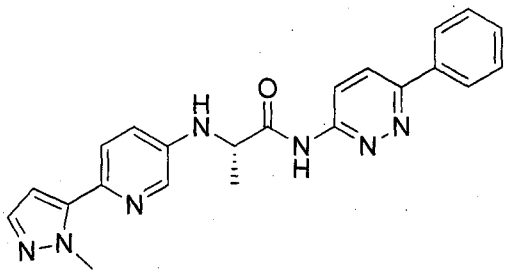
HPLC 97%, $[\alpha]_D$ -10.06°. ^{1}H NMR(400 MHz, DMSO-*d6*) δ (ppm): 10.28 (s, 1H), 9.23 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.7 Hz, 1H), 8.60-8.41 (m, 1H), 8.41-8.38 (m, 1H), 8.25-8.23 (dd, J = 2.6 Hz, J = 2.2 Hz, 1H), 8.06-8.04 (d, J = 8.3 Hz, 1H), 7.51-7.48 (m, 1H), 7.37 (d, J = 1.8 Hz, 1H), 7.10-7.07 (m, 1H), 7.04 (s, 1H), 6.72-6.70 (d, J = 7.9 Hz, 1H), 6.41 (d, J = 2.7 Hz, 1H), 6.20 (d, J = 1.7 Hz, 1H), 4.14 (s, 1H), 3.80 (s, 3H), 2.80-2.67 (m, 2H), 2.12-2.04 (m, 2H); MS (ESI) m/z 411.2 [C24H22N6O]+.

[000193] Example 92: (R)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)-N-(6-phenylpyridazin-3-yl)propanamide



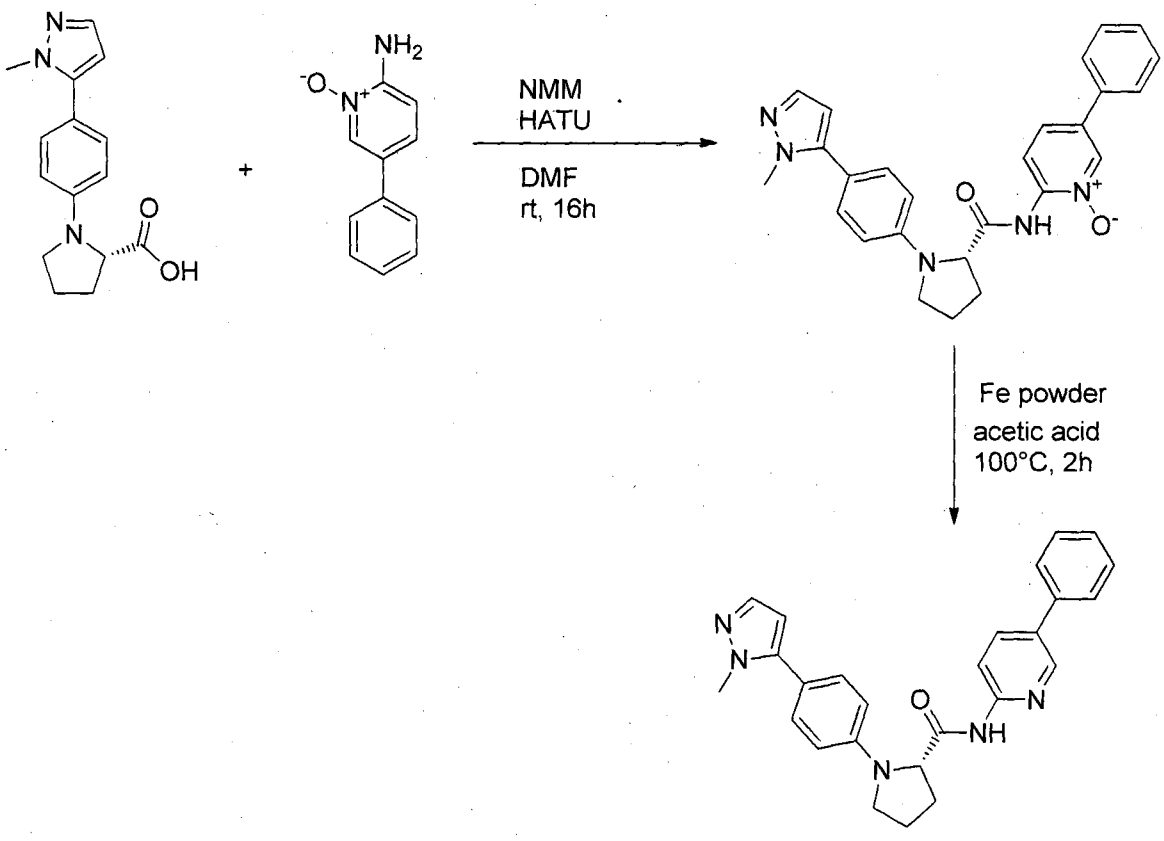
70% , LC-MS 98%, chiral HPLC 98%, $[\alpha]_D$ +122.51°.^{1}H NMR(400 MHz, CDCl3) δ (ppm): 11.47 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 2.7 Hz, 1H), 8.09 (d, J = 8.3 Hz, 2H), 7.61-7.46 (m, 2H), 7.37 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 2.6 Hz, 8.8 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 1.8 Hz, 1H), 4.49-4.40 (m, 1H), 4.03 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 400.2 [C22H21N7O+H]+.

[000194] Example 93: (S)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)-N-(6-phenylpyridazin-3-yl)propanamide



70%, LC-MS 98%, chiral HPLC 99%, $[\alpha]_D$ -102.52°. ^{1}H NMR(400 MHz, CDCl3) δ (ppm): 11.47 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 2.7 Hz, 1H), 8.09 (d, J = 8.3 Hz, 2H), 7.61-7.46 (m, 2H), 7.37 (d, J = 1.7 Hz, 1H), 7.06 (dd, J = 2.6 Hz, 8.8 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 1.8 Hz, 1H), 4.49-4.40 (m, 1H), 4.03 (s, 3H), 1.50 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 400.2 [C22H21N7O+H]+.

[000195] Example 94: (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)pyrrolidine-2-carboxamide

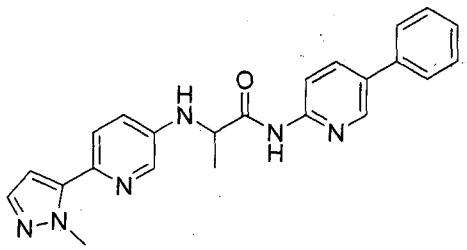


General procedure 3:

[000196] To a solution of (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxylic acid (244 mg, 0.900 mmol) in DMF (2 mL) was added HATU (513 mg, 1.349 mmol) and *N*-methyl morpholine (396 µl, 3.597 mmol). The reaction mixture was stirred at room temperature under inert atmosphere for 1 h, followed by the addition of 2-amino-5-phenylpyridine 1-oxide (168 mg, 0.900 mmol). The reaction mixture was left to stir for 16 h, then it was diluted with H_2O (25 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was purified by preparative HPLC (C18, eluent ACN, water, formic acid 0.1%) to afford (S)-2-(1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamido)-5-phenylpyridine 1-oxide (84 mg, 21%, HPLC 98%) as beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.57 (d, *J*=8.4 Hz, 1H), 8.44 (s, 1H), 7.58-7.43 (m, 7H), 7.33-7.28 (m, 2H), 6.78 (d, *J*=8.8 Hz, 2H), 6.23 (s, 1H), 4.30-4.27 (m, 1H), 4.00-3.95 (m, 1H), 3.88 (s, 3H), 3.45-3.39 (m, 1H), 2.52-2.35 (m, 2H), 2.26-2.17 (m, 2H); MS (ESI) *m/z* 440 $[C_{26}H_{25}N_5O_2 + H]^+$.

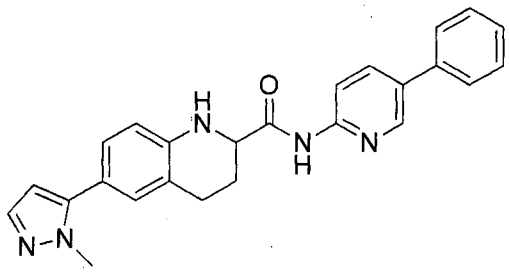
[000197] Iron dust (12mg, 0.215 mmol) was added to a solution of (S)-2-(1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamido)-5-phenylpyridine 1-oxide (63 mg, 0.143 mmol) in acetic acid (1.5 mL). The reaction mixture was heated at 100°C for 2 h, then it was diluted with H_2O and basified to pH 8 using saturated $NaHCO_3$ solution. It was then extracted with EtOAc (3x15 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparative HPLC (C18, eluent ACN, water, formic acid 0.1%) to afford (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)pyrrolidine-2-carboxamide (31 mg, 51%, HPLC 97%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.45-8.40 (m, 2H), 7.95-7.92 (m, 1H), 7.54-7.52 (m, 2H), 7.47-7.43 (m, 3H), 7.39-7.35 (m, 1H), 7.32-7.30 (m, 2H), 6.76 (d, *J*= 8.8 Hz, 2H), 6.22 (s, 1H), 4.20-4.17 (m, 1H), 3.83 (s, 4H), 3.38-3.31 (m, 1H), 2.44-2.38 (m, 2H), 2.16-2.11 (m, 2H); MS (ESI) *m/z* 424 $[C_{26}H_{25}N_5O + H]^+$.

[000198] Example 95: 2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)-N-(5-phenylpyridin-2-yl)propanamide



108 mg, 30%, HPLC 98%, beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.65 (d, *J*=2.0 Hz, 1H), 8.17-8.08 (m, 3H), 7.70-7.68 (m, 2H), 7.51-7.46 (m, 3H), 7.40-7.36 (m, 2H), 7.06-7.03 (m, 1H), 6.56 (d, *J*=8.4 Hz, 1H), 6.50 (d, *J*=2.0 Hz, 1H), 4.40-4.33 (m, 1H), 4.03 (s, 3H), 1.47 (d, *J*=6.8 Hz, 3H) ; MS (ESI) *m/z* 399 $[C_{23}H_{22}N_6O + H]^+$.

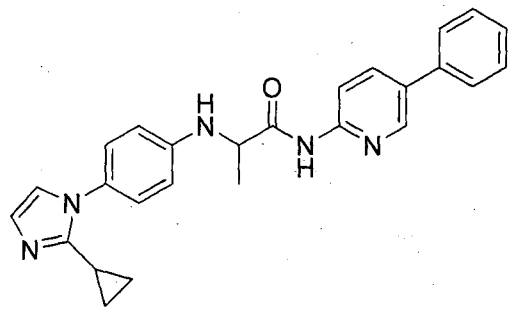
[000199] Example 96: 6-(1-methyl-1H-pyrazol-5-yl)-N-(5-phenylpyridin-2-yl)-1,2,3,4-tetrahydroquinoline-2-carboxamide



24 mg, 54%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.65 (d, *J* = 2.4 Hz, 1H), 8.23-8.16 (m, 1H), 8.16-8.08 (m, 1H), 7.76-7.67 (m, 2H), 7.52-7.42 (m, 2H), 7.42-7.33 (m, 2H), 7.11-7.05 (m, 1H), 7.03 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.20 (d, *J* = 2.0 Hz, 1H), 4.25-4.15 (m, 1H), 3.80 (s, 3H), 2.80-2.70 (m, 1H), 2.70-2.65 (m, 1H), 2.20-2.10 (m, 1H), 2.00-1.90 (m, 1H); MS (ESI) *m/z* 410 $[C_{25}H_{23}N_5O + H]^+$.

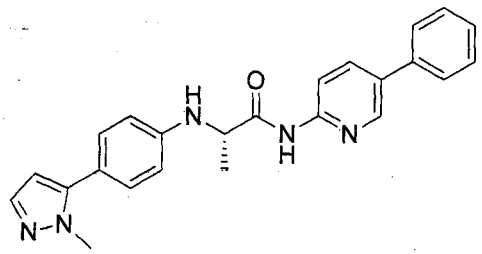
[000200] Racemate was separated by chiral column chromatography (Isomer 1: chiral HPLC 99%, $[\alpha]_D$ +20.87° (chloroform) and isomer-2: Chiral HPLC 99%, $[\alpha]_D$ -12.14° (chloroform).

[000201] Example 97: 2-(4-(2-cyclopropyl-1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



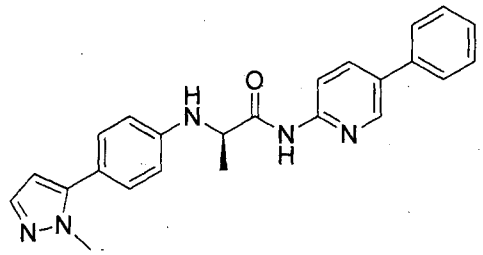
5 mg, 78%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.53 (d, J = 2.4Hz, 1H), 8.28-8.23 (m, 1H), 8.10-8.03 (m, 1H), 7.66-7.59 (m, 2H), 7.50-7.41 (m, 2H), 7.40-7.35 (m, 1H), 7.26-7.20 (m, 2H), 7.03 (s, 1H), 6.86 (s, 1H), 6.85-6.78 (m, 2H), 4.15-4.05 (m, 1H), 1.80-1.70 (m, 1H), 1.60 (d, J = 7.2Hz, 3H), 0.95-0.82 (m, 4H); MS (ESI) m/z 424 $[C_{26}H_{25}N_5O + H]^+$.

[000202] Example 98: (S)-2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



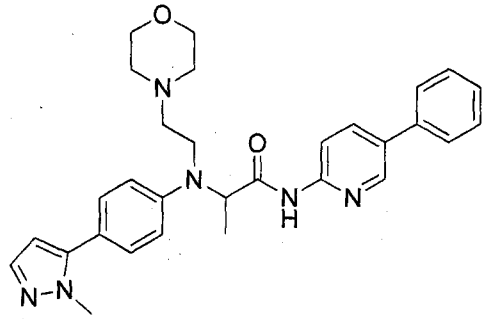
32 mg, 22%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.64 (d, J=2.4 Hz, 1H), 8.18-8.16 (m, 1H), 8.11-8.08 (m, 1H), 7.70-7.68 (m, 2H), 7.48 (t, J=7.2 Hz, 2H), 7.40-7.36 (m, 2H), 7.26-7.23 (m, 2H), 6.73-6.71 (m, 2H), 6.32 (d, J=8.0 Hz, 1H), 6.20 (d, J=2.0 Hz, 1H), 4.31-4.24 (m, 1H), 3.77 (s, 3H), 1.45 (d, J=6.8 Hz, 3H) ; MS (ESI) m/z 398 $[C_{24}H_{23}N_5O + H]^+$.

[000203] Example 99: (R)-2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



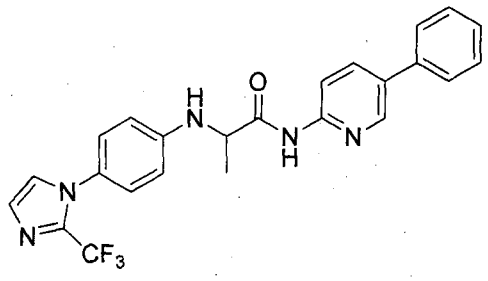
10 mg, 18%, HPLC 97%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.64 (d, *J*=2.0 Hz, 1H), 8.18-8.16 (m, 1H), 8.11-8.08 (m, 1H), 7.70-7.68 (m, 2H), 7.48 (t, *J*=7.2 Hz, 2H), 7.40-7.36 (m, 2H), 7.26-7.23 (m, 2H), 6.73-6.71 (m, 2H), 6.32 (d, *J*=8.0 Hz, 1H), 6.20 (d, *J*=2.0 Hz, 1H), 4.31-4.24 (m, 1H), 3.77 (s, 3H), 1.45 (d, *J*=7.2Hz, 3H) ; MS (ESI) *m/z* 398 $[C_{24}H_{23}N_5O + H]^+$.

[000204] Example 100: 2-((4-(1-methyl-1H-pyrazol-5-yl)phenyl)(2-morpholinoethyl)amino)-N-(5-phenylpyridin-2-yl)propanamide



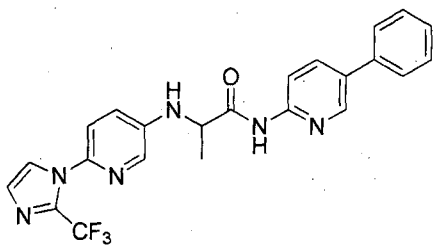
6 mg, 9%, HPLC 96%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.59 (d, *J*=2.4 Hz, 1H), 8.22-8.20 (m, 1H), 8.13-8.10 (m, 1H), 7.69-7.68 (m, 2H), 7.47 (t, *J*=7.2 Hz, 2H), 7.40-7.32 (m, 4H), 6.81 (d, *J*=8.8 Hz, 2H), 6.23 (d, *J*=1.6 Hz, 1H), 4.59 (q, *J*=6.8 Hz, 1H), 3.79 (s, 3H), 3.73-3.58 (m, 7H), 2.72-2.54 (m, 5H), 1.45 (d, *J*=7.2Hz, 3H) ; MS (ESI) *m/z* 511 $[C_{30}H_{34}N_6O_2 + H]^+$.

[000205] Example 101: N-(5-phenylpyridin-2-yl)-2-(4-(2-(trifluoromethyl)-1H-imidazol-1-yl) phenylamino) propanamide



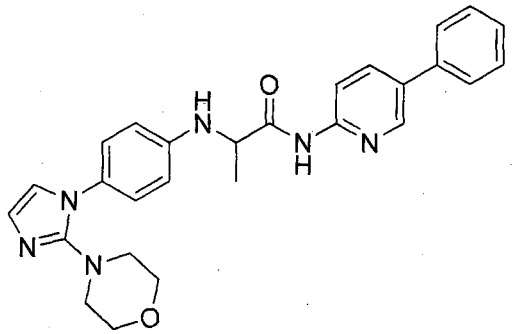
65 mg, 47%, LC-MS 96%, off-white solid. ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 10.71 (s, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.19-8.09 (m, 2H), 7.71 (d, J = 7.0, 2H), 7.55 (d, J = 0.9, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.19-7.16 (m, 3H), 6.71 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 7.9 Hz, 1H), 4.30 (t, J = 7.5 Hz, 1H), 1.45 (d, J = 7.0 Hz, 3H); MS (ESI) *m/z* 452.13 $[C_{24}H_{20}F_3N_5O + H]^+$.

[000206] Example 102: N-(5-phenylpyridin-2-yl)-2-(6-(2-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-3-ylamino)propanamide



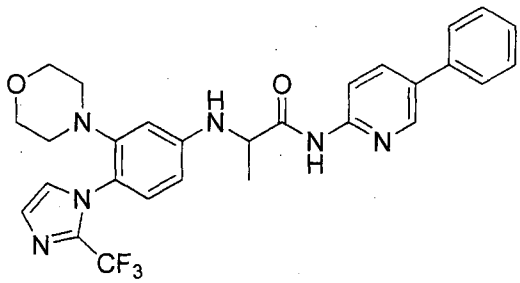
34 mg, 23%, LC-MS 96%. 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.86 (s, 1H), 8.67 (d, J = 2.2 Hz, 1H), 8.18-8.09 (m, 2H), 7.96 (d, J = 3 Hz, 1H), 7.71 (d, J = 6.6 Hz, 3H), 7.48 (t, J = 8 Hz, 2H), 7.45-7.35 (m, 2H), 7.21 (s, 2H), 7.14 (dd, J = 3, 8.7 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 4.38 (t, J = 7 Hz, 1H), 1.47 (d, J = 7 Hz, 3H); MS (ESI) m/z 453.16 [C23H19F3N6O+H]+.

[000207] Example 103: 2-(4-(2-morpholino-1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



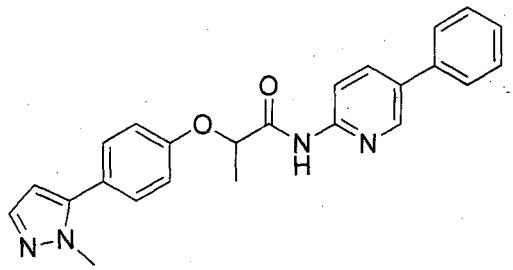
15 mg, 20%, LC-MS 99%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.13 (s, 1H), 8.46 (s, 1H), 8.38 (d, J = 8.4 Hz,1H), 7.95 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.2 Hz, 2H) ,7.40-7.32 (m, 3H), 6.79 (d, J = 14 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 4.15 (s, 1H), 3.96 (q, J = 7.2 Hz, 1H), 3.65 (t, J = 4.4 Hz, 4H), 3.0 (t, J = 5.2 Hz, 4H), 1.67 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 469.21 $[C_{27}H_{28}N_6O_2+H]^+$.

[000208] Example 104: 2-(3-morpholino-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



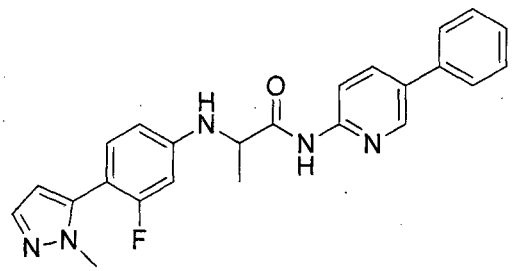
50 mg, 47%, LC-MS 95%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.75 (b r s, 1 H), 8.65 (d, J = 1.7 Hz, 1H), 8.18-8.09 (m, 2 H), 7.71-7.69 (d, , J = 7.4 Hz, 2 H), 7.53-7.37 (m, , 4 H), 7.21 (s, 1 H), 7.07-7.05 (d, J = 8.4 Hz 1H),6.49-6.47(d, , J = 7.9 Hz,3 H), 4.31 (,m 1 H), 3.43-3.34 (m, 4 H), 2.67-2.62 (m, 2 H), 2.42-2.33 (m,2 H),1.44-1.42(d, , J = 6.6 Hz,3H). MS (ESI) *m/z* 537.21 $[C28H27F3N6O2]^+$.

[000209] Example 105: 2-(4-(1-methyl-1H-pyrazol-5-yl)phenoxy)-N-(5-phenylpyridin-2-yl)propanamide



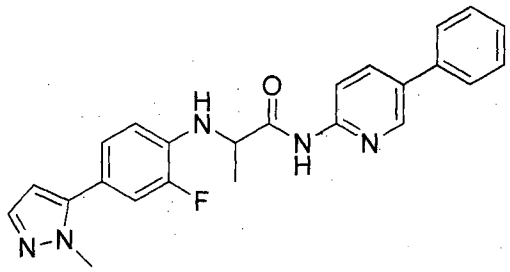
93 mg, 24%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.85 (s, 1H), 8.62 (s, 1H), 8.157-8.100 (m, 2H), 7.71-7.70 (m, 2H), 7.50-7.37 (m, 6H), 7.06-7.04 (m, 2H), 6.31 (s, 1H), 5.15 (q, *J*= 6.8 Hz, 1H), 3.80 (s, 3H), 1.59 (d, *J*= 6.4 Hz, 3H); MS (ESI) *m/z* 399 $[C_{24}H_{22}N_4O_2 + H]^+$.

[000210] Example 106: 2-(3-fluoro-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



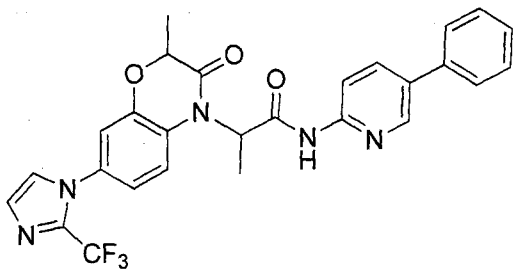
41 mg, 39%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.66 (d, *J* = 2.0 Hz, 1H), 8.20-8.12 (m, 1H), 8.12-8.05 (m, 1H), 7.72-7.65 (m, 2H), 7.52-7.42 (m, 2H), 7.42-7.33 (m, 2H), 7.20-7.12 (m, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.60-6.50 (m, 2H), 6.21 (d, *J* = 2.0 Hz, 1H), 4.40-4.30 (m, 1H), 3.66 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* 416 $[C_{24}H_{22}FN_5O + H]^+$.

[000211] Example 107: 2-(2-fluoro-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



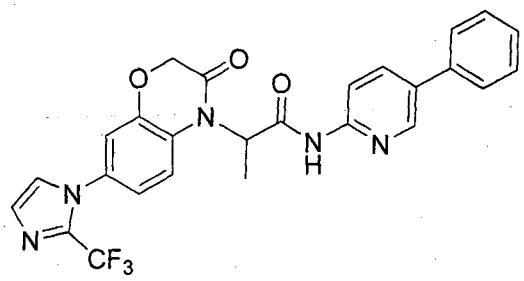
187 mg, 30%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.65 (d, J = 2.4 Hz, 1H), 8.20-8.12 (m, 1H), 8.12-8.05 (m, 1H), 7.72-7.65 (m, 2H), 7.52-7.42 (m, 2H), 7.42-7.33 (m, 2H), 7.32-7.25 (m, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.76 (t, J = 8.4 Hz, 1H), 6.29 (d, J = 1.6 Hz, 1H), 5.95 (d, J = 7.6 Hz, 1H), 4.40-4.30 (m, 1H), 3.80 (s, 3H), 1.51 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 416 $[C_{24}H_{22}FN_5O + H]^+$.

[000212] Example 108: 2-(2-methyl-3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-N-(5-phenylpyridin-2-yl)propanamide



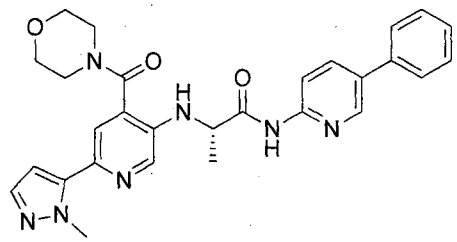
120 mg, 42%, LC-MS 97 %,, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 9.7 Hz, 2H), 7.70-7.68 (m, 3H), 7.50-7.34 (m, 4H), 7.27-7.17 (m, 3H), 5.51 (d, J = 7.0 Hz, 3H), 5.44 (d, J = 7.1 Hz, 3H), 4.87 (t, J = 7.0 Hz, 1H), 1.56-1.46 (m, 6H); MS (ESI) m/z 520.2 $[C_{27}H_{22}F_3N_5O_3+H]^+$.

[000213] Example 109: 2-(3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-N-(5-phenylpyridin-2-yl)propanamide



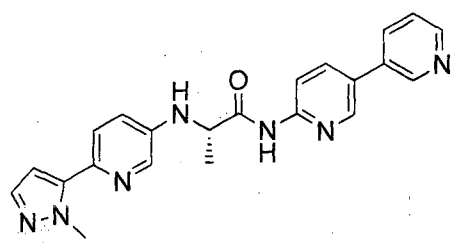
95 mg, 42%, LC-MS 95%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.76 (s, 1H), 8.62 (s, 1H), 8.12 (s, 2H), 7.72-7.67 (m, 3H), 7.50-7.39 (m, 3H), 7.25-7.17 (m, 4H), 5.51-5.50 (m, 1H), 4.79 (s, 2H), 1.56 (d, J = 7.1 Hz, 3H); MS (ESI) *m/z* 508.3 $[C_{26}H_{20}F_3N_5O_3 + H]^+$.

[000214] Example 110: (S)-2-(6-(1-methyl-1H-pyrazol-5-yl)-4-(morpholine-4-carbonyl)pyridin-3-ylamino)-N-(5-phenylpyridin-2-yl)propanamide



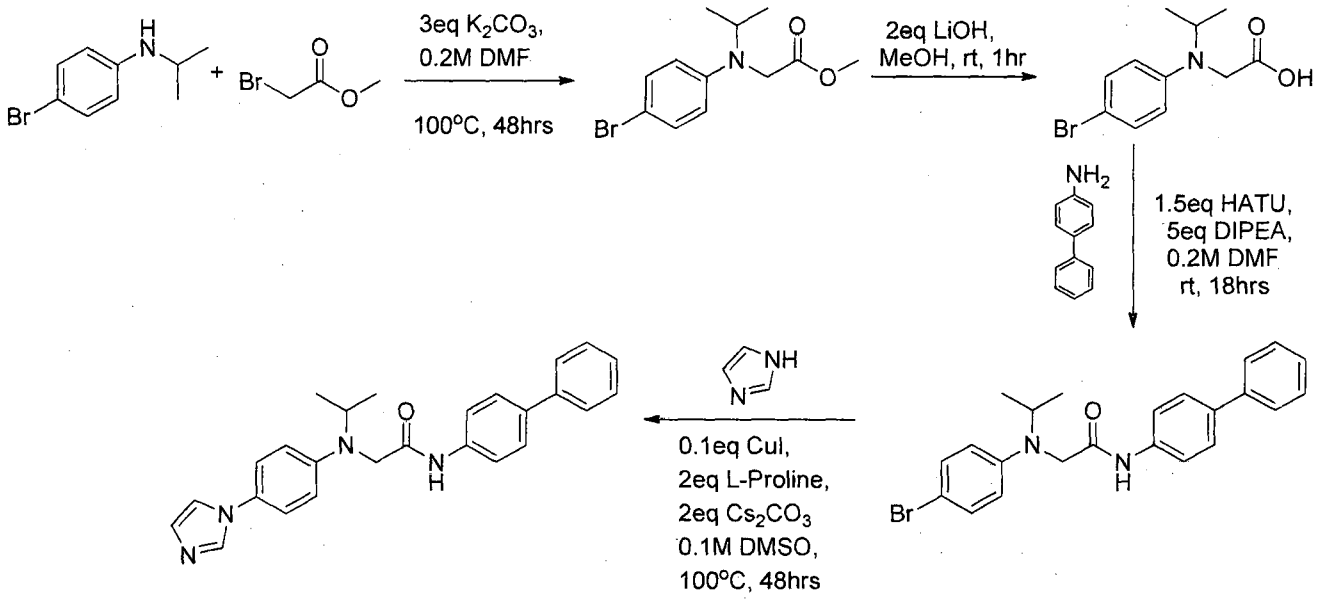
LC-MS 95%, $[\alpha]_D$ +70.03°. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.91 (s, 1H), 8.68 (d, J = 2.2 Hz, 1H), 8.17-8.10 (m, 3H), 7.72-7.70 (d, J = 7.5 Hz, 2H), 7.50-7.40 (m, 3H), 7.40-7.37 (m, 2H), 6.64-6.63 (d, J = 2.2 Hz, 1H), 5.92 (d, J = 7.5 Hz, 1H), 4.54- 4.50 (t, J = 7.5 Hz, 1H), 4.09 (s, 3H), 3.67 (m, 6H), 3.89-3.27 (m, 2H), 1.52-1.50 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 511 .23 $[C_{28}H_{29}N_7O_3]^+$.

[000215] Example 111: (S)-N-(3,3'-bipyridin-6-yl)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)propanamide



36% , LC-MS 98%, chiral HPLC 98%, $[\alpha]_D$ -72.58°. 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.86 (s, 1H), 8.94 (d, J = 2.0 Hz, 1H), 8.74 (s, 1H), 8.58 (d, J = 6.0 Hz, 1H), 8.19 (s, 2H), 8.14-8.11 (m, 2H), 7.52-7.48 (m, 2H), 7.37 (s, 1H), 7.05 (dd, J = 11.2 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 4.38 (t, J = 7.2 Hz, 1H), 4.03 (s, 1H), 1.46 (d, J = 6.8 Hz, 3H); MS (ESI) m/z 400.47 [C22H21N7O+H]+.

[000216] Example 112: 2-((4-(1H-imidazol-1-yl)phenyl)(isopropyl)amino)-N-(biphenyl-4-yl)acetamide



General procedure 4:

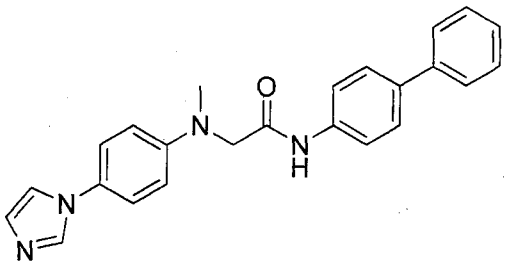
[000217] To 4-bromo-N-isopropylaniline hydrobromide (150 mg, 0.509 mmol) and K_2CO_3 (211 mg, 1.53 mmol) in DMF (1.02 mL) was added methyl bromoacetate (96 µl, 1.02 mmol). The mixture was stirred at 100°C under inert atmosphere for 48 h, then it was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure to afford methyl 2-((4-bromophenyl)(isopropyl)amino)acetate (140mg, 94%); MS (ESI) *m/z* 288 $[C_{12}H_{16}BrNO_2 + H]^+$.

[000218] Methyl 2-((4-bromophenyl)(isopropyl)amino)acetate (0.500 mmol) and LiOH (40 mg, 1.00 mmol) in water (1.25 mL) and CH_3OH (1.25 mL) was stirred for 2 h at room temperature. CH_3OH was removed from the reaction and the aqueous layer was acidified with conc HCl until pH~1. The mixture was concentrated under reduced pressure to afford 2-((4-bromophenyl)(isopropyl)amino)acetic acid; MS (ESI) *m/z* 274 $[C_{11}H_{14}BrNO_2 + H]^+$.

[000219] To a solution of 2-((4-bromophenyl)(isopropyl)amino)acetic acid (0.500 mmol) in DMF (2.50 mL) were added HATU (285 mg, 1.50 mmol), DIPEA (0.435 mL, 2.50 mmol) and 4-aminobiphenyl (85 mg, 0.500 mmol), The reaction mixture was stirred at room temperature under inert atmosphere for 18 h, then it was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent cyclohexane/EtOAc 70:30 to afford N-(biphenyl-4-yl)-2-((4-bromophenyl)(isopropyl)amino)acetamide (54 mg, 26%); MS (ESI) *m/z* 425 $[C_{23}H_{23}BrN_2O + H]^+$.

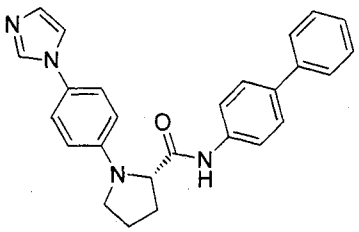
[000220] N-(biphenyl-4-yl)-2-((4-bromophenyl)(isopropyl)amino)acetamide (50 mg, 0.118 mmol), imidazole (16 mg, 0.236 mmol), CuI (2.2 mg, 0.012 mmol), L-proline (27 mg, 0.236 mmol), Cs_2CO_3 (77 mg, 0.236 mmol) in DMSO (1.20 mL) was stirred for 48 h at 100°C. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by preparative HPLC (C18, eluent ACN, water, formic acid 0.1%) to afford 2-((4-(1H-imidazol-1-yl)phenyl)(isopropyl)amino)-N-(biphenyl-4-yl)acetamide (13 mg, 26%, HPLC 99%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.14 (s, 1H), 7.76-7.69 (m, 2H), 7.67-7.60 (m, 4H), 7.58 (s, 1H), 7.48-7.38 (m, 4H), 7.36-7.29 (m, 1H), 7.10 (s, 1H), 6.86-6.78 (m, 2H), 4.30-4.15 (m, 1H), 4.03 (s, 2H), 1.21 (d, J = 6.4Hz, 6H); MS (ESI) *m/z* 411 $[C_{26}H_{26}N_4O + H]^+$.

[000221] Example 113: 2-((4-(1H-imidazol-1-yl)phenyl)(methyl)amino)-N-(biphenyl-4-yl)acetamide



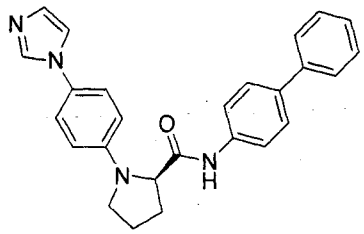
30 mg, 31%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.02 (bs, 1H), 7.73-7.67 (m, 2H), 7.67-7.59 (m, 4H), 7.55 (s, 1H), 7.48-7.38 (m, 4H), 7.35-7.29 (m, 1H), 7.04 (s, 1H), 6.83-6.76 (m, 2H), 4.23 (s, 2H), 3.10 (s, 3H); MS (ESI) *m/z* 383 $[C_{24}H_{22}N_4O + H]^+$.

[000222] Example 114: (S)-1-(4-(1H-imidazol-1-yl)phenyl)-N-(biphenyl-4-yl)pyrrolidine-2-carboxamide



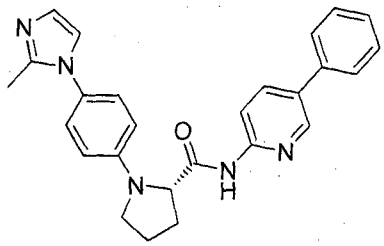
43 mg, 29 %, HPLC 98%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.75 (br s, 1H), 7.59-7.53 (m, 6H), 7.41 (t, *J*=7.2 Hz, 2H), 7.34-7.25 (m, 3H), 7.25-7.18 (m, 2H), 6.79 (d, *J*=9.2 Hz, 2H), 4.15-4.12 (m, 1H), 3.84-3.80 (m, 1H), 3.37-3.30 (m, 1H), 2.44-2.39 (m, 2H), 2.16-2.08 (m, 2H) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.60, 146.96, 140.41, 137.71, 136.42, 128.81, 127.66, 127.23, 126.87, 123.41, 120.27, 114.12, 65.41, 50.35, 31.70, 24.36; MS (ESI) *m/z* 409 $[C_{26}H_{24}N_4O + H]^+$.

[000223] Example 115: (R)-1-(4-(1H-imidazol-1-yl)phenyl)-N-(biphenyl-4-yl)pyrrolidine-2-carboxamide



59mg, 41%, HPLC 97%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.76 (br s, 1H), 7.59-7.53 (m, 6H), 7.41 (t, *J*=7.2 Hz, 2H), 7.34-7.25 (m, 3H), 7.25-7.20 (m, 2H), 6.79 (d, *J*=8.8 Hz, 2H), 4.15-4.12 (m, 1H), 3.84-3.80 (m, 1H), 3.37-3.30 (m, 1H), 2.44-2.39 (m, 2H), 2.16-2.08 (m, 2H) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.59, 146.95, 140.39, 137.69, 136.40, 128.79, 127.64, 127.22, 126.85, 123.44, 120.26, 114.14, 65.39, 50.34, 31.68, 24.35; MS (ESI) *m/z* 409 $[C_{26}H_{24}N_4O+ H]^+$.

[000224] Example 116: (S)-1-(4-(2-methyl-1H-imidazol-1-yl)phenyl)-N-(5-phenylpyridin-2-yl)pyrrolidine-2-carboxamide



8 mg, 4%, HPLC 97%, grey solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.45 (d, *J*=1.6 Hz, 1H), 8.42-8.40 (m, 1H), 7.96-7.93 (m, 1H), 7.54-7.52 (m, 2H), 7.47-7.44 (m, 2H), 7.40-7.36 (m, 1H), 7.18-7.16 (m, 2H), 6.99-6.93 (m, 2H), 6.76-6.74 (m, 2H), 4.19-4.16 (m, 1H), 3.87-3.83 (m, 1H), 3.38-3.31 (m, 1H), 2.43-2.39 (m, 2H), 2.31 (s, 3H), 2.17-2.14 (m, 2H); MS (ESI) *m/z* 424 $[C_{26}H_{25}N_5O + H]^+$.

[000225] Example 117: 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)-2-methylpropanamide

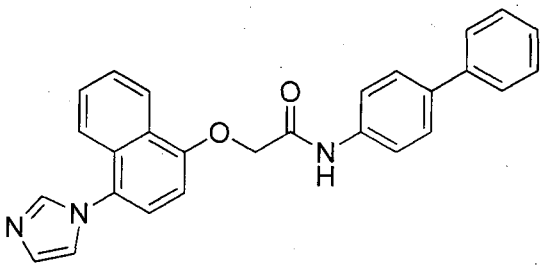
4-Iodophenol (1g, 4.55 mmol), sodium hydroxide (909 mg, 22.7 mmol) was refluxed in acetone (5.5 ml, 75 mmol) for 30 min. $CHCl_3$ (0.73 ml, 1.87 mmol) was then added and the resulting

mixture was refluxed for 4 h. Upon reaction completion, the mixture was concentrated under reduced pressure, acidified with conc HCl and the solids obtained were filtered, washed with water to afford 2-(4-iodophenoxy)-2-methylpropanoic acid (918mg, 66%); MS (ESI) *m/z* 307 $[C_{10}H_{11}IO_3 + H]^+$.

[000226] To a solution of 2-(4-iodophenoxy)-2-methylpropanoic acid (500 mg, 1.63 mmol) in DMF (3.3 mL) were added HATU (932 mg, 4.90 mmol), DIPEA (0.854 mL, 4.90 mmol) and 4-aminobiphenyl (290 mg, 1.72 mmol), The reaction mixture was stirred at room temperature under inert atmosphere for 18 h, then it was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent cyclohexane/EtOAc 90:10) to afford N-(biphenyl-4-yl)-2-(4-iodophenoxy)-2-methylpropanamide (556 mg, 75%); MS (ESI) *m/z* 459 $[C_{22}H_{20}INO_2 + H]^+$.

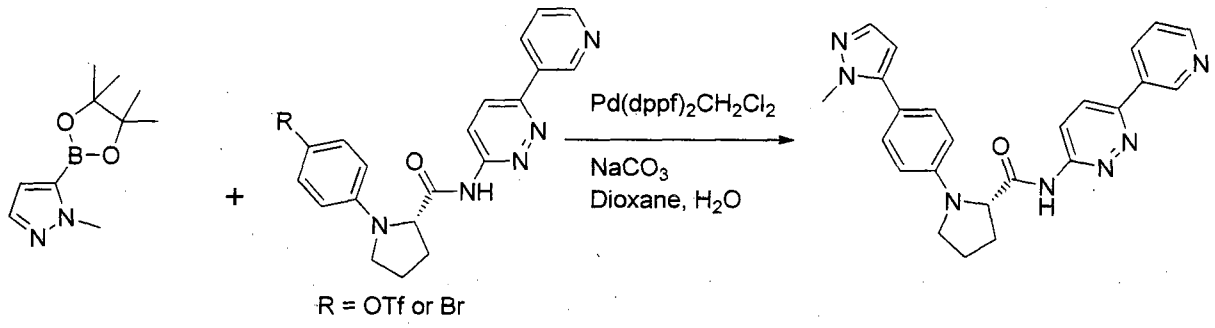
[000227] N-(biphenyl-4-yl)-2-(4-iodophenoxy)-2-methylpropanamide (100 mg, 0.219 mmol), imidazole (76.1 mg, 0.438 mmol), CuI (4.2 mg, 0.0219 mmol), L-proline (50.4 mg, 0.438 mmol), Cs_2CO_3 (143 mg, 0.438 mmol) in DMSO (0.44 mL) was stirred for 18 h at 100°C. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CH_2Cl_2/CH_3OH 97:3) to afford 2-(4-(1H-imidazol-1-yl)phenoxy)-N-(biphenyl-4-yl)-2-methylpropanamide (20 mg, 23%, HPLC 99%) as an off- white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.13 (s, 1H), 7.83-7.78 (m, 2H), 7.66-7.60 (m, 5H), 7.60-7.53 (m, 2H), 7.47-7.41 (m, 2H), 7.36-7.30 (m, 1H), 7.09-7.03 (m, 3H), 1.59 (s, 6H); MS (ESI) *m/z* 398 $[C_{25}H_{23}N_3O_2 + H]^+$.

[000228] Example 118: 2-(4-(1H-imidazol-1-yl)naphthalen-1-yloxy)-N-(biphenyl-4-yl)acetamide



2 mg, 1.6%, HPLC 98%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (bs, 1H), 8.47 (d, J = 2.0Hz, 1H), 7.91 (s, 1H), 7.79-7.72 (m, 2H), 7.70-7.61 (m, 6H), 7.54 (d, J = 8.0Hz, 1H), 7.50 (s, 1H), 7.48-7.41 (m, 2H), 7.41-7.30 (m, 2H), 7.12 (s, 1H), 7.05 (d, J = 8.0Hz, 1H), 5.05 (s, 2H); MS (ESI) m/z 420 $[C_{27}H_{21}N_3O_2 + H]^+$.

[000229] Example 119: (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(6-(pyridin-3-yl)pyridazin-3-yl)pyrrolidine-2-carboxamide

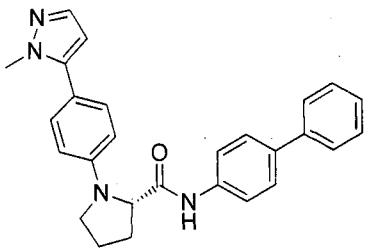


General procedure 5:

[000230] 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (53 mg, 0.256 mmol), (S)-1-(4-bromophenyl)-N-(6-(pyridin-3-yl)pyridazin-3-yl)pyrrolidine-2-carboxamide (90 mg, 0.213 mmol), $Pd(dppf)_2CH_2Cl_2$ (17 mg, 0.021 mmol) and Na_2CO_3 (45 mg, 0.426 mmol) was dissolved in dioxane (3 mL) and water (1 mL). The reaction mixture was heated at reflux for 16 h, then it was diluted with H_2O (25 mL) and extracted with EtOAc (3x25 mL). The combined organic layer was filtered over celite, dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was purified by preparative HPLC (C18, eluent ACN, water, formic acid 0.1%) to afford (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(6-(pyridin-3-yl)pyridazin-3-yl)pyrrolidine-2-carboxamide (22 mg, 24%, AUC HPLC 96%) as

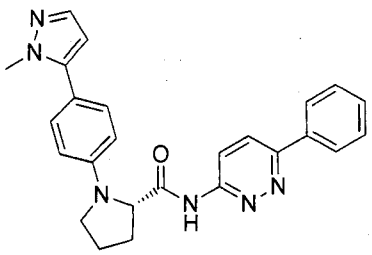
white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 9.18 (d, *J*= 2.0 Hz, 1H), 8.72-8.68 (m, 2H), 8.37-8.35 (m, 1H), 7.93 (d, *J*= 9.6 Hz, 1H), 7.47-7.43 (m, 2H), 7.32 (d, *J*= 8.8 Hz, 2H), 6.77 (d, *J*= 8.8 Hz, 2H), 6.22 (d, *J*= 2.0 Hz, 1H), 4.25-4.22 (m, 1H), 3.93-3.88 (m, 4H), 3.41-3.35 (m, 1H), 2.48-2.41 (m, 2H), 2.19-2.12 (m, 2H); MS (ESI) *m/z* 426 $[C_{24}H_{23}N_7O + H]^+$.

[000231] Example 120: (S)-N-(biphenyl-4-yl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamide



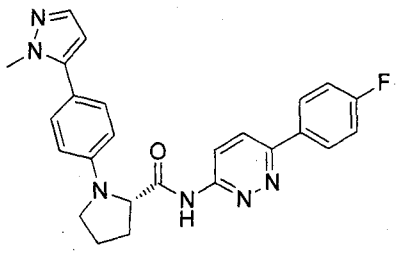
19mg, 12%, HPLC 99%, beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.62-7.56 (m, 6H), 7.51 (d, *J*=1.6 Hz, 1H), 7.46-7.42 (m, 2H), 7.37-7.34 (m, 3H), 6.83-6.81 (m, 2H), 6.26 (s, 1H), 4.21-4.18 (m, 1H), 3.90-3.83 (m, 4H), 3.41-3.34 (m, 1H), 2.45-2.39 (m, 2H), 2.19-2.10 (m, 2H); MS (ESI) *m/z* 423 $[C_{27}H_{26}N_4O + H]^+$.

[000232] Example 121: (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(6-phenylpyridazin-3-yl)pyrrolidine-2-carboxamide



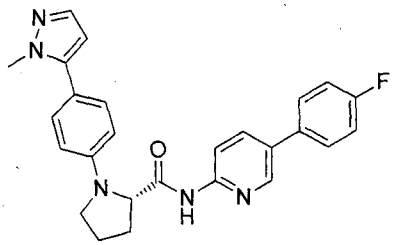
13 mg, 13%, HPLC 99%, brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 8.38-8.36 (m, 1H), 8.24-8.22 (m, 1H), 8.10-8.08 (m, 2H), 7.56-7.50 (m, 3H), 7.37-7.32 (m, 3H), 6.65-6.63 (m, 2H), 6.22 (d, *J*=1.6 Hz, 1H), 4.59-4.57 (m, 1H), 3.78 (s, 3H), 3.66-3.61 (m, 1H), 3.42-3.36 (m, 1H), 2.43-2.32 (m, 1H), 2.18-2.06 (m, 3H) ; MS (ESI) *m/z* 425 $[C_{25}H_{24}N_6O + H]^+$.

[000233] Example 122: (S)-N-(6-(4-fluorophenyl)pyridazin-3-yl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamide



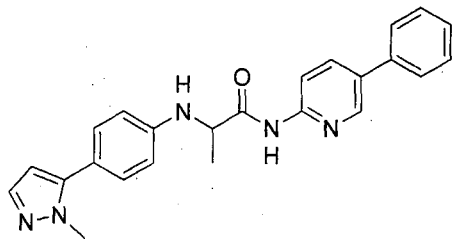
13 mg, 13%, HPLC 99%, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 8.37-8.35 (m, 1H), 8.25-8.22 (m, 1H), 8.17-8.13 (m, 2H), 7.39-7.32 (m, 5H), 6.64 (d, *J*=8.8 Hz, 2H), 6.22 (d, *J*=2.0 Hz, 1H), 4.59-4.56 (m, 1H), 3.78 (s, 3H), 3.66-3.61 (m, 1H), 3.42-3.36 (m, 1H), 2.49-2.32 (m, 1H), 2.17-2.12 (m, 3H) ; MS (ESI) *m/z* 443 $[C_{25}H_{23}FN_6O + H]^+$.

[000234] Example 123: (S)-N-(5-(4-fluorophenyl)pyridin-2-yl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamide



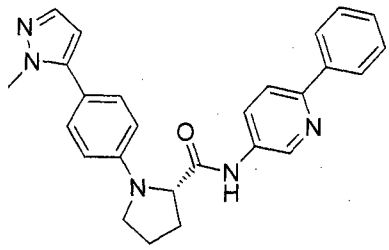
10 mg, 10%, HPLC 95%, yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.64 (d, *J*=2,0 Hz, 1H), 8.15-8.09 (m, 2H), 7.77-7.73 (m, 2H), 7.37-7.28 (m, 5H), 6.63 (d, *J*=8.8 Hz, 2H), 6.22 (d, *J*=2.0 Hz, 1H), 4.52-4.50 (m, 1H), 3.78 (s, 3H), 3.66-3.62 (m, 1H), 3.40-3.35 (m, 1H), 2.38-2.32 (m, 1H), 2.11-2.02 (m, 3H) ; MS (ESI) *m/z* 442 $[C_{26}H_{24}FN_5O + H]^+$.

[000235] Example 124: 2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



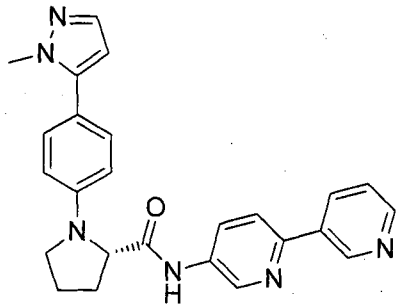
15%, LC-MS 99%, off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.66 (s, 1H), 8.65 (s, 1H), 8.18 (d, J = 8.4 Hz,, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 8.0 Hz, 2H), 7.40-7.36 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H) ,6.72 (d, J = 8.0 Hz, 2H), 6.37 (d, J = 8.0 Hz,1H), 6.21 (s, 1H), 4.29 (q, J = 8.0 Hz,1H), 3.77 (s, 3H), 1.43 (d, J = 5.5 Hz, 3H); MS (ESI) *m/z* 385.08 $[C_{24}H_{23}N_5O+H]^+$.

[000236] Example 125: (S)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(6-phenylpyridin-3-yl)pyrrolidine-2-carboxamide



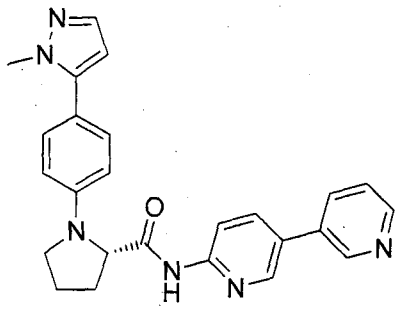
80mg, 53%, HPLC 96%, off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J=2.8 Hz, 1H), 8.40 (s, 1H), 8.30-8.27 (m, 1H), 7.96 (d, J=7.2 Hz, 2H), 7.73 (d, J=8.4 Hz, 1H), 7.51-7.36 (m, 6H), 6.83 (d, J=8.8 Hz, 2H), 6.26 (d, J=1.6 Hz, 1H), 4.23-4.20 (m, 1H), 3.89-3.87 (m, 4H), 3.39-3.36 (m, 1H), 2.47-2.41 (m, 2H), 2.22-2.09 (m, 2H); MS (ESI) *m/z* 424 $[C_{26}H_{25}N_5O + H]^+$.

[000237] Example 126: (S)-N-(2,3'-bipyridin-5-yl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamide



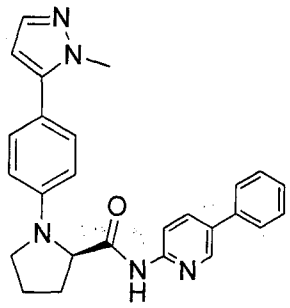
28 mg, 26%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.21 (d, J = 1.6 Hz, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.61-8.57 (m, 1H), 8.41-8.34 (m, 1H), 8.23-8.17 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.51-7.45 (m, 1H), 7.40-7.30 (m, 3H), 6.64 (d, J = 8.8 Hz, 2H), 6.23 (d, J = 1.6 Hz, 1H), 4.40-4.30 (m, 1H), 3.79 (s, 3H), 3.70-3.60 (m, 1H), 3.40-3.30 (m, 1H), 2.40-2.30 (m, 1H), 2.15-2.00 (m, 3H); MS (ESI) *m/z* 425 $[C_{25}H_{24}N_6O + H]^+$.

[000238] Example 127: (S)-N-(3,3'-bipyridin-6-yl)-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)pyrrolidine-2-carboxamide



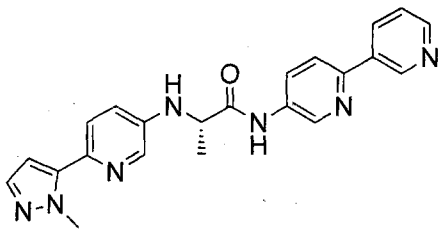
26 mg, 8%, HPLC 99%, white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H), 8.93 (d, J = 1.6 Hz, 1H), 8.73 (d, J = 1.6 Hz, 1H), 8.61-8.57 (m, 1H), 8.21-8.15 (m, 2H), 8.15-8.10 (m, 1H), 7.52-7.45 (m, 1H), 7.40-7.30 (m, 3H), 6.63 (d, J = 8.8 Hz, 2H), 6.22 (d, J = 1.6 Hz, 1H), 4.55-4.50 (m, 1H), 3.79 (s, 3H), 3.70-3.60 (m, 1H), 3.45-3.35 (m, 1H), 2.40-2.30 (m, 1H), 2.15-1.95 (m, 3H); MS (ESI) *m/z* 425 $[C_{25}H_{24}N_6O + H]^+$.

[000239] Example 128: (R)-1-(4-(1-methyl-1H-pyrazol-5-yl) phenyl)-N-(5-phenylpyridin-2-yl) pyrrolidine-2-carboxamide



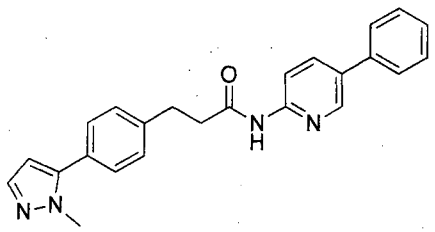
200 mg 47%, LC-MS 98%, $[\alpha]_D$ +200°. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.73 (s, 1H), 8.66 (s, 1H), 8.16-8.09 (m, 2H), 7.70 (d, J = 7.4 Hz, 2H),7.48 (t, J = 7.5 Hz, 2H), 7.40-7.32 (m, 4H), 6.63 (d, J = 8.3 Hz, 2H), 6.22 (s, 1H), 4.52 (d, J = 8.3 Hz, 1H), 3.7 (s, 3H), 3.63 (m, 4H), 3.36 (t, J = 8.3 Hz, 1H), 2.35 (t, J = 7.0 Hz, 1H), 2.11 (d, J = 7.5 Hz, 3H); MS (ESI) *m/z* 424.24 $[C_{26}H_{25}N_5O+H]^+$.

[000240] Example 129: **(S)-N-(2,3'-bipyridin-5-yl)-2-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-ylamino)propanamide**

[000241] 

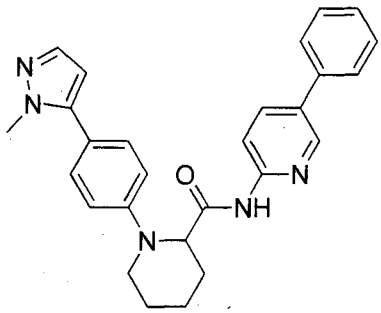
[000242] 600 mg, 23 %, chiral HPLC 97%, $[\alpha]_D$ -107.2°, c = 0.5% (1:1 CH_3OH:$CHCl_3$), an off-white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ (ppm): 10.50 (s, 1H), 9.21 (s, 1H), 8.90 (d, J = 2.2 Hz, 1H), 8.59 (d, J = 3.9 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 8.23–8.20 (dd, J = 2.6, 8.7 Hz, 1H), 8.12 (d, J = 2.6 Hz, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.51–7.47 (m, 2H), 7.37 (d, J = 1.7 Hz, 1H), 7.05–7.02 (dd, J = 2.7, 8.8 Hz, 1H), 6.56 (d, J = 7.5 Hz, 1H), 6.50 (d, J = 1.8 Hz, 1H), 4.22 (t, J = 7.0 Hz, 1H), 4.03 (s, 3H), 1.49 (d, J = 6.6 Hz, 3H); MS (ESI) *m/z* 400.25 $[C_{22}H_{21}N_7O+H]^+$.

[000243] Example 130: 3-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)propanamide



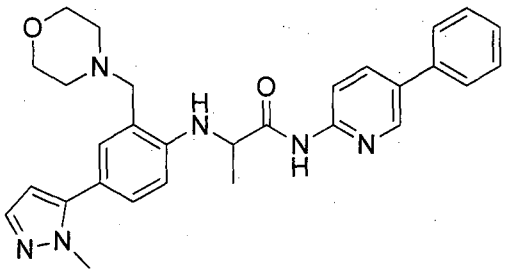
48 mg, 31%, HPLC 99%, brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J*=2.0 Hz, 1H), 8.28 (d, *J*=8.8 Hz, 1H), 7.93-7.90 (m, 2H), 7.56-7.54 (m, 2H), 7.50-7.44 (m, 3H), 7.39-7.32 (m, 5H), 6.27 (s, 1H), 3.87 (s, 3H), 3.13 (t, *J*=7.6 Hz, 2H), 2.77 (t, *J*=8.0 Hz, 2H); MS (ESI) *m/z* 383 $[C_{24}H_{22}N_4O + H]^+$.

[000244] Example 131: 1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)piperidine-2-carboxamide



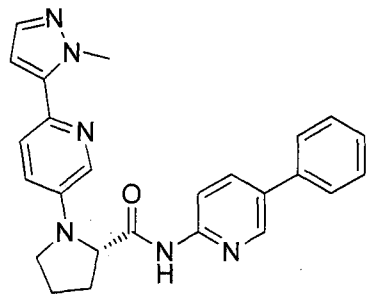
34 mg, 11%, HPLC 95%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.49-8.48 (m, 1H), 8.37-8.34 (m, 1H), 7.95-7.92 (m, 1H), 7.57-7.55 (m, 2H), 7.50-7.46 (m, 3H), 7.41-7.35 (m, 3H), 7.12-7.10 (m, 2H), 6.27 (s, 1H), 4.36 (t, *J*= 4.8 Hz, 1H), 3.89 (s, 3H), 3.58-3.53 (m, 1H), 3.46-3.41 (m, 1H), 2.33-2.31 (m, 1H), 2.02-1.98 (m, 1H), 1.79-1.73 (m, 4H); MS (ESI) *m/z* 438 $[C_{27}H_{27}N_5O + H]^+$.

[000245] Example 132: 2-(4-(1-methyl-1H-pyrazol-5-yl)-2-(morpholinomethyl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



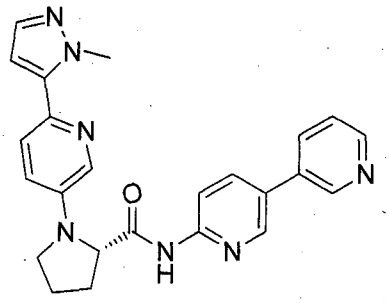
16 mg, 33%, HPLC 99%, off- white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H), 8.66 (d, J = 2.4 Hz, 1H), 8.20-8.11 (m, 1H), 8.11-8.05 (m, 1H), 7.72-7.65 (m, 2H), 7.51-7.45 (m, 2H), 7.42-7.35 (m, 2H), 7.30-7.20 (m, 2H), 7.20-7.15 (m, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.22 (d, J = 1.6 Hz, 1H), 4.50-4.30 (m, 1H), 3.78 (s, 3H), 3.70-3.60 (m, 5H), 3.60-3.50 (m, 1H), 2.50-2.30 (m, 4H), 1.49 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 497 $[C_{29}H_{32}N_6O_2 + H]^+$.

[000246] Example 133: (S)-1-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)-N-(5-phenylpyridin-2-yl)pyrrolidine-2-carboxamide



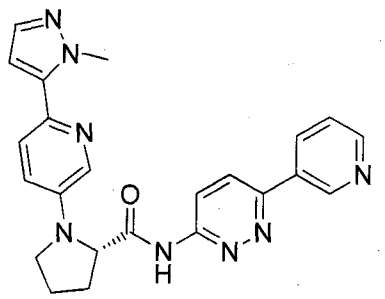
23%, HPLC 98%, $[\alpha]_D$ -227.06°. 1H NMR (400 MHz, CDCl3) δ (ppm): 8.79 (s, 1H), 8.44 (d, J = 1.3 Hz, 1H), 8.40 (d, J = 8.3 Hz, 1H), 8.20 (d, J = 3.1 Hz, 1H), 7.95 (dd, J = 2.2, 8.8 Hz, 1H), 7.54-7.37 (m, 7H), 7.03 (dd, J = 3.1, 8.8 Hz, 1H), 6.44 (d, J = 1.8 Hz, 1H), 4.21 (t, J = 6.5 Hz, 1H), 4.16 (s, 3H), 3.92-3.88 (m, 1H), 3.39-3.37 (m, 1H), 2.45-2.42 (m, 2H), 2.19-2.13 (m, 2H); MS (ESI) m/z 425.47 [C25H24N6O+H]+.

[000247] Example 134: (S)-N-(3,3'-bipyridin-6-yl)-1-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)pyrrolidine-2-carboxamide



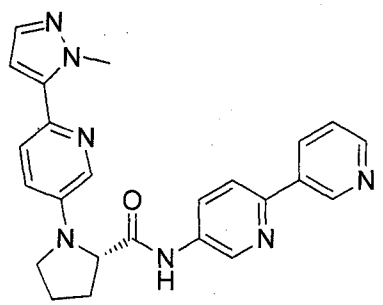
24%, HPLC 99 %, $[\alpha]_D$ -228.19 °. H NMR (400 MHz, DMSO-*d6*) δ (ppm): 10.94 (s, 1H), 8.95 (s, 1H), 8.75 (d, J = 0.9 Hz, 1H), 8.59 (d, J = 4.0 Hz, 1H), 8.20-8.13 (m, 3H), 8.02 (d, J = 2.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.52-7.50 (m, 1H), 7.38 (d, J = 1.7 Hz, 1H), 6.99 (dd, J = 2.6, 8.8 Hz, 1H), 6.53 (d, J = 1.8 Hz, 1H), 4.62 (d, J = 7.4 Hz, 1H), 4.05 (s, 3H), 3.67-3.63 (m, 1H), 3.47-3.41 (m, 1H), 2.39-2.32 (m, 1H), 2.14-2.04 (m, 3H); MS (ESI) m/z 426.2 [C24H23N7O+H]+.

[000248] Example 135: (S)-1-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)-N-(6-(pyridin-3-yl)pyridazin-3-yl)pyrrolidine-2-carboxamide



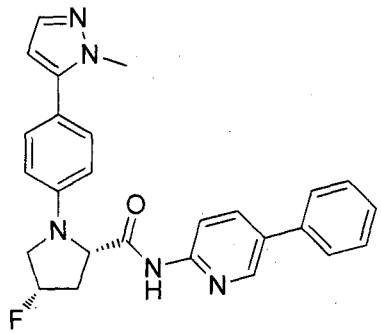
25%, HPLC 99 %.^{1}H NMR (400 MHz, CDCl3) δ (ppm): 9.35 (s, 1H), 9.19 (d, J = 1.8 Hz, 1H), 8.72-8.68 (m, 2H), 8.37 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 3.0 Hz, 1H), 7.95 (d, J = 3.0 Hz, 1H), 7.48-7.44 (m, 3H), 7.05 (dd, J = 2.7, 8.4 Hz, 1H), 6.44 (d, J = 1.8 Hz, 1H), 4.28 (dd, J = 3.1, 8.8 Hz, 1H), 4.15 (s, 3H), 3.95 (t, J = 6.8 Hz, 1H), 3.44-3.38 (m, 1H), 2.51-2.42 (m, 2H), 2.22-2.15 (m, 2H); MS (ESI) m/z 427.21 [C24H22N8O+H]+.

[000249] Example 136: (S)-N-(2,3'-bipyridin-5-yl)-1-(6-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)pyrrolidine-2-carboxamide



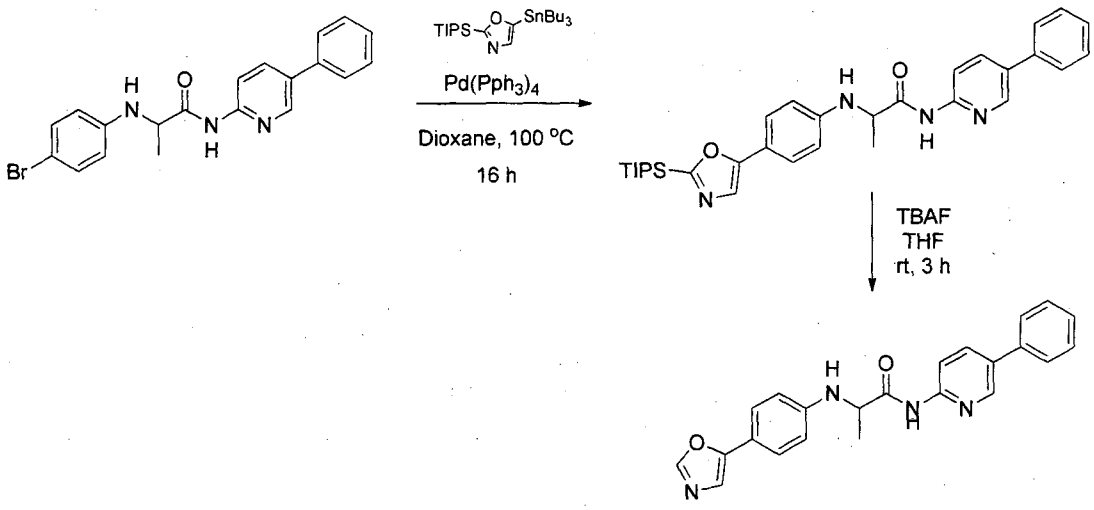
41%, LC-MS 98%, chiral HPLC 99%, $[\alpha]_D$ -203° , white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 8.63-8.61 (m, 2H), 8.32-8.24 (m, 4H), 7.74 (d, J = 8.8 Hz, 1H), 7.50-7.47 (m, 2H), 7.40-7.37 (m, 1H), 7.06 (dd, J = 3.1, 8.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 4.22 (t, J = 6.2 Hz, 1H), 4.17 (s, 3H), 3.92 (t, J = 7.25 Hz, 1H), 3.44-3.37 (m, 1H), 2.49-2.43 (m, H), 2.20-2.12 (m, 1H); MS (ESI) *m/z* 426.2 $[C_{24}H_{23}N_7O+H]^+$.

[000250] Example 137: (2S,4S)-4-fluoro-1-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)pyrrolidine-2-carboxamide



^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.97 (s, 1H), 8.46 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 2.2, 8.4 Hz, 1H), 7.54-7.33 (m, 9H), 6.78 (d, J = 8.8 Hz, 2H), 6.22 (s, 1H), 5.54 (m, 0.5H), 5.37 (m, 0.5H), 4.32 (d, J = 9.9 Hz, 1H), 4.16-4.06 (m, 1H), 3.86 (s, 3H), 3.68-3.60 (m, 1H), 3.52-3.47 (m, 1H), 2.79-2.71 (m, 1H), 2.60-2.56 (m, 1H); MS (ESI) *m/z* 442.16 $[C_{26}H_{24}FN_5O+H]^+$.

[000251] Example 138: 2-(4-(oxazol-5-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide



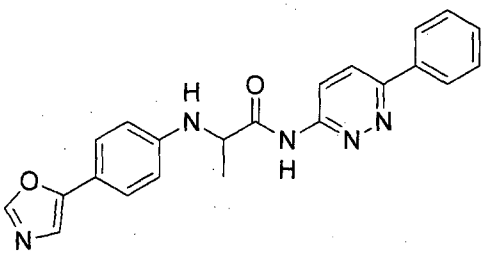
[000252] General procedure 6:

[000253] To a stirred solution of 2-(4-bromophenylamino)-N-(5-phenylpyridin-2-yl)propanamide (200 mg, 1.0 eq) in dioxane (5 mL) was added 5-(tributylstannyl)-2-(triisopropylsilyl)oxazole (377 mg, 1.3 eq) and $Pd(PPh_3)_4$ (34 mg, 0.06 eq) and the reaction mixture was heated at 100 °C for 16 h. After completion, filtered and concentrated under reduced pressure, poured in to ice cold water and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and purified by column chromatography (silica gel, eluent EtOAc/hexane 30:70) to afford 150 mg (55%, LC-MS 67%) of N-(5-phenylpyridin-2-yl)-2-(4-(2-(triisopropylsilyl) oxazol-5-yl) phenylamino) propanamide as a pale yellow solid.

[000254] To a stirred solution of N-(5-phenylpyridin-2-yl)-2-(4-(2-(triisopropylsilyl) oxazol-5-yl) phenylamino) propanamide (150 mg, 1.0 eq) in anhydrous THF (5 mL) was added 1 M TBAF solution (0.41 mL, 1.5 eq) stirred at rt for 4 h. The was concentrated under reduced pressure suspended in water and extracted with EtOAc (3 x 10 mL). Purification by column chromatography (silica gel, eluent EtOAc/hexane 50:50) to afford 100 mg crude of crude product which was again purified by preparative HPLC to afford 45 mg of 2-(4-(oxazol-5-yl) phenylamino)-N-(5-phenylpyridin-2-yl)propanamide (40%, LC-MS 99%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.66 (s, 1H), 8.65 (s, 1H), 8.27 (s, 1H), 8.1 (dd, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.49-7.34 (m, 6H), 6.71 (d, J = 8.0 Hz, 2H) , 6.43 (d, J = 8.0 Hz, 1H), 4.30 (q, 1H), 1.45 (d, J = 8.0 Hz, 3H); MS (ESI) m/z 385.08 $[C_{23}H_{20}N_4O_2+H]^+$.

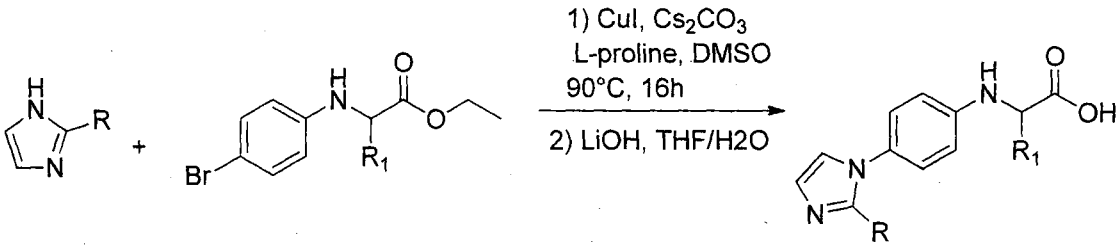
[000255] Example 139: 3-(4-(oxazol-5-yl)phenylamino)-1-(6-phenylpyridazin-3-yl)butan-2-one



30 mg, 20%, LC-MS 99%, off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 11.37 (s, 1H), 8.38 (d, J = 9.2 Hz, 1H), 8.27-8.22 (m, 2H), 8.08 (d, J = 6.8 Hz, 2H), 7.57-7.43 (m, 5H), 7.34 (s, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.4 Hz, 1H), 4.38 (t, J = 8.8 Hz, 1H), 1.47 (d, J = 6.4 Hz, 3H); MS (ESI) m/z 386.2 $[C_{22}H_{19}N_5O_2+H]^+$.

Key intermediate synthesis:

[000256] Intermediate 1: 2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)-N-(5-phenylpyridin-2-yl)propanamide

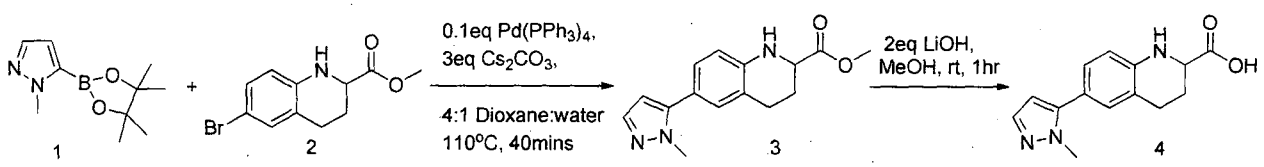


R = CH3, Et, Ph, CF3, Cyclopropyl, Isopropyl
R1 = H, CH3, isopropyl

2-methyl-1H-imidazole (603 mg, 7.349 mmol), ethyl 2-(4-bromophenylamino)propanoate (1 g, 3.675 mmol), CuI (70 mg, 0.367 mmol), L-proline (846 mg, 7.349 mmol), and Cs_2CO_3 (2.39 g, 7.349 mmol) was dissolved in DMSO (10 mL). The reaction mixture was heated at 90°C for 16 h, then it was diluted with water (100 mL) and extracted with EtOAc (30 mL x 3). The combined organic extracts were concentratrated and the residue purified by column chromatography (silica gel, eluent EtOAc/Hexane 70:30) to afford ethyl 2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)propanoate as yellow oil (417 mg, 37%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11-7.09 (m, 3H), 6.82 (s, 1H), 6.62 (d, *J*=6.8 Hz, 2H), 6.30 (d, *J*=8.0Hz, 1H), 4.13-4.06 (m, 3H), 2.18 (s, 3H), 1.39 (d, *J*=6.8 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H); MS (ESI) *m/z* 274 [$C_{15}H_{19}N_3O_2$ + H]$^+$.

[000257] To ethyl 2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)propanoate (490 mg, 1.793 mmol) in H_2O (1 mL) and THF (1 mL) was added lithium hydroxide (86 mg, 3.585 mmol). The reaction mixture was stirred at room temperature for 1 h, and was then acidified using 1M HCl solution. Solvent was then evaporated in vacuon to afford 2-(4-(2-methyl-1H-imidazol-1-yl)phenylamino)propanoic acid (360 mg, off-white solid) and it was used further without purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 7.58 (s, 1H), 7.25 (d, *J*=9.2 Hz, 2H), 6.69 (d, *J*=8.8 Hz, 2H), 6.47 (br s, 1H), 4.06-4.02 (m, 1H), 2.43 (s, 3H), 1.40 (d, *J*=6.8 Hz, 3H); MS (ESI) *m/z* 246 [$C_{13}H_{15}N_3O_2$ + H]$^+$.

[000258] Intermediate 2: 6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid



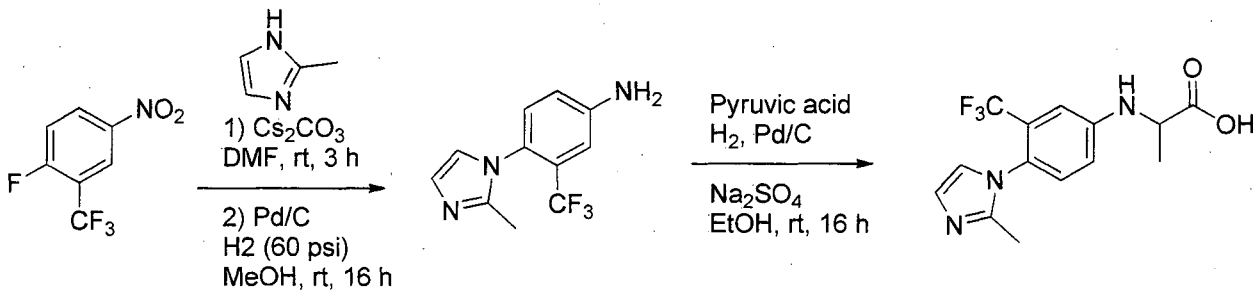
1 2 3 4

The suspension of 1-methyl-1H-pyrazole-5-boronic acid pinacol ester **1**(277 mg, 1.33 mmol), methyl 6-bromo-1,2,3,4-tetrahydro-2-quinolinecarboxylate **2** (300 mg, 1.11 mmol), $Pd(PPh_3)_4$ (128 mg, 0.111 mmol), Cs_2CO_3 (1.09 g, 3.33 mmol) in dioxane: water (4:1, 5.5 ml) was irradiated in the microwave reactor at 110°C for 40 min. The mixture was concentrated under

reduced pressure, diluted with water (20 mL) and extracted with EtOAc/CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure.This residue was dissolved in CH_2Cl_2, passed through a pad of celite and the filtrate was collected and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent cyclohexane/EtOAc 30:70 to afford methyl 6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylate **3** (46 mg, 15%) as a white solid; MS (ESI) *m/z* 272 $[C_{15}H_{17}N_3O_2 + H]^+$.

[000259] Methyl 6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylate **3** (46 mg, 0.170 mmol) and LiOH (8 mg, 0.339 mmol) in water (0.90 mL) and CH_3OH (0.90 mL) was stirred for 1 h at room temperature. CH_3OH was removed from the reaction and the aqueous layer was acidified with conc HCl until pH~1. The mixture was concentrated under reduced pressure to afford 6-(1-methyl-1H-pyrazol-5-yl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid **4**; MS (ESI) *m/z* 258 $[C_{14}H_{15}N_3O_2 + H]^+$.

[000260] Intermediate 3: -(4-(2-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenylamino)propanoic acid

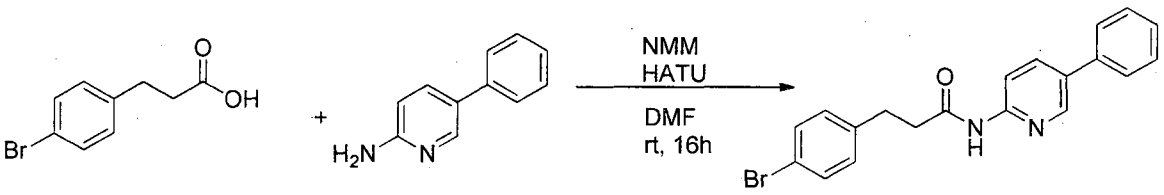


To a well stirred solution of the 1-fluoro-4-nitro-2-(trifluoromethyl)benzene (2 g, 1.0 eq) in DMF (50 mL) was added Cs_2CO_3 (2.64 g, 2 eq), 2-methyl imidazole (1.1 g, 1.4eq) and stirred at rt for 3 h. The reaction mixture was poured into ice-water and the compound was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with ice-water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-methyl-1-(4-nitro-2-(trifluoromethyl)phenyl)-1H-imidazole (1.5 g, 58%, LC-MS 93%) as a pale brown viscous liquid.

[000261] To a stirred solution of 2-methyl-1-(4-nitro-2-(trifluoromethyl)phenyl)-1H-imidazole (1.5 g, 1 eq) in MeOH (30 mL) was added 10% Pd/C (300 mg) and hydrogenated under H_2 (60 psi). The reaction mixture was stirred at rt for 12 h. The reaction mixture was filtered through celite pad and washed with MeOH. Filtrate was concentrated under reduced pressure to afford 4-(2-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)aniline (1.2 g, 90%, LC-MS 96%) as a pale brown solid.

[000262] To a stirred solution of 4-(2-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)aniline (500 mg, 1 eq) in EtOH-cyclohexane (1:1, 10 mL) was added pyruvic acid (0.6 mL, 4 eq), Pd/C (100 mg), Na_2SO_4 (350 mg, 1.2 eq). The reaction mixture was hydrogenated under H_2 (balloon pressure) at rt for 16 h. The reaction mixture was filtered through celite bed and washed with EtOH and the filtrate was concentrated. The crude compound was purified by preparative HPLC to afford 2-(4-(2-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenylamino)propanoic acid (150 mg, 23%, LC-MS 99%) as a white solid.

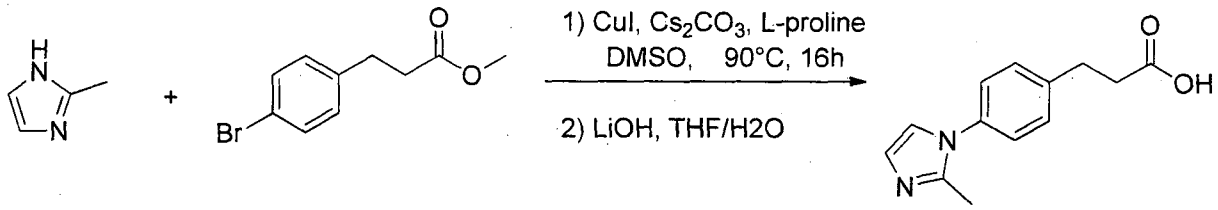
[000263] Intermediate 4: 3-(4-(1-methyl-1H-pyrazol-5-yl)phenyl)-N-(5-phenylpyridin-2-yl)propanamide



To a solution of 3-(4-bromophenyl)propanoic acid (200 mg, 0.873 mmol) in DMF (2 mL) was added HATU (498 mg, 1.310 mmol) and *N*-methyl morpholine (384 µl, 3.492 mmol). The reaction mixture was stirred at room temperature under inert atmosphere for 30 min, followed by the addition of 5-phenylpyridin-2-amine (163 mg, 0.960 mmol). The reaction mixture was left to stir for 16 h, then it was diluted with H_2O (20 mL) and extracted with EtOAc (3x20 mL). The combined organic layer was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was washed with methanol and dried in vacuum oven at 50°C overnight to afford a white solid (158 mg, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.62 (d,

J=2.0 Hz, 1H), 8.17-8.15 (m, 1H), 8.09-8.06 (m, 1H), 7.71-7.68 (m, 2H), 7.49-7.46 (m, 4H), 7.40-7.36 (m, 1H), 7.24-7.22 (m, 2H), 2.89 (t, *J*=7.6 Hz, 2H), 2.72 (t, *J*=7.6 Hz, 2H).

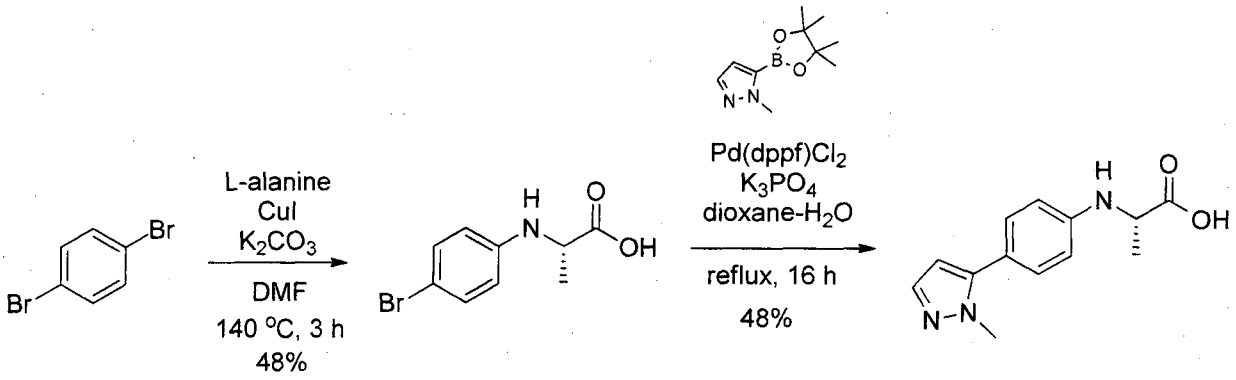
[000264] Intermediate 5: 3-(4-(2-methyl-1H-imidazol-1-yl)phenyl)propanoic acid



2-Methyl-1H-imidazole (608 mg, 7.404 mmol), methyl 3-(4-bromophenyl)propanoate (900 mg, 3.702 mmol), CuI (70 mg, 0.370 mmol), L-proline (852 mg, 7.404 mmol), and Cs_2CO_3 (2.42 g, 7.404 mmol) was dissolved in DMSO (10 mL). The reaction mixture was heated at 90°C for 16 h, then it was diluted with water (100 mL) and extracted with EtOAc (30 mL x 3). The combined organic extracts were concentratrated and the residue purified by column chromatography (silica gel, eluent Hexane/EtOAc 30:70) to afford methyl 3-(4-(2-methyl-1H-imidazol-1-yl)phenyl)propanoate as yellow oil (309 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.29 (m, 2H), 7.21-7.19 (m, 2H), 7.01 (d, *J*=1.6 Hz, 1H), 6.97 (d, *J*=1.6 Hz, 1H), 3.69 (s, 3H), 3.02 (t, *J*=7.6 Hz, 2H), 2.68 (t, *J*=7.6 Hz, 2H), 2.34 (s, 3H).

[000265] Methyl 3-(4-(2-methyl-1H-imidazol-1-yl)phenyl)propanoate (308 mg, 1.261 mmol) was added to a solution of LiOH (61 mg, 2.522 mmol) in THF (1 mL) and H_2O (1 mL) and stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure and the residue was acidifed to pH 1 using 1M HCl. It was then concentrated and the residue dried at 50°C under vacuum to afford 3-(4-(2-methyl-1H-imidazol-1-yl)phenyl)propanoic acid. The crude product (400 mg) was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 7.63 (d, *J*=1.6 Hz, 1H) 7.46-7.44 (m, 5H), 2.91 (t, *J*=7.6 Hz, 2H), 2.60 (t, *J*=7.6 Hz, 2H), 2.43 (s, 3H) ; MS (ESI) *m/z* 231 $[C_{13}H_{14}N_2O_2 + H]^+$.

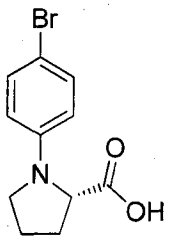
[000266] Intermediate 5: (S)-N-(3,3'-bipyridin-6-yl)-2-(4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanamide



To a stirred solution of 1,4-dibromobenzene (10 g, 1 eq) in anhydrous DMF (10 mL) was added L-alanine (3.8 g, 1 eq), K_2CO_3 (8.85 g, 1.5 eq) and CuI (406 mg, 0.05 eq) under argon. The reaction mixture was stirred at 140 °C for 3 h. After completion, ice water and ethyl acetate were added to the reaction mixture and filtered through celite pad and washed with water. The separated aqueous layer was acidified using 1N HCl and extracted with ethyl acetate. The combined organic layer was washed with ice water, brine, dried and concentrated to afford (S)-2-(4-bromophenylamino) propanoic acid (5 g, 48%, LC-MS 56%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 12.52 (bs, 1H), 7.20 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 8.8 Hz, 2H), 3.91 (q, J = 6.4 Hz, 1H), 1.36 (d, J = 7.2 Hz, 3H); MS (ESI) m/z 244 [C9H10BrNO2+H]+.

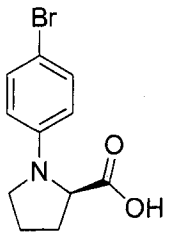
[000267] To a well stirred solution of (S)-2-(4-bromophenylamino) propanoic acid (2.6 g, 10.69 mmol) in dioxane-water (4:1, 100 mL) were added K_3PO_4 (8.3 g, 32.07 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.3 g, 16.04 mmol) and $Pd(dppf)Cl_2$ (436 mg, 5 mol%) under Ar and the reaction mixture was heated at 100 °C for 16 h. The reaction mixture was evaporated under reduced pressure and the residue was poured into ice-water and the compound was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with ice water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a solid which was purified by column chromatography (silica gel, eluent EtOAc/hexane 40:60) to afford (S)-2-(4-(1-methyl-1H-pyrazol-5-yl) phenylamino) propanoic acid (1.7 g, 48%, LC-MS 91%) as a yellow solid.

[000268] ((S)-1-(4-Bromophenyl)pyrrolidine-2-carboxylic acid



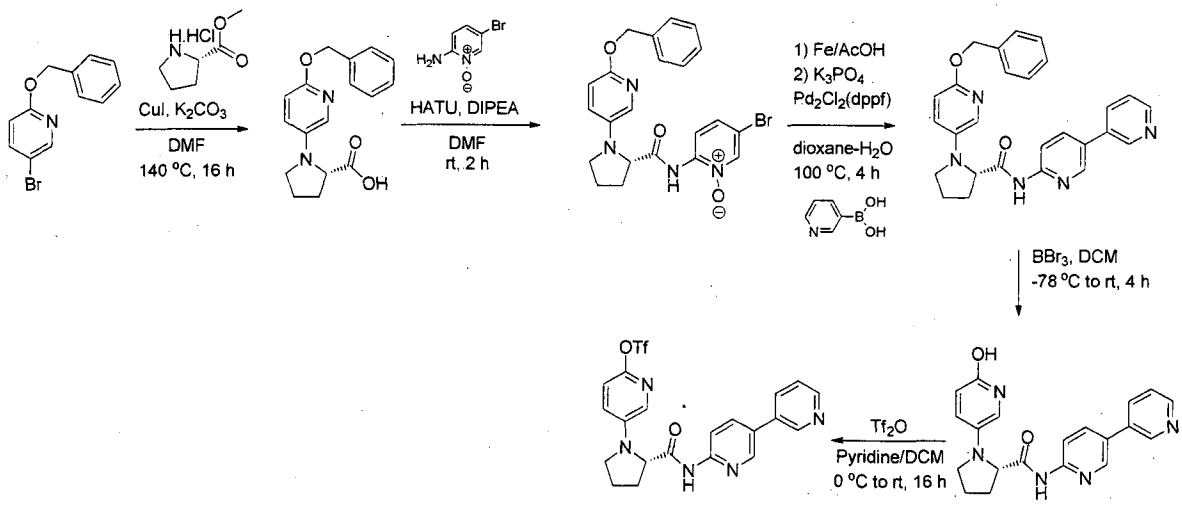
37% , LC-MS 85%. 1H NMR (400 MHz, DMSO-*d6*) δ (ppm): 12.65 (b, 1H), 7.29 (d, J = 9.2 Hz, 2H), 6.42 (d, J = 8.8 Hz, 2H), 4.15-4.13 (m, 1H), 3.40-3.35 (m, 1H), 3.29-3.23 (m, 1H), 2.31-2.21 (m, 1H), 2.07-1.94 (m, 3H); MS (ESI) m/z 271.9 [C11H12BrNO2+H]+.

[000269] (R)-1-(4-Bromophenyl) pyrrolidine-2-carboxylic acid



70% , LC-MS 77%. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 12.65 (bs, 1H), 7.29 (d, J = 8.8, 2H), 6.47 (d, J = 9.2 Hz, 2H), 4.15 (dd, J = 2, 8.4 Hz, 1H), 3.40-3.30 (m, 1H), 3.29-3.18 (m, 1H), 2.50-2.18 (m, 1H), 2.10-1.94 (m, 4H); MS (ESI) m/z 271.9 [C11H12BrNO2+H]+.

[000270] Intermediate 6:



To a solution of 2-(benzyloxy)-5-bromopyridine (2.0 g, 7.60 mmol) in 25 mL of DMF was added CuI (290 mg, 1.52 mmol), K_2CO_3 (2.1 g, 15.21 mmol) and L-prolinemethyl ester hydrochloride (1.5 g, 9.12 mmol) at rt under argon. The reaction mixture was heated at 140 °C for 16 h. TLC indicated presence of some SM and formation of a polar spot. The reaction mixture was cooled to rt, poured in to ice cold water (500 mL) and extracted with EtOAc (2 × 100 mL) to remove staring material. The aqueous layer was acidified with sat. $KHSO_4$ solution and then extracted with EtOAc (2 × 250 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 1.7 g of (S)-1-(6-(benzyloxy)pyridin-3-yl)pyrrolidine-2-carboxylic acid (45%, LC-MS 84%).

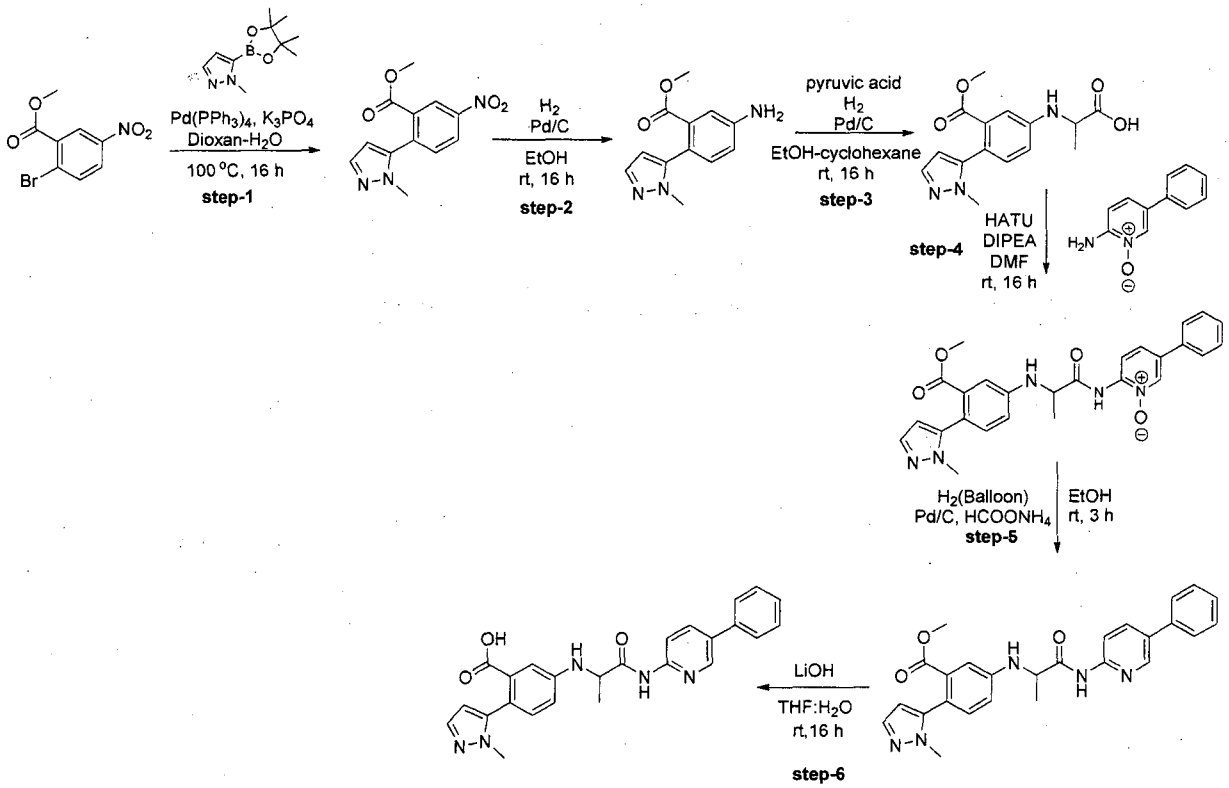
[000271] To a solution of (S)-1-(6-(benzyloxy)pyridin-3-yl)pyrrolidine-2-carboxylic acid (3.0 g, 3.36 mmol) in DMF (50 mL) was added DIPEA (5.4 mL, 30.20 mmol), HATU (7.65 g, 20.13 mmol) and 2,3'-bipyridin-5-amine (1.89 g, 11.07 mmol) and the reaction mixture was stirred at rt for 16 h. TLC indicated complete consumption of SM and formation of a new less polar spot. The reaction mixture was poured into ice water (150 mL) and stirred for 30 min. The precipitated solids were filtered and washed with water and dried to give crude product. The crude product was purified by column chromatography (silica gel, eluent MeOH: $CHCl_3$ 2:98) to afford (S)-N-(2,3'-bipyridin-5-yl)-1-(6-(benzyloxy)pyridin-3-yl)pyrrolidine-2-carboxamide (1.6 g, 35%, LC-MS 95%) as an off-white solid.

[000272] To a solution of ((S)-N-(2,3'-bipyridin-5-yl)-1-(6-(benzyloxy)pyridin-3-yl)pyrrolidine-2-carboxamide (600 mg, 3.55 mmol) in CH_2Cl_2 (25 mL) cooled to -78 °C, was added BBr_3 (11 mL, 1M in DCM, 7.09 mmol). The reaction mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was concentrated under reduced pressure. The crude product was washed with diethyl ether and dried to afforded 2.5 g of (S)-N-(2,3'-bipyridin-5-yl)-1-(6-hydroxypyridin-3-yl)pyrrolidine-2-carboxamide HBr salt.

[000273] To a solution of (S)-N-(2,3'-bipyridin-5-yl)-1-(6-hydroxypyridin-3-yl)pyrrolidine-2-carboxamide HBr salt from above (2.5 g, 6.92 mmol) in 10 mL of pyridine and 25 mL of DCM was cooled to 0 °C, then added triflicanhydride (2.35 mL, 13.85 mmol) at 0 °C to rt for 16 h. TLC indicated absence of SM and formation of a less polar spot. The reaction mixture was poured in to sat. $NaHCO_3$ solution (100 mL) and extracted with EtOAc (2 × 100 mL). The

combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (silica gel, eluent MeOH: $CHCl_3$ 2:98) to afford 1.4 g of (S)-5-(2-(2,3'-bipyridin-5-ylcarbamoyl)pyrrolidin-1-yl)pyridin-2-yl trifluoromethanesulfonate. The material was used in the next step without further purification.

[000274] Intermediate 7: 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoic acid



Step-1: methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzoate

[000275] To a stirred solution of methyl 2-bromo-5-nitrobenzoate (10 g, 38.46 mmol) was treated 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.2 g, 46.15 mmol) using K_3PO_4 (16.3 g, 76.92 mmol), $Pd(PPh_3)_4$ (2.2 g, 1.92 mmol) in 300 mL of 1,4 dioxane and water (9:1) at rt to 100 °C. TLC after 16 h indicated absence of starting material and a new polar spot was seen. After completion, the reaction mass was filtered and concentrated

under reduced pressure. The crude residue was purified by column chromatography (silica gel, eluent EtOAc and petroleum ether 30:70%) to methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzoate (5 g, 50%, LC-MS 99%).

Step-2: methyl 5-amino-2-(1-methyl-1H-pyrazol-5-yl)benzoate

[000276] To a stirred solution of methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-nitrobenzoate (5 g, 1 eq) was reduced with H_2 (60 psi) using Pd/C (1 g, 1.2 eq) in 250 mL of ethanol at rt. TLC after 16 h indicated absence of starting material and a new polar spot was seen. After completion, the reaction mass was filtered and washed with ethanol 30 (mL) and concentrated under reduced pressure. The crude residue was purified by column chromatography (neutral alumina, eluent EtOAc and petroleum ether 30:70%) to afford methyl 5-amino-2-(1-methyl-1H-pyrazol-5-yl)benzoate (2.8 g, 63.6%, LC-MS 91%).

Step-3: 2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanoic acid

[000277] To a stirred solution of methyl 5-amino-2-(1-methyl-1H-pyrazol-5-yl)benzoate (2.5 g, 1 eq) in EtOH (100 mL) was added pyruvic acid (0.87 mL, 1.2 eq), Pd/C (500 mg), Na_2SO_4 (2.3 g, 1.5 eq). The reaction mixture was hydrogenated under H_2 (balloon) at rt for 6 h. After completion, the reaction mass was filtered through celite bed and washed with EtOH and the filtrate was concentrated to afford 2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanoic acid (3 g, 93.7%, LC-MS 74%).

Step-4: 2-(2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanamido)-5-phenylpyridine 1-oxide

[000278] To a stirred solution of 2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanoic acid (3.0 g, 1 eq) in 30 mL of DMF was added 2-amino-5-phenylpyridine 1-oxide (2.2 g, 1.2 eq), HATU (5.6 g, 1.5 eq) and DIPEA (2.8 g, 3 eq) and the reaction mixture was stirred at rt. TLC after 16 h indicated absence of starting material and a new non polar spot was seen. After completion, the reaction mass was poured into water (1 x 100 mL) and extracted with EtOAc (1 x 50 mL). The combined organic layers were washed with

brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, eluent MeOH/DCM 3:97) to afford 2-(2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanamido)-5-phenylpyridine 1-oxide (2.4 g, 52.1%, LC-MS 87%).

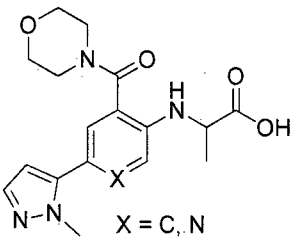
Step-5: methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoate

[000279] A solution of 2-(2-(3-(methoxycarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)phenylamino)propanamido)-5-phenylpyridine 1-oxide (1.9 g, 1 eq) in 50 mL of ethanol was stirred with Pd/C (1.9 g) and $HCOONH_4$ (5.7 g) at 100 °C under H_2 (balloon) at rt. TLC after 1 h indicated absence of starting material and a new non polar spot was seen. After completion, the reaction mass was filtered on celite bed and washed with ethanol and filtrate was concentrated. The crude residue was purified by column chromatography (neutral alumina, eluent EtOAc and petroleum ether 20:80) to afford methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoate (1 g, 55.5%, LC-MS 98.8%). ^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 9.07 (s, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.95-7.93 (dd, J = 2.4 Hz, J = 2.0 Hz, 1H), 7.55-7.44 (m, 5H), 7.40-7.73 (m, 1H), 7.31-7.37 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.83-6.82 (dd, J = 2.8 Hz, J = 2.8 Hz, 1H), 4.33 (d, J = 3.2 Hz, 1H), 4.04 (m, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 1.68 (d, J = 6.8 Hz, 3H); MS (ESI) *m/z* 456 [M+1].

Step-6: 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoic acid

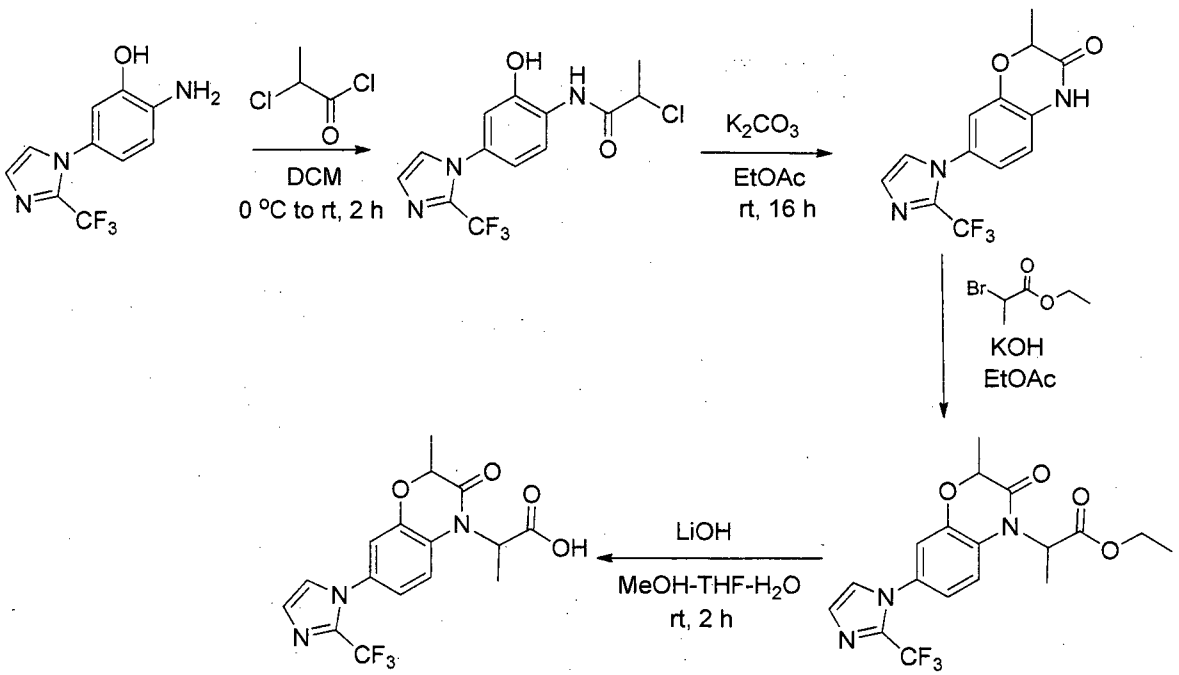
[000280] To a stirred solution of methyl 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoate (200 mg, 1 eq) in 6 mL of THF-H_2O, was added LiOH (75 mg, 4 eq) and the reaction mixture was stirred at rt. TLC after 16 h indicated absence of starting material and a new polar spot was seen. After completion, the reaction mass was concentrated and adjusted to pH 2 with 1N HCl and extracted with EtOAc (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford to 70 mg of material which was further purified by preparative HPLC to afford 2-(1-methyl-1H-pyrazol-5-yl)-5-(1-oxo-1-(5-phenylpyridin-2-ylamino)propan-2-ylamino)benzoic acid (30 mg,

36.8%, LC-MS 99.0%). ^{1}H NMR (400 MHz, DMSO- d_6) δ (ppm): 12.67 (s, 1H), 10.73 (s, 1H), 8.65 (d, J = 2.4 Hz, 1H), 8.32 (s, 1H), 8.16-8.09 (m, 2H) 7.70 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.40-7.32 (m, 2H), 7.18 (d, J = 1.6 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.82 (dd, J = 2.4 Hz, , J = 2.4 Hz , 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.04 (d, J = 1.6 Hz, 1H), 4.35 (t, J = 7.2 Hz, 1H), 3.50 (s, 3H), 1.45 (d, J = 7.2 Hz, 3H); MS (ESI) *m/z* 442 [M+1].

[000281] 

were synthesized by using the above method.

[000282] Intermediate 7: 2-(2-methyl-3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)propanoic acid



To a solution of 2-amino-5-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenol (600 mg, 4.12 mmol) in 50 mL of DCM was added 2-chloropropanoyl chloride (0.36 mL, 3.07 mmol) at 0 °C to rt for 2 h. TLC indicated presence of some SM and formation of a new less polar spot. The reaction mixture was poured into 250 mL of petroleum ether and stirred for 30 min. The precipitated

solids were filtered and dried to afford to afford 2-chloro-N-(2-hydroxy-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)propanamide (620 mg, 92%, LC-MS 77%).

[000283] To a solution of 2-chloro-N-(2-hydroxy-4-(2-(trifluoromethyl)-1H-imidazol-1-yl)phenyl)propanamide (620 mg, 1.86 mmol) in 50 mL of EtOAc was added K_2CO_3 (771 mg, 5.58 mmol) and stirred at rt for 16 h. TLC indicated absence of SM and a new polar spot. The reaction mixture was poured into water (250 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-methyl-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (1.0 g, 94%, LC-MS 87%)..

[000284] To a solution of 2-methyl-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (500 mg, 1.68 mmol) in acetone (25 mL) were added KOH (141 mg, 2.52 mmol) and ethyl 2-bromopropanoate (305 mg, 1.68 mmol) at rt. The reaction mixture was heated at reflux for 4 h. TLC indicated absence of SM and formation of a less polar spot. The reaction mixture was cooled to rt, poured into water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give crude product. The crude compound was purified by column chromatography (silica gel, eluent EtOAc/hexane 20:80) to afford ethyl 2-(2-methyl-3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)propanoate (500 mg, 75%, LC-MS 92%).

[000285] To a stirred solution of ethyl 2-(2-methyl-3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)propanoate **6** (500 mg, 1.0 eq) in 30 mL of MeOH-THF-H_2O was added LiOH (106 mg, 2.0 eq) at rt and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated, the aqueous layer was extracted with ethyl acetate to remove impurities. The aqueous layer was acidified with sat. $KHSO_4$ and extracted with EtOAc (2 x 100 mL). The combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford 2-(2-methyl-3-oxo-7-(2-(trifluoromethyl)-1H-imidazol-1-yl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)propanoic acid (300 mg, 65%, LC-MS.

Application example 1

Materials and Methods:

Cell lines and culture conditions:

[000286] HEK293-STF cell line was modified from Human embryonic kidney cell line HEK293 transfected with the STF reporter. HEK293-STF3A cell line was further modified from HEK293-STF cell line to express Wnt3A. This cell line was used to identify compounds that regulate either early or late signaling components of the Wnt pathway. L-Wnt3A (ATCC, #CRL-2647) cell line was used for providing Wnt3A conditioned media. The three cell lines were grown in DMEM with 10% FBS incubated in 37°C with 5% CO2.

Cell viability assay:

[000287] 5000 cells in 75 µl culture media were seeded in each well of black 96 well plates (Greiner #655090) and incubated overnight at 37°C. 25 µl of serially diluted compound was added to the cells giving final concentration of 50 µM to 1.5 nM. After 1 day of treatment, 100 µl of CellTiter-Glo® Luminescent Cell Viability Assay reagent (#G7571, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® microplate reader.

STF3A assay:

[000288] $2x10^4$ HEK293-STF3A cells in 75 µl culture media were seeded in each well of white 96 well plates (Greiner #655098) and incubated overnight at 37°C. 25 µl serially diluted compound was added to the cells to give final concentration of 50 µM to 1.5 nM. After 1 day of treatment, 100 µl of Steady-Glo® Luciferase Assay reagent (#E2520, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® plate reader.

STF/WNT3A conditioned medium (STF/WNT3A CM) assay:

[000289] L-Wnt3A cells were cultured in three T-175 flasks at 3×104 cells/ml in 30 ml culture medium per flask. After 4 days of incubation, the Wnt3A conditioned media were harvested and then centrifuged at 2000 rpm for 10 minutes to remove the debris. The Wnt3A conditioned media were stored at -20 °C if not used immediately.

[000290] 2x104 HEK293-STF cells in 25 µl culture media were added in each well of white 96 well plates (Greiner #655098). 25 µl serially diluted compound was added to the cells. After 4 hours of incubation, 100 µl Wnt-3A conditioned medium was added to the cells. The final concentration of compound ranged from 33 µM to 1 nM. After incubation for 1 day at 37°C, 100 µl of Steady-Glo® Luciferase Assay reagent (#E2520, Promega) was added to each well and incubated for 10 minutes at room temperature. Luminescence was measured using Tecan Safire2® microplate reader.

Results:

	STF3a IC50 uM
Example 1	< 0.1
Example 2	> 5
Example 3	> 5
Example 4	> 5
Example 5	< 1
Example 6	> 5
Example 7	< 5
Example 8	> 5
Example 9	> 5
Example10	< 5
Example 11	< 1
Example 12	> 5
Example 13	< 0.1
Example 14	< 0.1
Example 15	< 0.1
Example 16	< 0.1

	STF3a IC50 uM
Example 36	> 5
Example 37	< 5
Example 38	> 5
Example 39	< 5
Example 40	< 0.1
Example 41	< 0.1
Example 42	< 0.1
Example 43	> 5
Example 44	> 5
Example 45	< 5
Example 46	< 1
Example 47	< 1
Example 48	< 5
Example 49	< 0.1
Example 50	< 1
Example 51	< 0.1

Example 17	> 5
Example 18	< 1
Example 19	< 0.1
Example 20	< 0.1
Example 21	< 0.1
Example 22	< 0.1
Example 23	< 0.1
Example 24	< 0.1
Example 25	> 5
Example 26	> 5
Example 27	< 0.1
Example 28	< 0.1
Example 29	> 5
Example 30	< 0.1
Example 31	< 0.1
Example 32	< 0.1
Example 33	> 5
Example 34	< 0.1
Example 35	< 0.1

Example 52	> 5
Example 53	> 5
Example 54	< 1
Example 55	> 5
Example 56	> 5
Example 57	< 0.1
Example 58	< 0.1
Example 59	< 5
Example 60	< 0.1
Example 61	< 1
Example 62	< 0.1
Example 63	< 1
Example 64	< 1
Example 65	> 5
Example 66	< 1
Example 67	< 1
Example 68	> 5
Example 69	> 5
Example 70	< 1

	STF3a IC50 uM
Example 71	< 0.1
Example 72	< 0.1
Example 73	< 0.1
Example 74	< 0.1
Example 75	< 0.1
Example 76	< 0.1
Example 77	< 0.1
Example 78	< 1
Example 79	< 0.1
Example 80	< 0.1

	STF3a IC50 uM
Example 106	< 0.1
Example 107	< 0.1
Example 108	< 0.1
Example 109	< 0.1
Example 110	< 0.1
Example 111	< 0.1
Example 112	> 5
Example 113	< 0.1
Example 114	< 0.1
Example 115	> 5

Example 81	< 0.1
Example 82	< 0.1
Example 83	< 0.1
Example 84	< 0.1
Example 85	< 1
Example 86	< 5
Example 87	< 0.1
Example 88	< 0.1
Example 89	< 1
Example 90	< 1
Example 91	< 1
Example 92	< 5
Example 93	< 0.1
Example 94	< 0.1
Example 95	< 0.1
Example 96	< 0.1
Example 97	< 0.1
Example 98	< 0.1
Example 99	< 1
Example 100	< 0.1
Example 101	< 0.1
Example 102	< 0.1
Example 103	< 0.1
Example 104	< 0.1
Example 105	< 0.1

Example 116	< 0.1
Example 117	> 5
Example 118	< 0.1
Example 119	< 0.1
Example 120	< 0.1
Example 121	< 0.1
Example 122	< 0.1
Example 123	< 1
Example 124	< 0.1
Example 125	< 0.1
Example 126	< 0.1
Example 127	< 0.1
Example 128	> 5
Example 129	< 0.1
Example 130	< 0.1
Example 131	< 5
Example 132	< 0.1
Example 133	< 0.1
Example 134	<0.1
Example 135	< 0.1
Example 136	< 0.1
Example 137	< 0.1
Example 138	< 0.1
Example 139	< 0.1

In some embodiments of the invention, those compounds in the above tables listed as having IC50>5μm are explicitly excluded. In other embodiments, those compounds in the above tables listed as having IC50 >5 μm or as having IC50 >1 μm are explicitly excluded. In yet other embodiments, those compounds in the above tables listed as having IC50>5 μm or as having IC50<5 μm or as having IC50 >1 μm are explicitly excluded. In yet further embodiments, all of the compounds listed in the above tables are excluded with the exception of those listed as having IC50<0.1 μm.

Efficacy: MMTV-WNT1 Tumor Model

[000291] To test the *in vivo* efficacy of Compounds 129 and 136 to prevent the growth of Wnt driven tumors, fragments from two independent MMTV-WNT1 tumors were orthotopically transplanted into female nude mice. The mice were treated with either vehicle or Compound 129 or Compound 136 at 30 mg/kg once daily for 21 days. Tumor volumes were measured on alternate days. Treatment with Compound 129 and 136 decreased tumor growth in all the treated mice. A significant decrease in tumor weights collected at sacrifice was also observed. Results are shown in Figs. 2 and 3.

CLAIMS

1. A compound of structure I for modulating WNT activity:

$$Ar^1\text{-}Ar^2\text{-}X\text{-}C(R^1R^2)\text{-}C(=O)\text{-}N(R^3)\text{-}Ar^3\text{-}Ar^4$$

(I)

wherein:

Ar^1, Ar^2, Ar^3 and Ar^4 are, independently, optionally substituted aryl or heteroaryl groups;

R^1 and R^3 are, independently, H or optionally substituted alkyl groups;

R^2 is H or an optionally substituted alkyl group or an alkylene group which, together with the carbon atom to which it is attached and X, forms a non-aromatic ring or an alkylene group which, together with the carbon atom to which it is attached and X and two adjacent atoms of Ar^2, forms a non-aromatic ring;

X is O, CR^4R^5, CH_2O, N or NR^4, wherein if X is N, it is bonded to R^2;

R^4 is H, optionally substituted alkyl or an alkylene chain, optionally containing a heteroatom and/or a carbonyl group, which, together with the C or N to which it is attached and two adjacent atoms of Ar^2, forms a non-aromatic ring; and

R^5 is H, NH_2 or an optionally substituted alkyl group;

2. The compound of claim 1 wherein R^1 and R^3 are both H.

3. The compound of claim 1 or claim 2 wherein X is O, NH or CH_2

4. The compound of any one of claims 1 to 3 wherein R^2 is H or methyl or X is a nitrogen atom and R^2 is $(CH_2)_3$ and is attached to said nitrogen atom so as to form a 5-membered ring.

5. The compound of any one of claims 1 to 4 wherein Ar^1 is a 5-membered heterocyclic ring containing 1 or 2 ring nitrogen atoms.

6. The compound of any one of claims 1 to 5 wherein Ar^2 is a 6-membered ring.

7. The compound of claim 6 wherein Ar^1 and X are in a 1,4-relationship on Ar^2.

8. The compound of claim 6 or claim 7 wherein Ar^2 is a phenyl or pyridyl.

9. The compound of any one of claims 1 to 8 wherein Ar^3 is a 6-membered ring.

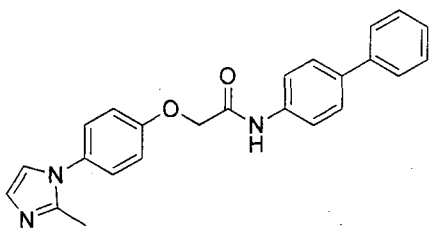
10. The compound of claim 9 wherein Ar^4 and the nitrogen atom attached to Ar^3 are in a 1,4-relationship on Ar^3.

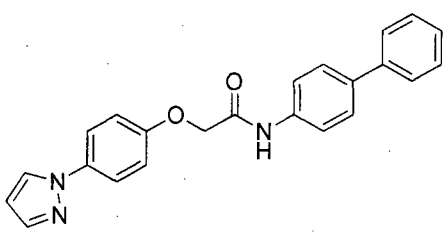
11. The compound of claim 9 or claim 10 wherein Ar^3 is a phenyl ring or contains 1 or 2 ring nitrogen atoms.

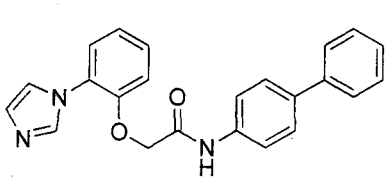
12. The compound of any one of claims 1 to 11 wherein Ar^4 is a 6-membered ring.

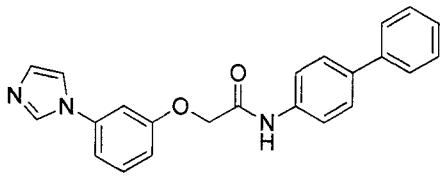
13. The compound of claim 1 wherein Ar^4 is a phenyl ring or contains 1 or 2 ring nitrogen atoms.

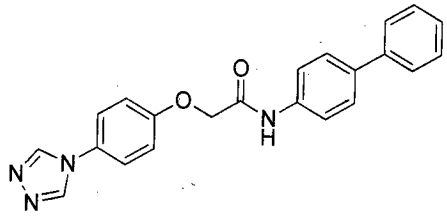
14. The compound of any one of claims 1 to 13 which is one of the following compounds:

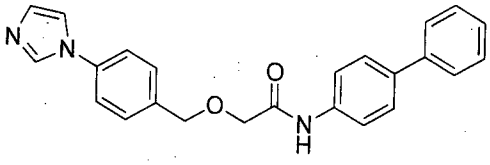


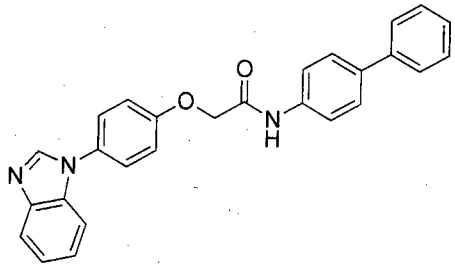


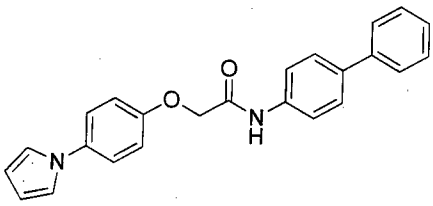


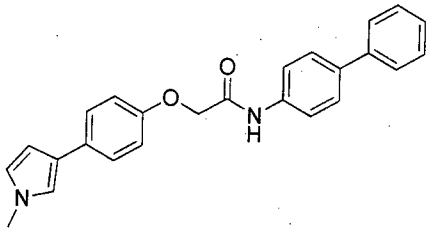


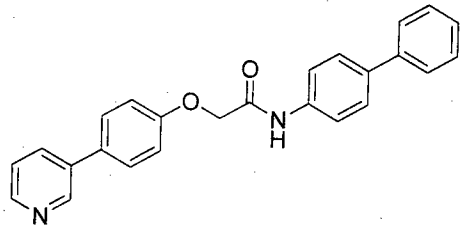


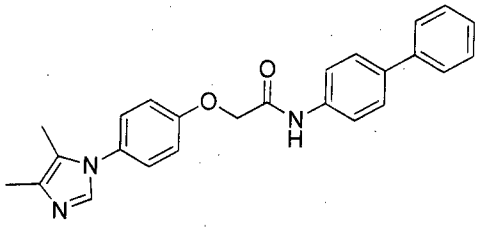


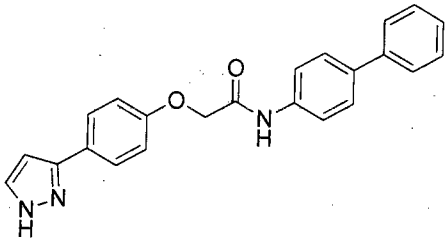


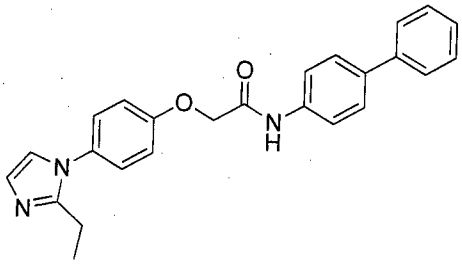


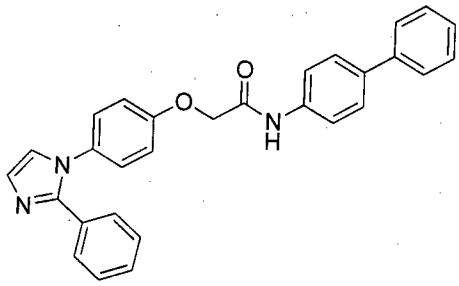


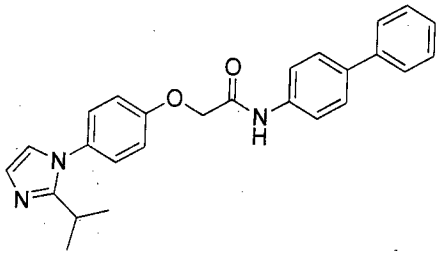


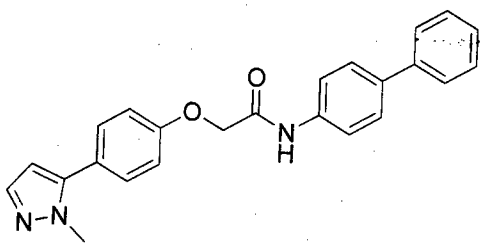


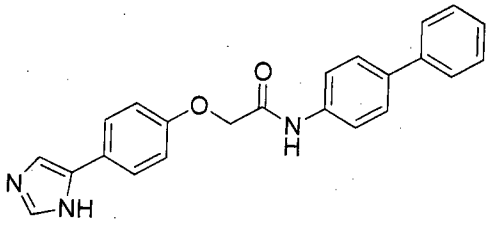


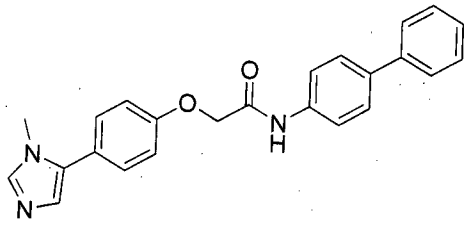


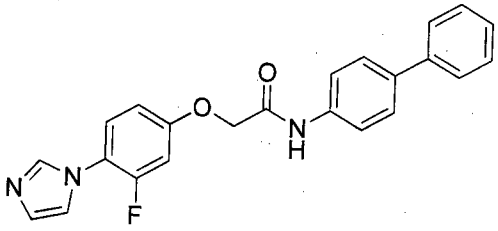


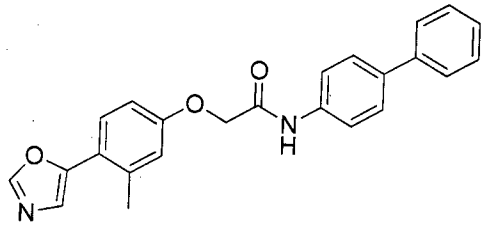


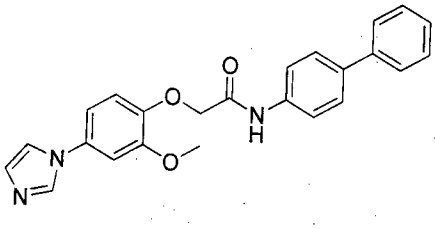


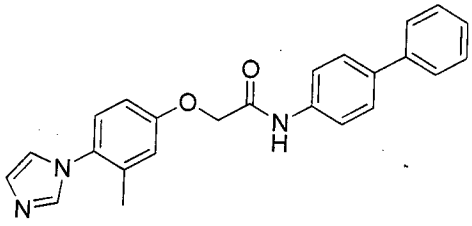


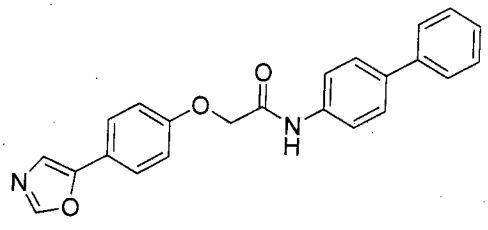


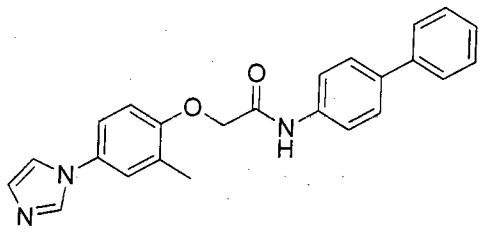


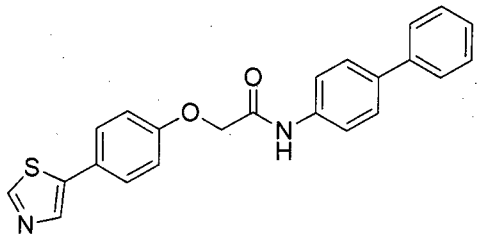


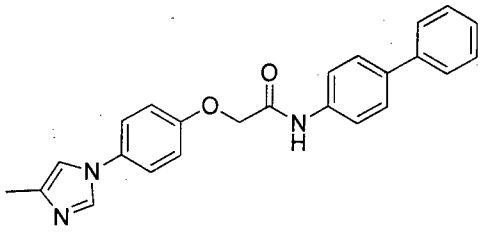


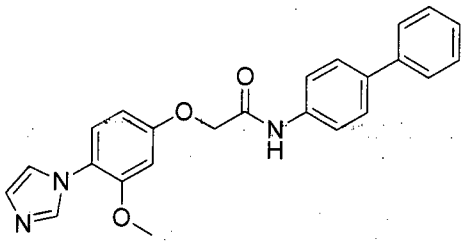


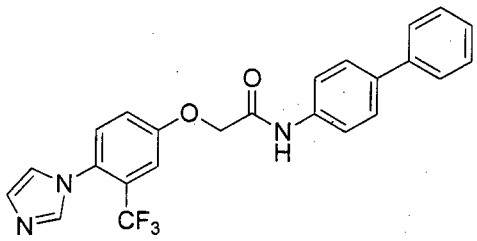


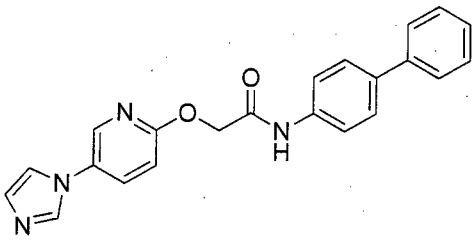


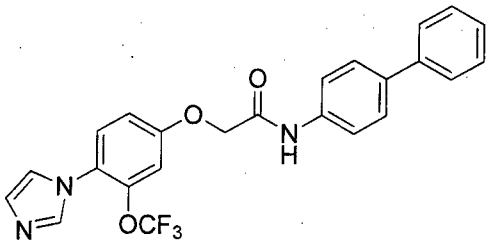


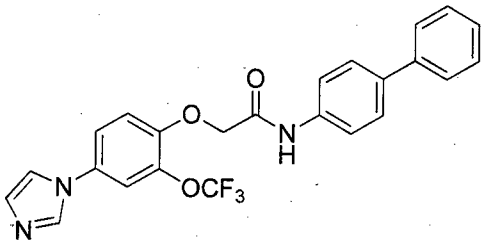


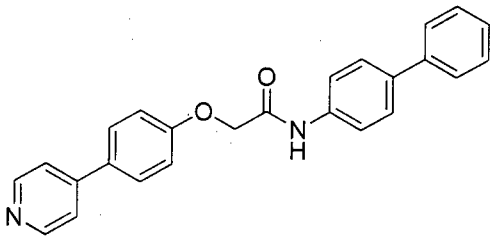


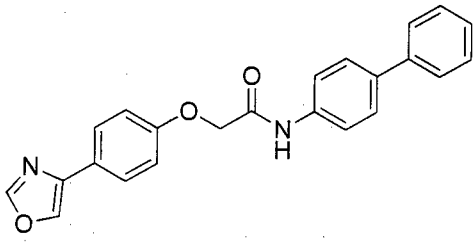


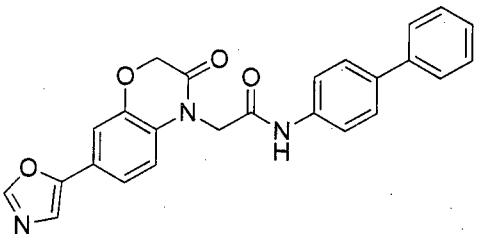


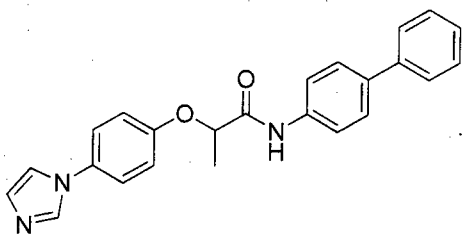


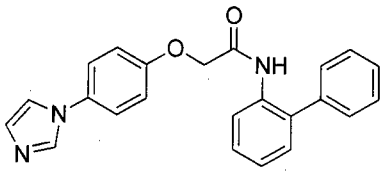


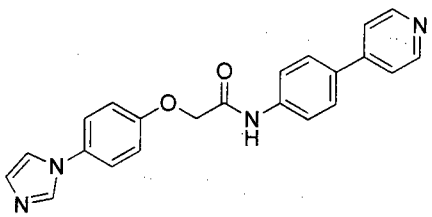


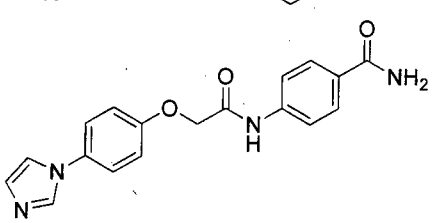


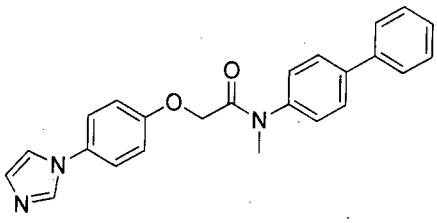


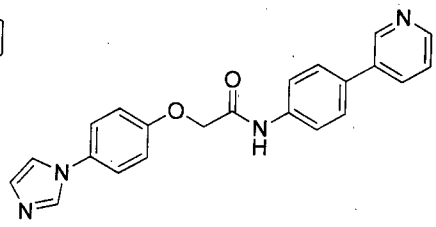


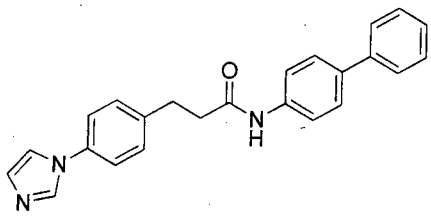


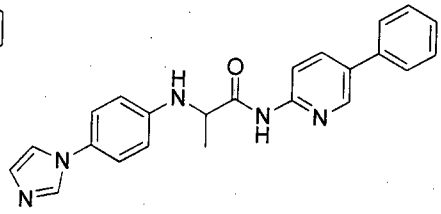


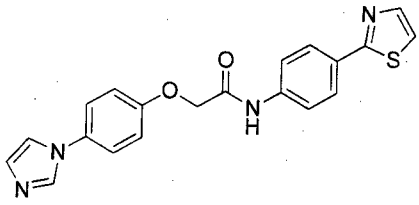


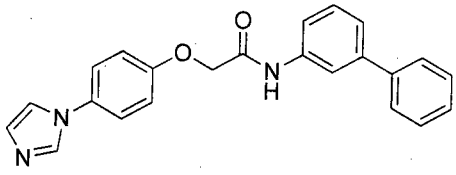


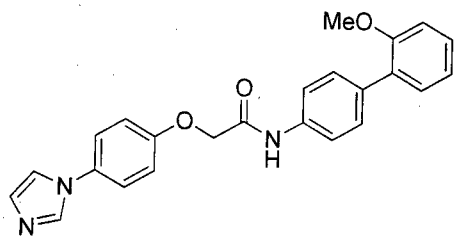


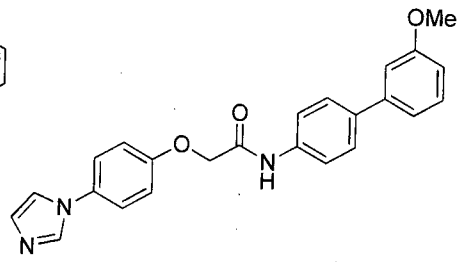


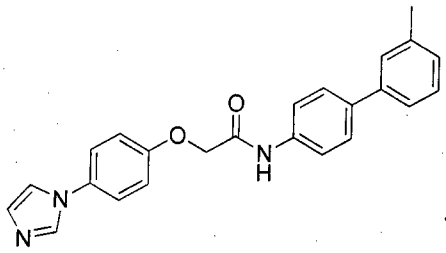


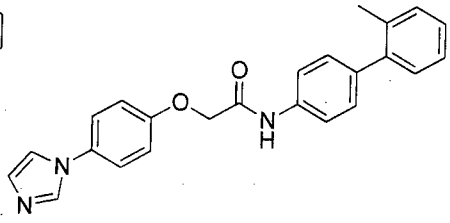


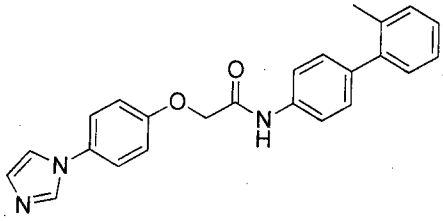


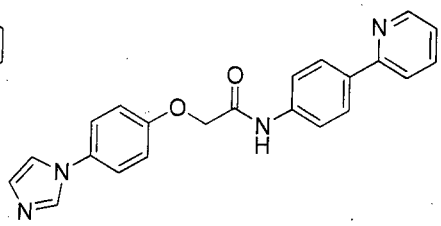


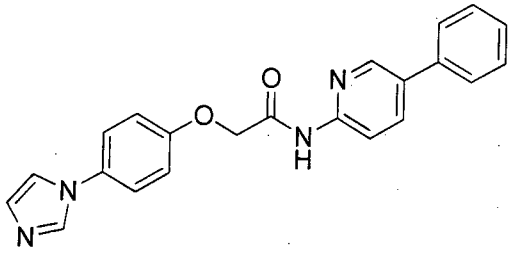


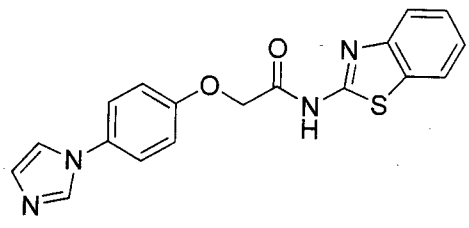


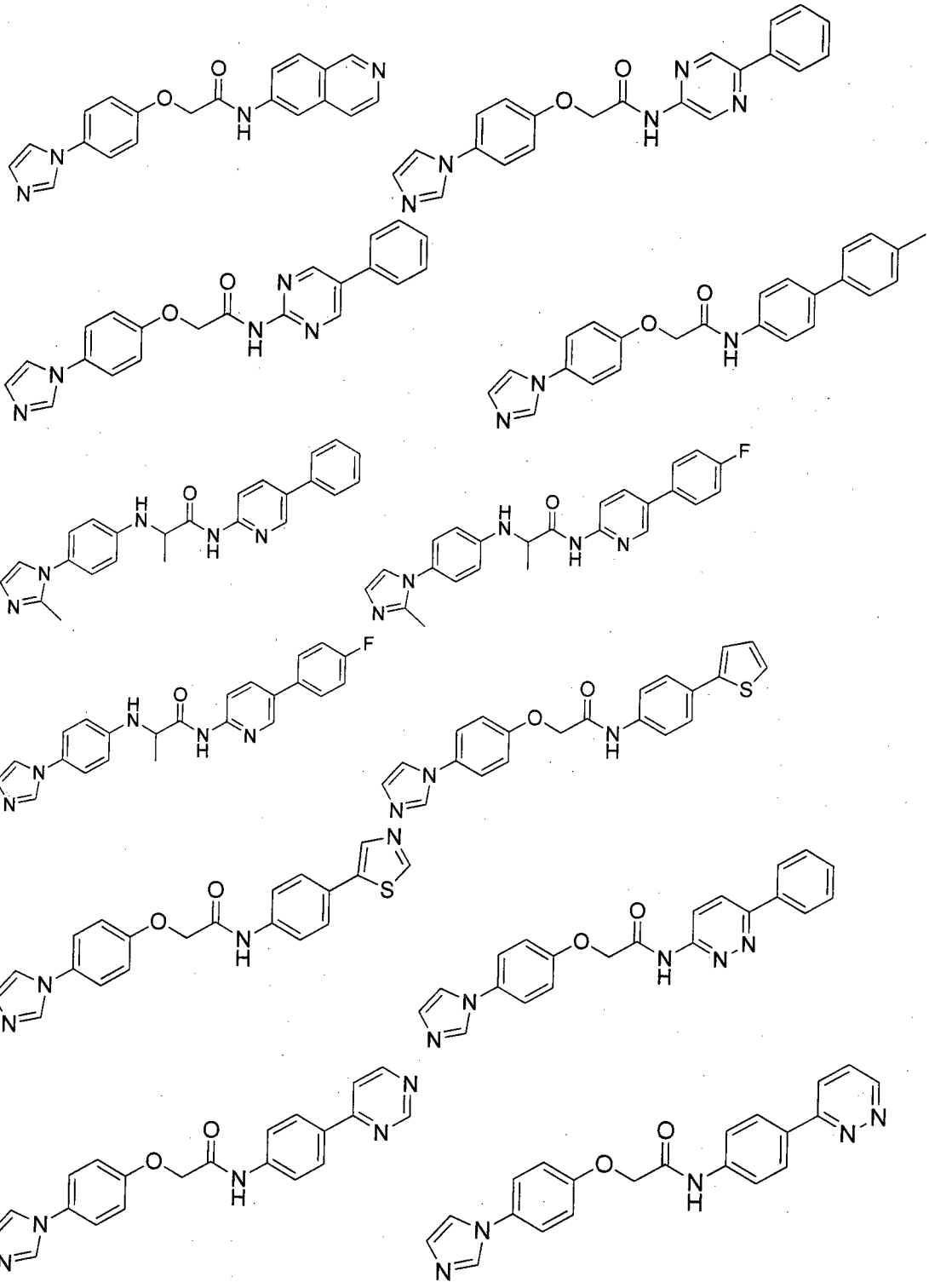


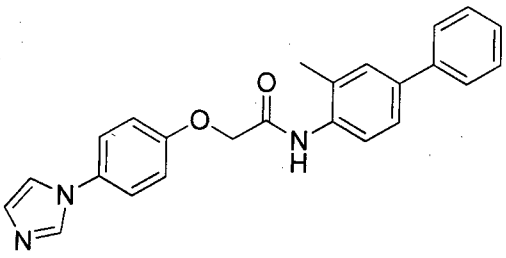


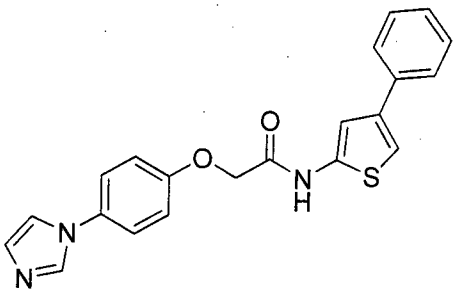


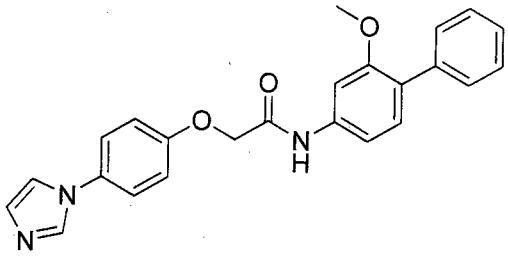


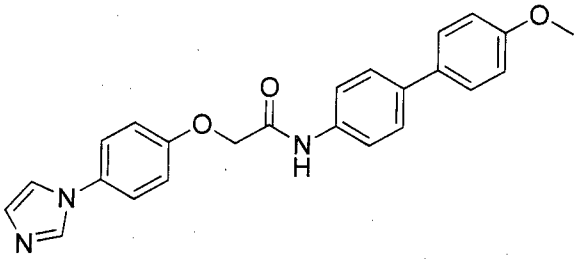


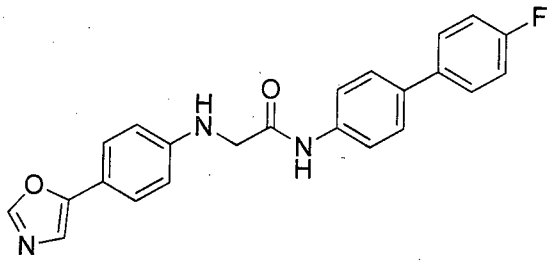


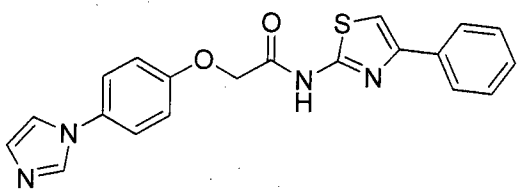


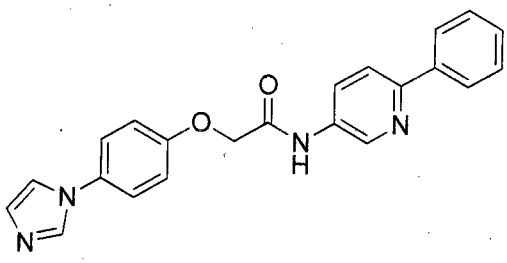


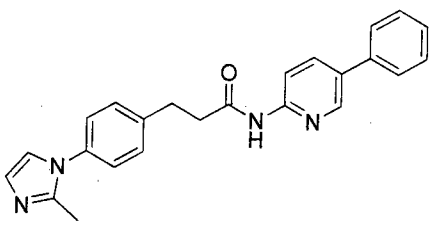


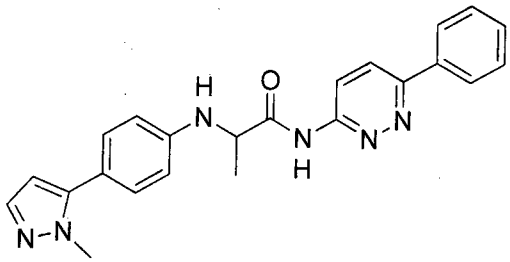


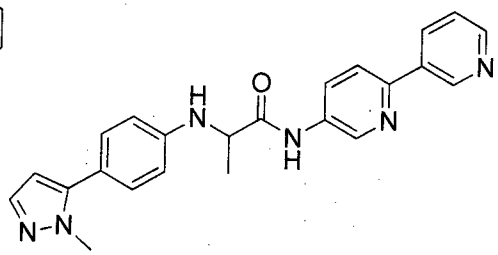


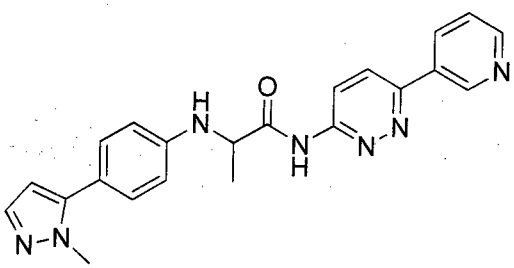


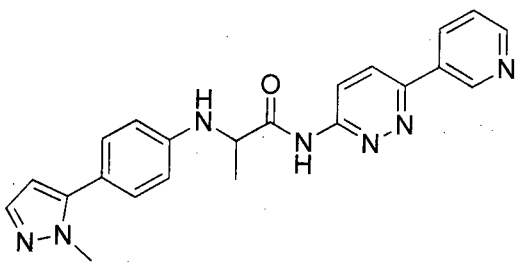


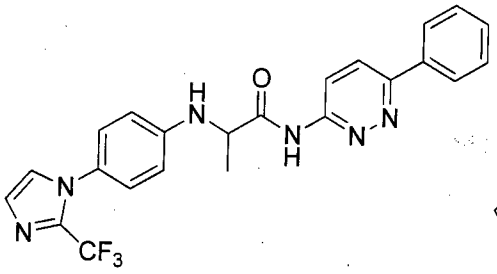


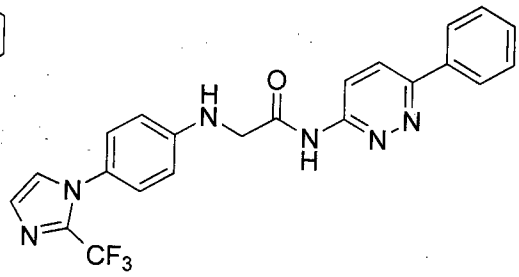


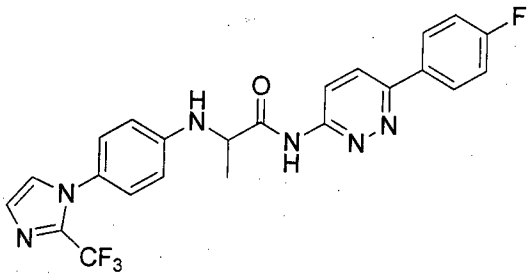


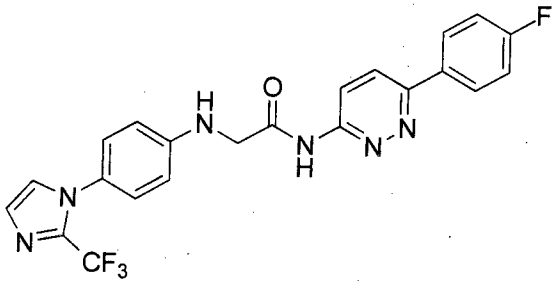


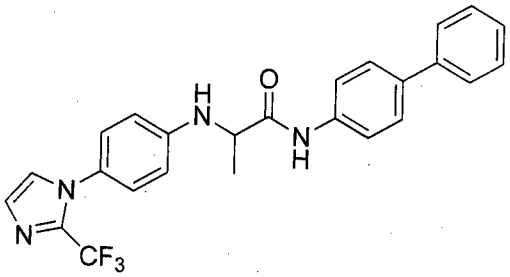


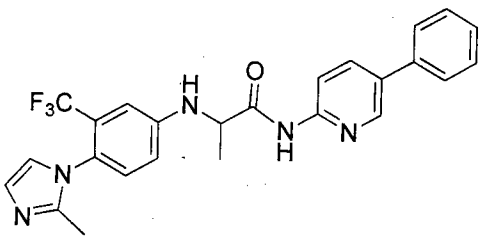


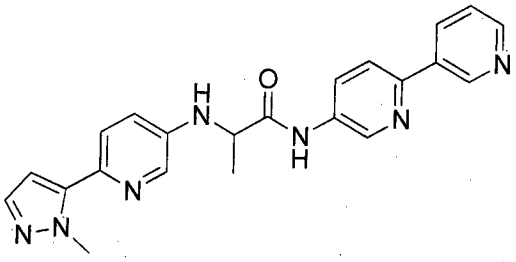


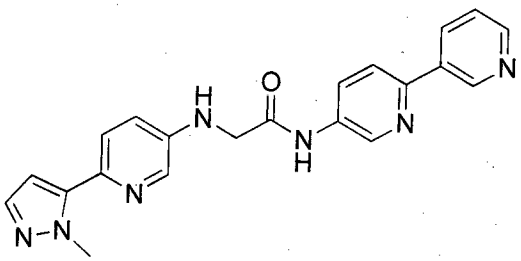


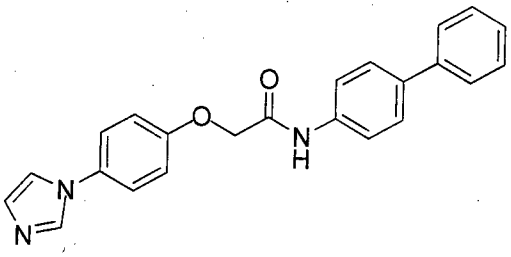


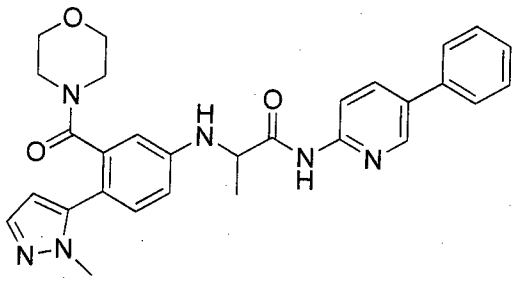


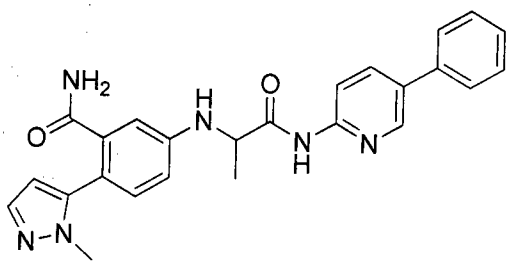


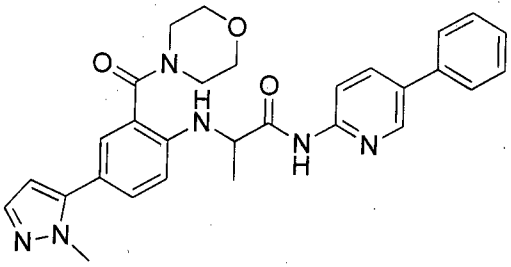


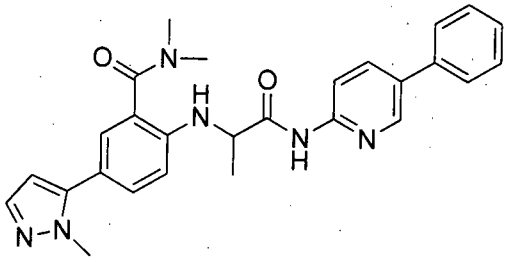


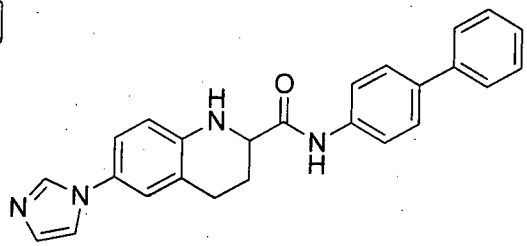


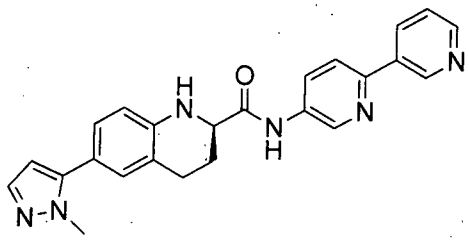


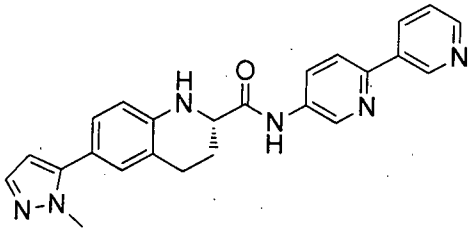


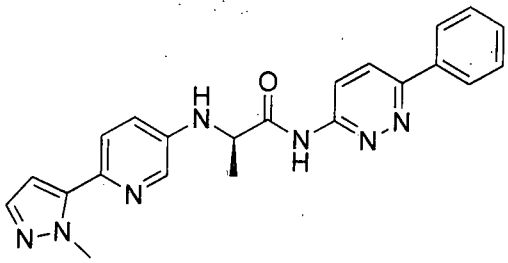


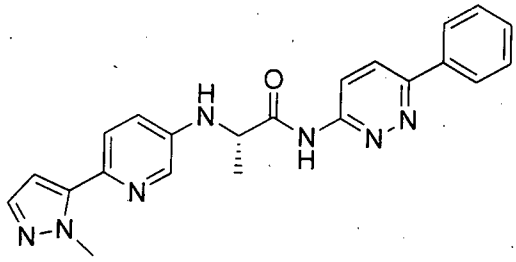


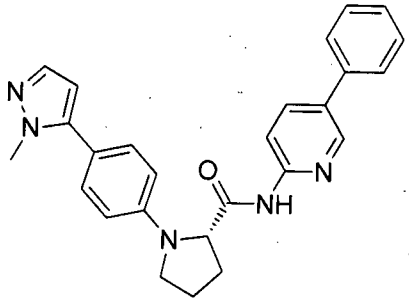


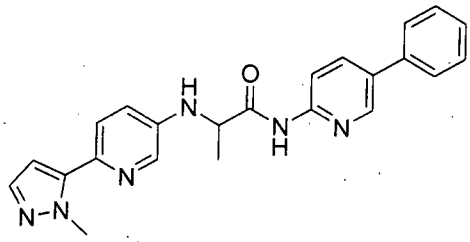


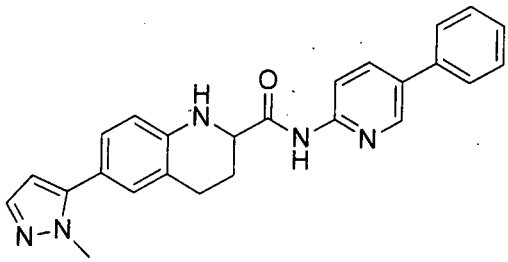


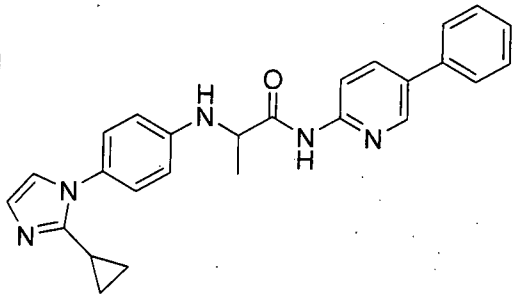


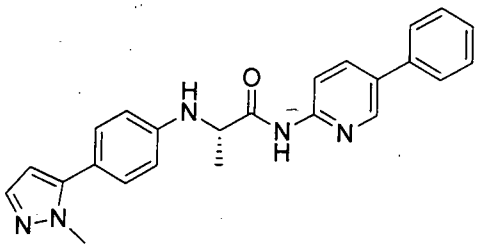


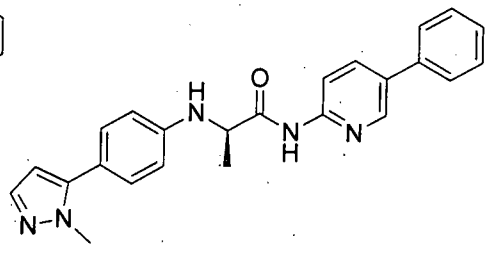


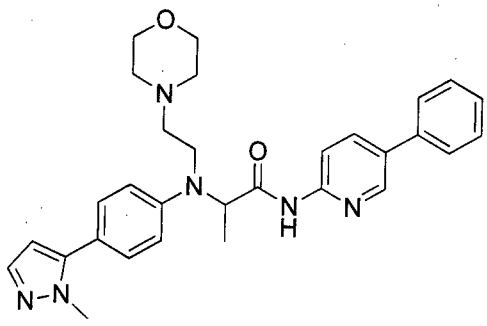


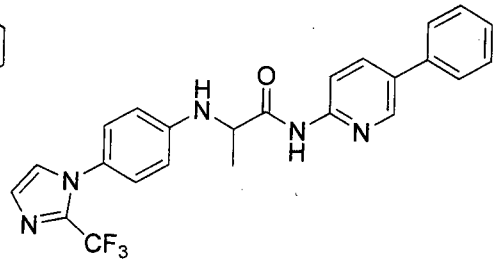


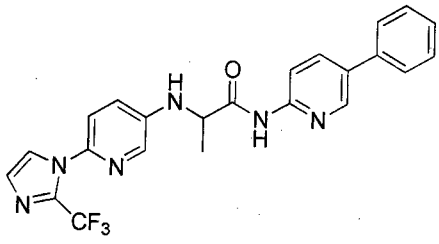


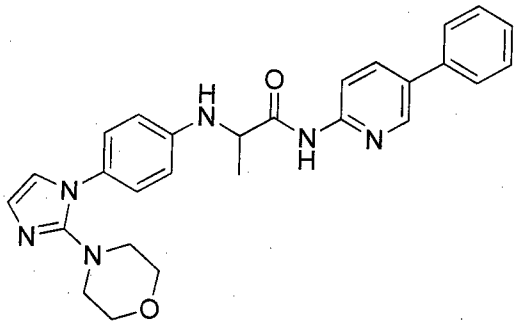


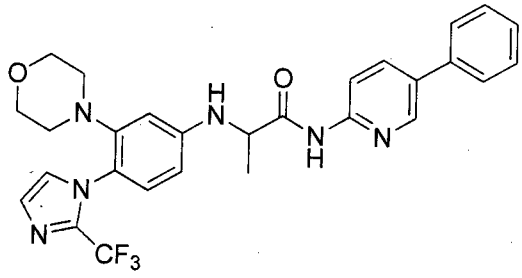


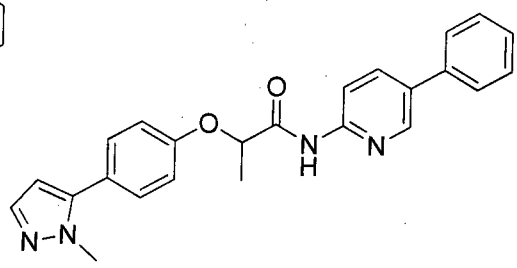


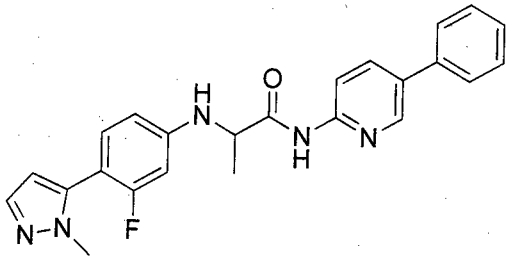


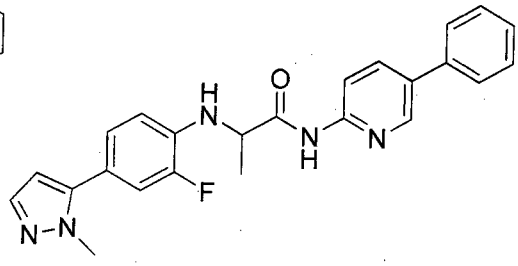


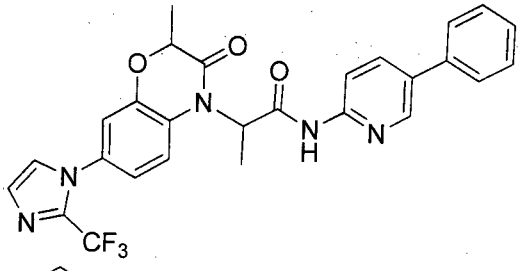


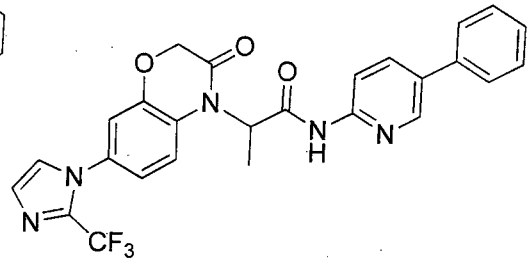


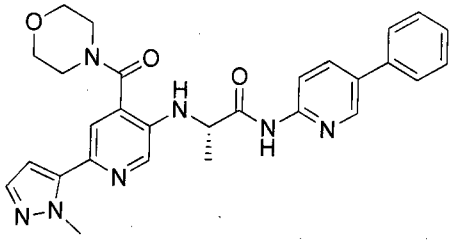


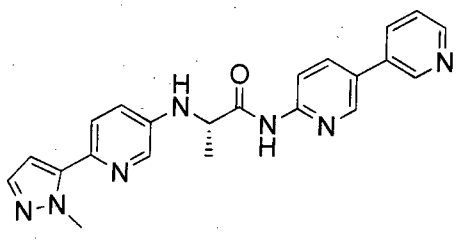


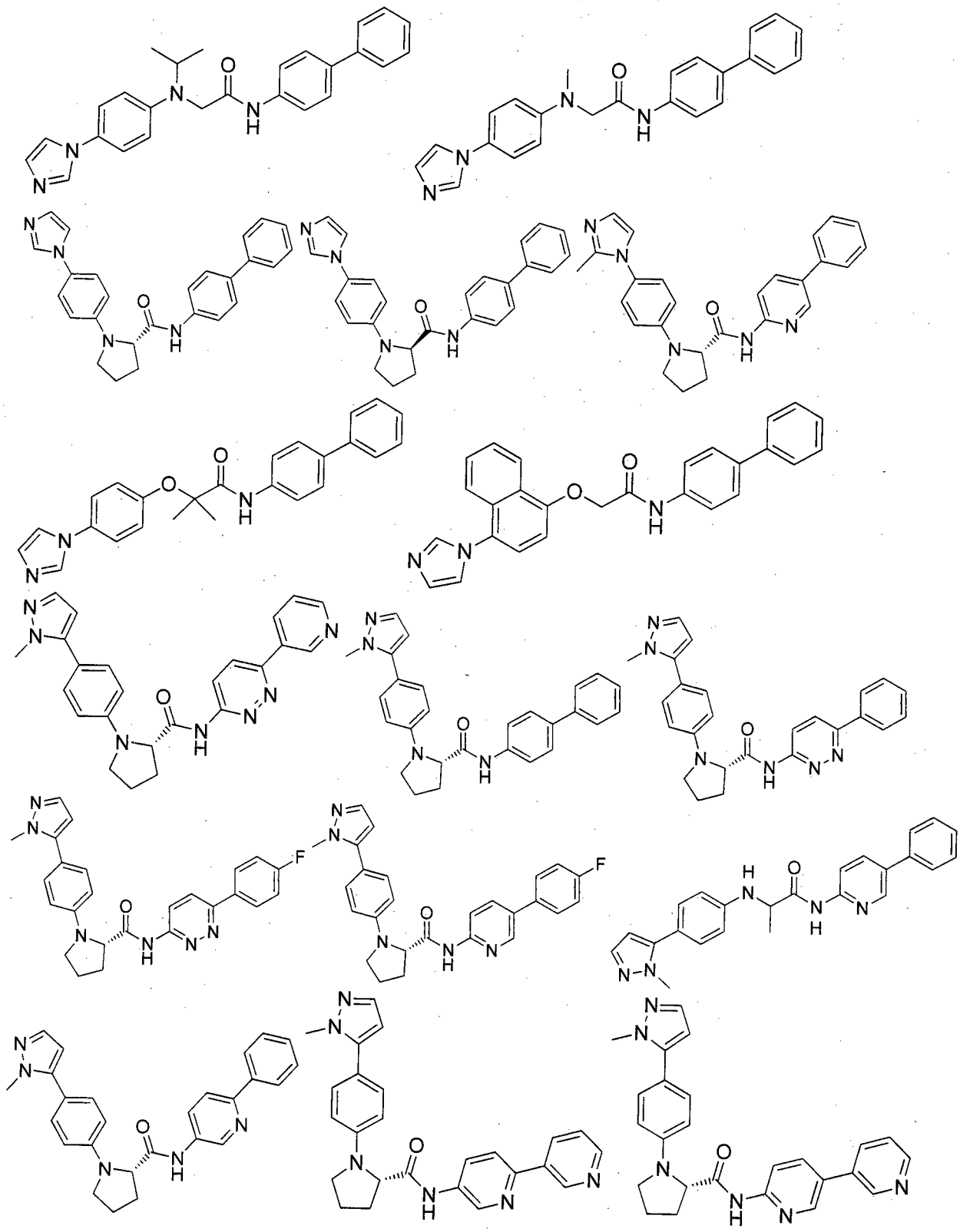


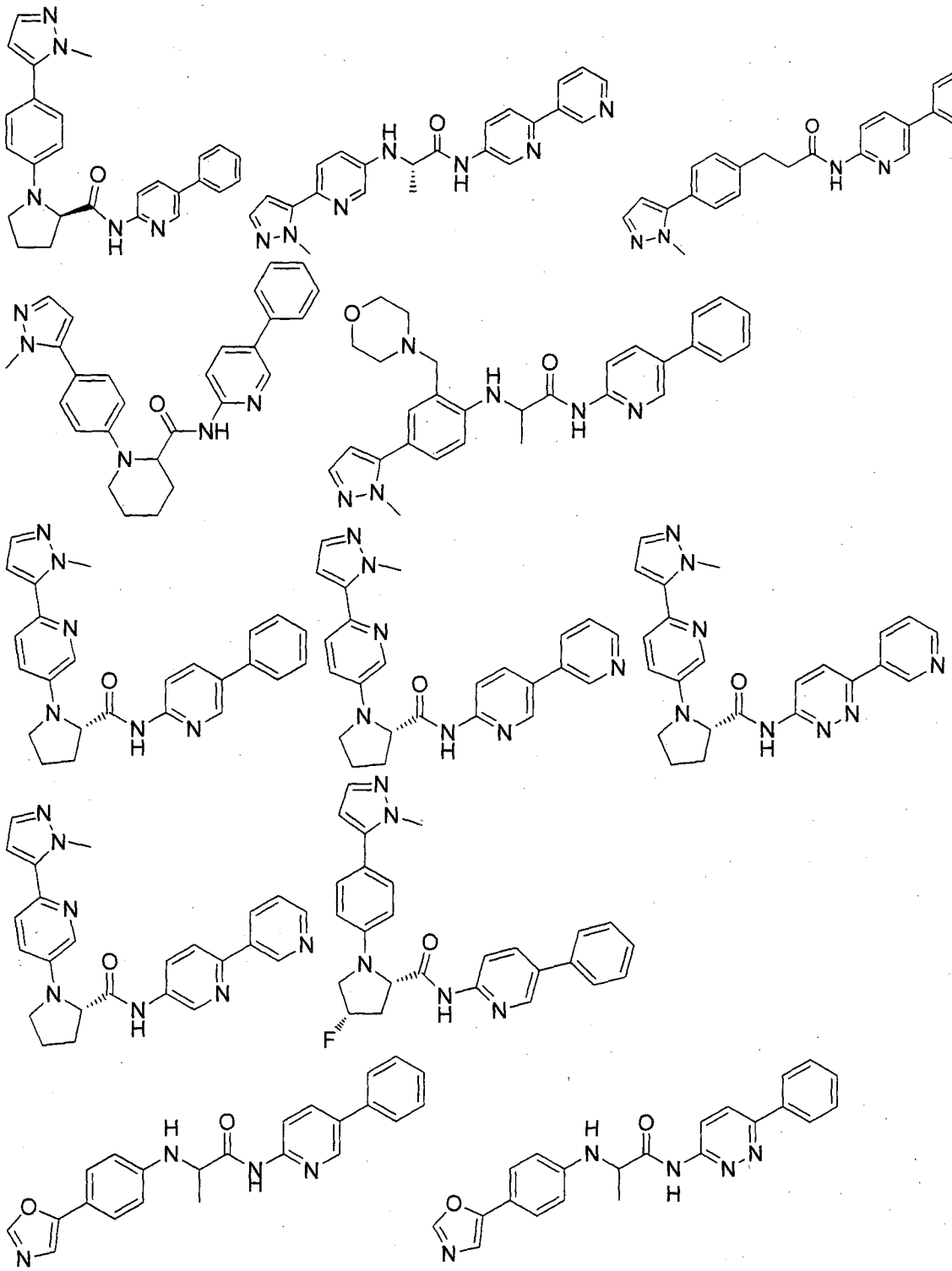












15. The compound of any one of claims 1 to 14 having a IC_{50} against HEK293-STF3A cells of less than about 5μm.

16. The compound of any one of claims 1 to 14 having a IC_{50} against HEK293-STF3A cells of less than about 1μm.

17. The compound of any one of claims 1 to 14 having a IC_{50} against HEK293-STF3A cells of less than about 0.1μm.

18. A process for making a compound of structure I as described in claim 1, said process comprising either:

coupling a compound of structure II with a compound of structure III

Ar^1-Ar^2-X-$C(R^1R^2)$-C(=O)-OH (II) $HN(R^3)$-Ar^3-Ar^4 (III)

or

coupling a compound of structure IV with a compound of structure V

Ar^1-Ar^2-X-H (IV) Hal- $C(R^1R^2)$-C(=O)$N(R^3)$-Ar^3-Ar^4 (V)

or

coupling an Ar^1 derivative with an Ar^2-X-$C(R^1R^2)$-C(=O)-$N(R^3)$-Ar^3-Ar^4 derivative

wherein R^1, R^2, R^3, X, Ar^1, Ar^2, Ar^3 and Ar^4 are as defined in claim 1 and Hal is a halogen.

19. A pharmaceutical composition comprising the compound of any one of claims 1 to 17 and one or more pharmaceutically acceptable carriers, diluents and/or adjuvants.

20. Use of a compound according to any one of claims 1 to 17 for the manufacture of a medicament for the treatment of a condition characterised by excessive WNT activity.

21. The use of claim 20 wherein the condition is a cancer or a fibrotic disease or a degenerative disease.

22. A compound according to any one of claims 1 to 17 for use in therapy.

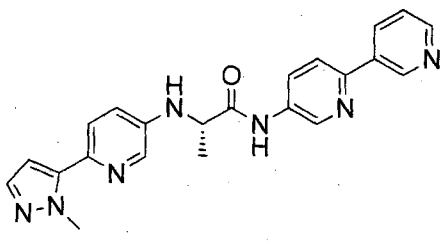
23. A method of treating a condition characterised by excessive WNT activity, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 17 or of a composition according to claim 19.

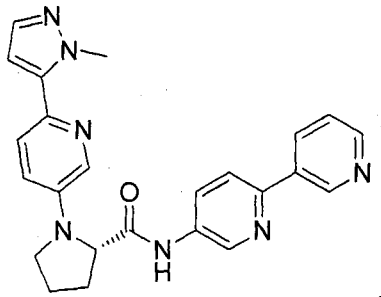
24. The method of claim 23 wherein the condition is a cancer or a fibrotic disease or stem cell or diabetic retinopathy or a degenerative disease.

25. Use of a compound according to any one of claims 1 to 17 for treating a condition characterised by excessive WNT activity.

26. Use of a compound according to any one of claims 1 to 17 for modulating WNT activity.

27. A compound according to any one of claims 1 to 17 when used for modulating WNT activity.

28. A compound according to claim 1 which is  or



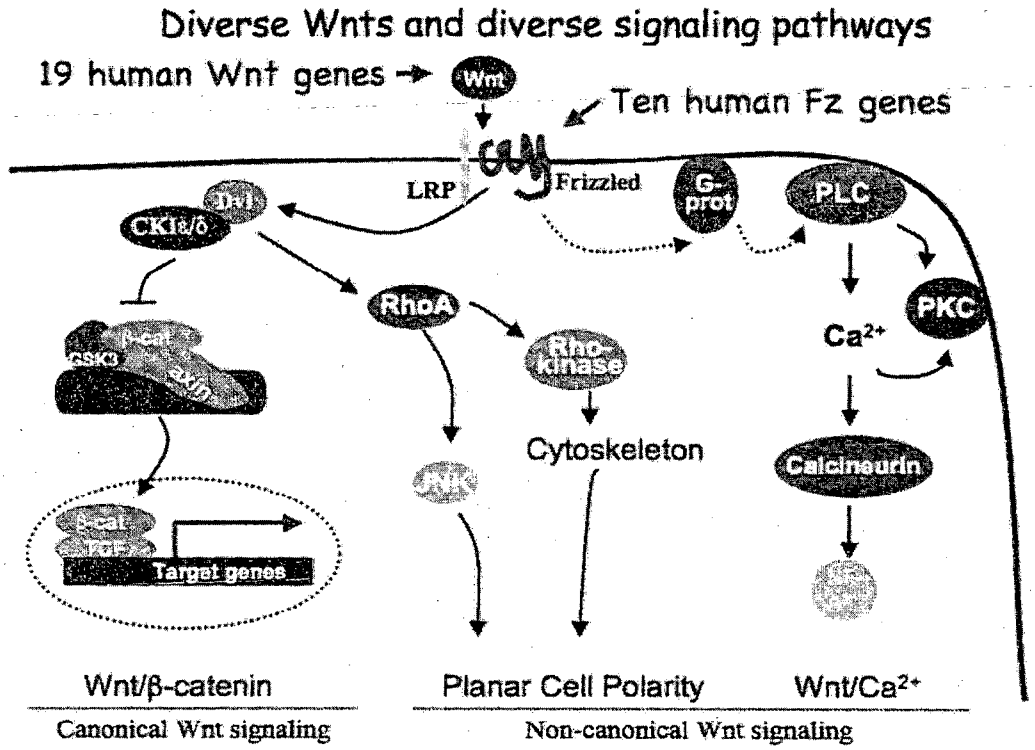
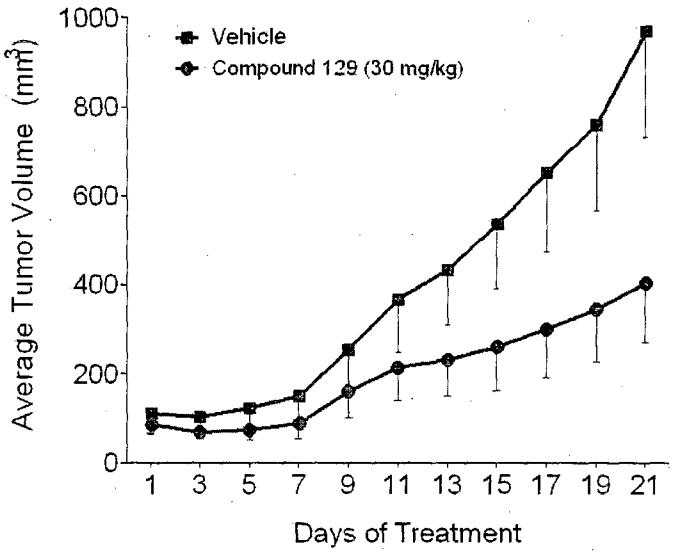
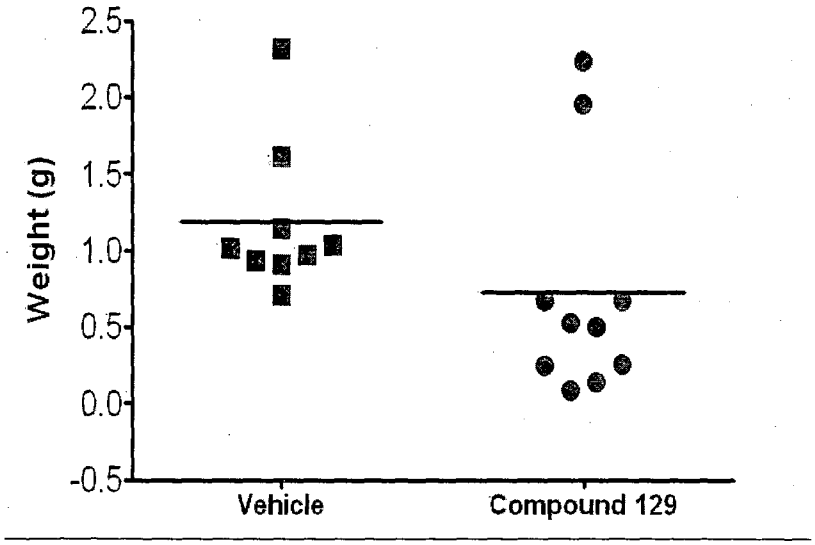

Diverse Wnts and diverse signaling pathways
19 human Wnt genes
Wnt
Ten human Fz genes
LRP
Frizzled
G-prot
PLC
Dvl
CKIε/δ
RhoA
Rho-dhase
PKC
Ca2+
Cytoskeleton
Calcineurin
Target genes
Wnt/β-catenin
Canonical Wnt signaling
Planar Cell Polarity
Wnt/Ca2+
Non-canonical Wnt signaling

Figure1


Vehicle
Compound 129 (30 mg/kg)
Average Tumor Volume (mm3)
1000
800
600
400
200
0
1 3 5 7 9 11 13 15 17 19 21
Days of Treatment


Weight (g)
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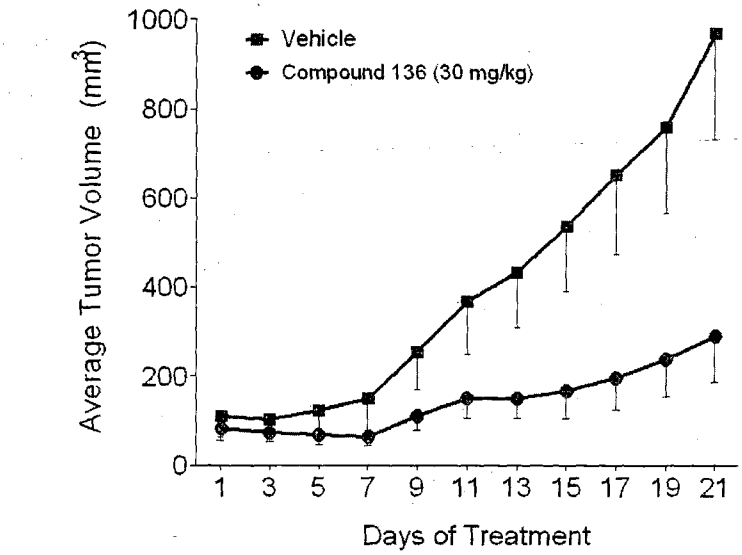
2.0
1.5
1.0
0.5
0.0
-0.5
Vehicle
Compound 129

Figure 2


Vehicle
Compound 136 (30 mg/kg)
Average Tumor Volume (mm3)
1000
800
600
400
200
0
1 3 5 7 9 11 13 15 17 19 21
Days of Treatment

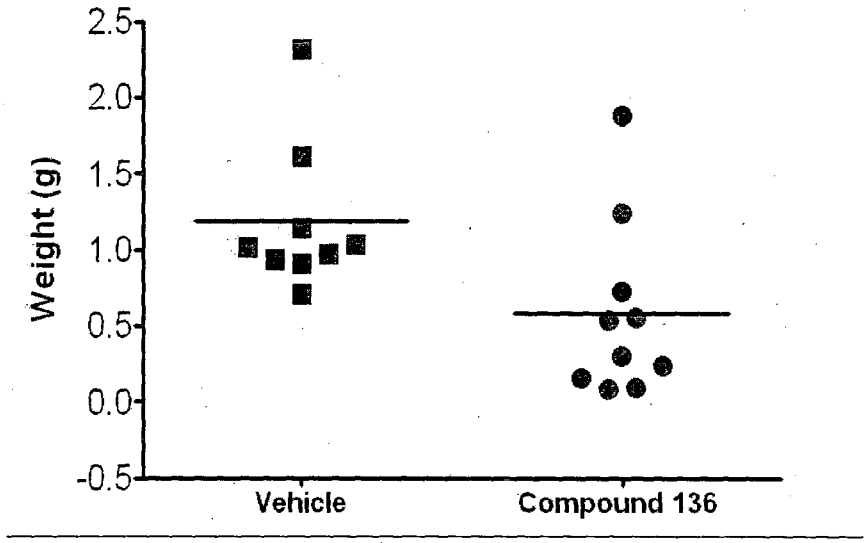

Weight (g)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
Vehicle
Compound 136

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2014/000183

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

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)

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)

STN Registry and CAplus: Substructure search based on compounds of structure I

PatentScope, Espacenet and AusPat: Inventor and Applicant Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] 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
30 June 2014	30 June 2014

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Benjamin Harris AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. (02) 6283 2272

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/SG2014/000183**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/076734 A1 (EUROSCREEN S.A.) 30 June 2011 Page 240 lines 12-17 Example 230, page 159 line 33 to page 160 line 7, page 206 lines 8-22 Method E, page 10 lines 2-19	1, 3, 4, 6-8, 12, 13 and 18-25
X	WO 2010/066682 A1 (EUROSCREEN S.A.) 17 June 2010 Page 248 lines 26-31 Example 230, page 167 lines 5-9, page 212 lines 4-16 Method E, page 13 line 7 to page 14 line 12	1, 3, 4, 6-8, 12, 13 and 18-25
X	EP 0271975 A1 (SHIONOGI SEIYAKU KABUSHIKI KAISHA TRADING UNDER THE NAME OF SHIONOGI & CO. LTD.) 22 June 1988 Page 18 table 2 Example 104, page 4 lines 34-48, page 6 lines 36-39, pages 5-6 Examples 1, 2 and 5	1, 3, 4, 9, 11, 12, 13, 18, 19 and 22
X	CAS RN 805273-65-8, STN Entry Date 30 December 2004 Whole Document	1, 3, 4, 6-8, 12, 13 and 22
X	CAS RN 1241148-41-3, STN Entry Date 15 September 2010 Whole Document	1, 3, 4, 9, 11, 12, 13 and 22
X	CAS RN 1319965-39-3, STN Entry Date 19 August 2011 Whole Document	1, 3, 4, 9, 11, 12, 13 and 22
X	CAS RN 1010535-46-2, STN Entry Date 28 March 2008 Whole Document	1, 3, 4, 12, 13 and 22
X	CAS RN 1211827-54-1, STN Entry Date 19 March 2010 Whole Document	1, 3, 4, 12, 13 and 22
X	CAS RN 1319808-85-9, STN Entry Date 19 August 2011 Whole Document	1, 3, 4, 12, 13 and 22
X	CAS RN 926766-32-7, STN Entry Date 18 March 2007 Whole Document	1, 3, 4, 12, 13 and 22
X	CAS RN 1302297-95-5, STN Entry Date 29 May 2011 Whole Document	1, 3, 4, 12, 13 and 22

Supplemental Box – IPC Marks

C07D 417/12 (2006.01)
C07D 413/14 (2006.01)
C07D 413/12 (2006.01)
C07D 413/04 (2006.01)
C07D 409/12 (2006.01)
C07D 403/12 (2006.01)
C07D 401/14 (2006.01)
C07D 401/12 (2006.01)
C07D 401/04 (2006.01)
C07D 277/24 (2006.01)
C07D 263/32 (2006.01)
C07D 249/08 (2006.01)
C07D 235/08 (2006.01)
C07D 233/58 (2006.01)
C07D 231/12 (2006.01)
C07D 213/30 (2006.01)
C07D 207/325 (2006.01)
C07D 207/323 (2006.01)
A61K 31/538 (2006.01)
A61K 31/5377 (2006.01)
A61K 31/506 (2006.01)
A61K 31/501 (2006.01)
A61K 31/496 (2006.01)
A61K 31/444 (2006.01)
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A61K 31/4184 (2006.01)
A61K 31/4178 (2006.01)
A61K 31/4164 (2006.01)
A61K 31/415 (2006.01)
A61K 31/402 (2006.01)
A61K 31/40 (2006.01)
A61P 35/00 (2006.01)
A61P 3/10 (2006.01)

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/SG2014/000183**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2011/076734 A1	30 June 2011	None	
WO 2010/066682 A1	17 June 2010	AU 2009326108 A1	17 Jun 2010
		CA 2745843 A1	17 Jun 2010
		CN 102245574 A	16 Nov 2011
		CR 20110318 A	09 Sep 2011
		EA 201100921 A1	30 Dec 2011
		EC SP11011082 A	30 Sep 2011
		EP 2364297 A1	14 Sep 2011
		JP 2012510979 A	17 May 2012
		KR 20110097930 A	31 Aug 2011
		MX 2011006006 A	08 Sep 2011
		US 2011230477 A1	22 Sep 2011
EP 0271975 A1	22 June 1988	EP 0271975 B1	24 Jun 1992
		AR 246967 A1	31 Oct 1994
		AU 598850 B2	05 Jul 1990
		AU 7740187 A	25 Feb 1988
		BR 8704345 A	19 Apr 1988
		CN 87106464 A	23 Mar 1988
		CN 1018922 B	04 Nov 1992
		JP S63152367 A	24 Jun 1988
		JP H0480034 B2	17 Dec 1992
		KR 940010176 B1	22 Oct 1994
		US 4888044 A	19 Dec 1989
		ZA 8706305 A	29 Feb 1988

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/SG2014/000183**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.