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Canadian Intellectual Property Office

CA 2986631 C 2020/06/02

(11)(21) **2 986 631**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(22) **Date de dépôt/Filing Date:** 2010/12/15

(41) **Mise à la disp. pub./Open to Public Insp.:** 2011/07/14

(45) **Date de délivrance/Issue Date:** 2020/06/02

(62) **Demande originale/Original Application:** 2 785 037

(30) **Priorité/Priority:** 2009/12/21 (US61/288,544)

(51) **Cl.Int./Int.Cl.** ***C07D 471/04*** (2006.01),
A61K 31/437 (2006.01), ***A61K 31/444*** (2006.01),
A61K 31/4745 (2006.01), ***A61K 31/5025*** (2006.01),
A61P 35/00 (2006.01)

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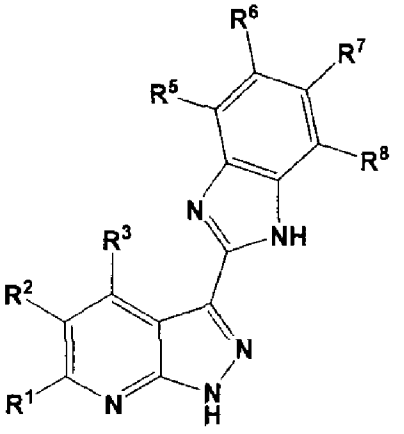
(54) **Titre : 1H-PYRAZOLO[3,4-B]PYRIDINES ET LEURS UTILISATIONS THERAPEUTIQUES**
(54) **Title: 1H-PYRAZOLO[3,4-B]PYRIDINES AND THEREAPEUTIC USES THEREOF**



Ia

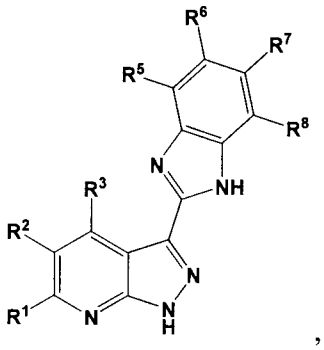
(57) **Abrégé/Abstract:**
Provided herein are compounds according to formula (Ia):

(see formula Ia),

and pharmaceutically acceptable salts thereof, and compositions comprising the same, for use in various methods, including treating cancers such as colon, ovarian, pancreatic, breast, liver, prostate and hematologic cancers.

ABSTRACT

Provided herein are compounds according to formula (Ia):



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Ia

and pharmaceutically acceptable salts thereof, and compositions comprising the same, for use in various methods, including treating cancers such as colon, ovarian, pancreatic, breast, liver, prostate and hematologic cancers.

1H-PYRAZOLO[3,4-*B*]PYRIDINES AND THERAPEUTIC USES THEREOF

RELATED APPLICATIONS

[0001] This application is a divisional of Canadian patent application no. 2,785,037, filed on December 15, 2010.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the field of therapeutic oncology. More particularly, it concerns the use of a 1H-pyrazolo[3,4-*b*]pyridine compound or salts or analogs thereof, in the treatment of cancer, particularly colon, ovarian, pancreatic, breast, liver, prostate and hematologic cancers.

Description of the Related Art

[0003] Pattern formation is the activity by which embryonic cells form ordered spatial arrangements of differentiated tissues. Speculation on the mechanisms underlying these patterning effects usually centers on the secretion of a signaling molecule that elicits an appropriate response from the tissues being patterned. More recent work aimed at the identification of such signaling molecules implicates secreted proteins encoded by individual members of a small number of gene families.

[0004] A longstanding idea in cancer biology is that cancers arise and grow due to the formation of cancer stem cells, which may constitute only a minority of the cells within a tumor but are nevertheless critical for its propagation. Stem cells are appealing as the cell of origin for cancer because of their pre-existing capacity for self-renewal and for unlimited replication. In addition, stem cells are relatively long-lived in comparison to other cells within tissues, providing a greater opportunity to accumulate the multiple additional mutations that may be required to increase the rate of cell proliferation and produce clinically significant cancers. Of particular recent interest in the origin of cancer is the observation that the Wnt signaling pathway, which has been implicated in stem cell self-renewal in normal tissues, upon continuous activation has also been associated with the initiation and growth of many types of cancer. This

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pathway thus provides a potential link between the normal self-renewal of stem cells and the aberrantly regulated proliferation of cancer stem cells.

[0005] The Wnt growth factor family includes more than 10 genes identified in the mouse and at least 19 genes identified in the human. Members of the Wnt family of signaling molecules mediate many important short-and long-range patterning processes during invertebrate and vertebrate development. The Wnt signaling pathway is known for its important role in the inductive interactions that regulate growth and differentiation, and plays important roles in the homeostatic maintenance of post-embryonic tissue integrity. Wnt stabilizes cytoplasmic β-catenin, which stimulates the expression of genes including c-myc, c jun, fra-l, and cyclin Dl. In addition, misregulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. More recently, the Wnt pathway has been implicated in the maintenance of stem or progenitor cells in a growing list of adult tissues that now includes skin, blood, gut, prostate, muscle and the nervous system.

[0006] Pathological activation of the Wnt pathway is also believed to be the initial event leading to colorectal cancer in over 85% of all sporadic cases in the Western world. Activation of the Wnt pathway has also been extensively reported for hepatocellular carcinoma, breast cancer, ovarian cancer, pancreatic cancer, melanomas, mesotheliomas, lymphomas and leukemias. In addition to cancer, inhibitors of the Wnt pathway can be used for stem cell research or for the treatment of any diseases characterized by aberrant Wnt activation such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis as well as mycotic and viral infections and bone and cartilage diseases. As such, it is a therapeutic target that is of great interest to the field.

[0007] In addition to cancer, there are many cases of genetic diseases due to mutations in Wnt signaling components. Examples of some of the many diseases are Alzheimer's disease [*Proc. Natl. Acad. Sci. U S A*(**2007**), *104(22)*, 9434-9], osteoarthritis, polyposis coli [*Science*(**1991**), *253(5020)*, 665-669], bone density and vascular defects in the eye (osteoporosis-pseudoglioma syndrome, OPPG)[*N. Engl. J. Med.* (**2002**), *346(20)*, 1513-21], familial exudative vitreoretinopathy[*Hum. Mutat.* (**2005**), *26(2)*, 104-12], retinal angiogenesis [*Nat. Genet.* (**2002**), *32(2)*, 326-30], early coronary disease

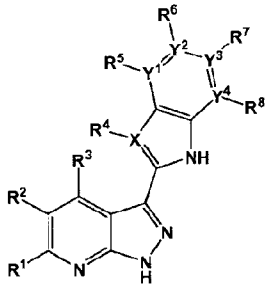
[*Science*(**2007**), *315(5816)*, 1278-82], tetra-amelia syndrome [*Am. J. Hum. Genet.* (**2004**), *74(3)*, 558-63], Müllerian-duct regression and virilization [*Engl. J. Med.* (**2004**), *351(8)*, 792-8], SERKAL syndrome [*Am. J. Hum. Genet.* (**2008**), *82(1)*, 39-47], diabetes mellitus type 2 [*Am. J. Hum. Genet.* (**2004**), *75(5)*, 832-43; *N. Engl. J. Med.* (**2006**), *355(3)*, 241-50], Fuhrmann syndrome [*Am. J. Hum. Genet.* (**2006**), *79(2)*, 402-8], Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome [*Am. J. Hum. Genet.* (**2006**), *79(2)*, 402-8], odonto-onycho-dermal dysplasia [*Am. J. Hum. Genet.* (**2007**), *81(4)*, 821-8], obesity [*Diabetologia* (**2006**), *49(4)*, 678-84], split-hand/foot malformation [*Hum. Mol. Genet.* (**2008**), *17(17)*, 2644-53], caudal duplication syndrome [*Am. J. Hum. Genet.* (**2006**), *79(1)*, 155-62], tooth agenesis [*Am. J. Hum. Genet.* (**2004**), *74(5)*, 1043-50], Wilms tumor [*Science* (**2007**), *315(5812)*, 642-5], skeletal dysplasia [*Nat. Genet.* (**2009**), *41(1)*, 95-100], focal dermal hypoplasia [*Nat. Genet.* (**2007**), *39(7)*, 836-8], autosomal recessive anonychia [*Nat. Genet.* (**2006**), *38(11)*, 1245-7], neural tube defects [*N. Engl. J. Med.* (**2007**), *356(14)*, 1432-7], alpha-thalassemia (ATRX) syndrome [*The Journal of Neuroscience* (**2008**), *28(47)*, 12570 –12580], fragile X syndrome [*PLoS Genetics* (**2010**), *6(4)*, e1000898], ICF syndrome, Angelman syndrome [*Brain Research Bulletin* (**2002**), *57(1)*, 109-119], Prader-Willi syndrome [*Journal of Neuroscience* (**2006**), *26(20)*, 5383-5392], Beckwith-Wiedemann Syndrome [*Pediatric and Developmental Pathology* (**2003**), *6(4)*, 299-306] and Rett syndrome.

SUMMARY OF THE INVENTION

[0008] The present invention makes available methods and reagents, involving contacting a cell with an agent, such as an aromatic compound, in a sufficient amount to antagonize Wnt activity, e. g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling components.

[0009] Some embodiments disclosed herein include Wnt inhibitors containing a 1H-pyrazolo[3,4-*b*]pyridine core. Other embodiments disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

[0010] One embodiment disclosed herein includes a compound having the structure of formula **I** or a pharmaceutically acceptable salt thereof:



I

I

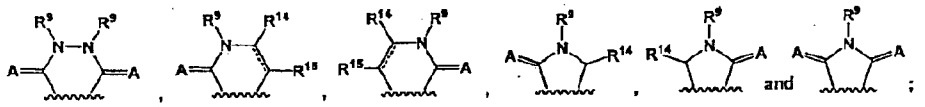
[0011] In some embodiments of formula (I):

R^1, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

If R^1 and R^3 are H then R^2 is independently selected from the group consisting of $-C(=O)NH(C_{1-9}\text{ alkyl}R^9)$, $-C(=S)NH(C_{1-9}\text{ alkyl}R^9)$, $-C(=O)N(R^{10})_2$, $-C(=S)N(R^{10})_2$, $-C(=NR^{11})N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{13}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{13}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{13}$ and $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{13}$;

If R^1 and R^3 are not both H then R^2 is independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

alternatively, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6 or R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^9 is independently selected from the group consisting of H, -C_{1-9} alkyl, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

alternatively, two adjacent R^9s may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl;

each R^{10} is independently selected from the group consisting of -C_{1-9} alkyl, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

each R^{11} is independently selected from the group consisting of –OR^9 and R^9;

R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, -CF_3, carbocyclyl, heterocyclyl, aryl, heteroaryl, -(C_{1-9}alkyl)$_n$$OR^9$, -($C_{1-9}$ alkyl)$_n$$SR^9$, -($C_{1-9}$ alkyl)$_n$$S(=O)R^{10}$, -($C_{1-9}$ alkyl)$_n$$SO_2R^9$, -($C_{1-9}$ alkyl)$_n$$N(R^9)SO_2R^9$, -($C_{1-9}$ alkyl)$_n$$SO_2N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$C(=A)N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)R^9$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)CH(R^9)_2$, -$NO_2$, -CN, -($C_{1-9}$ alkyl)$_n$$CO_2R^9$ and -(C_{1-9} alkyl)$_n$$C(=A)R^9$;

R^{13} is 1-5 substituents each selected from the group consisting of -$N(R^9)C(=A)N(R^9)_2$, -$C(=A)N(R^9)_2$, -$N(R^9)C(=A)R^9$, -$N(R^9)C(=A)CH(R^9)_2$, -$N(R^9)SO_2R^9$ and -SO_2(C_{1-9} alkyl);

R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclylR^{12}, -(C_{1-9} alkyl)$_n$heterocyclylR^{12}, -(C_{1-9} alkyl)$_n$arylR^{12}, -(C_{1-9} alkyl)$_n$heteroarylR^{12}, -(C_{1-9} alkyl)$_n$$OR^9$, -($C_{1-9}$ alkyl)$_n$$SR^9$, -($C_{1-9}$ alkyl)$_n$$S(=O)R^{10}$, -($C_{1-9}$ alkyl)$_n$$SO_2R^9$, -($C_{1-9}$ alkyl)$_n$$N(R^9)SO_2R^9$, -($C_{1-9}$ alkyl)$_n$$SO_2N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$C(=A)N(R^9)_2$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)R^9$, -($C_{1-9}$ alkyl)$_n$$N(R^9)C(=A)CH(R^9)_2$, -$NO_2$, -CN, -($C_{1-9}$ alkyl)$_n$$CO_2R^9$ and -(C_{1-9} alkyl)$_n$$C(=A)R^9$;

alternatively, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine;

each A is independently selected from O, S and NR^{11};

X is nitrogen and R^4 is absent;

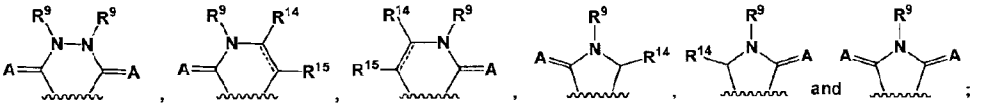
Y^1, Y^2, Y^3 and Y^4 are each carbon; and

each n is 0 or 1, or a pharmaceutically acceptable salt thereof.

[0012] In other embodiments of formula **(I)**:

R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

alternatively, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^9 is independently selected from the group consisting of H, C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}$ and $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}$;

alternatively, two adjacent R^9s may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl;

each R^{10} is independently selected from the group consisting of C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}$ and $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}$;

each R^{11} is independently selected from the group consisting of $-OR^9$ and R^9;

R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, carbocyclylR^{12}, heterocyclylR^{12}, arylR^{12}, heteroarylR^{12}, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n$carbocyclyl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$heterocyclyl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$aryl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$heteroaryl$R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

alternatively, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine;

each A is independently selected from O, S and NR^{11};

X is carbon or nitrogen;

Y^1, Y^2, Y^3 and Y^4 are independently selected from the group consisting of carbon and nitrogen;

with the proviso that if X is nitrogen that at least one of Y^1, Y^2, Y^3 and Y^4 are nitrogen;

If X is nitrogen then R^4 is absent;

If Y^1 is nitrogen then R^5 is absent;

If Y^2 is nitrogen then R^6 is absent;

If Y^3 is nitrogen then R^7 is absent;

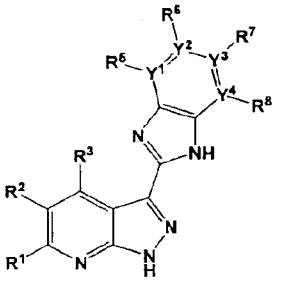
If Y^4 is nitrogen then R^8 is absent; and

each n is 0 or 1, or a pharmaceutically acceptable salt thereof.

[0013] Some embodiments include stereoisomers and pharmaceutically acceptable salts of a compound of general formula (**I**).

[0014] Some embodiments include pro-drugs of a compound of general formula (**I**).

[0014a] In a more particular embodiment, there is provided a compound or pharmaceutically acceptable salt thereof having the structure of formula Ib:

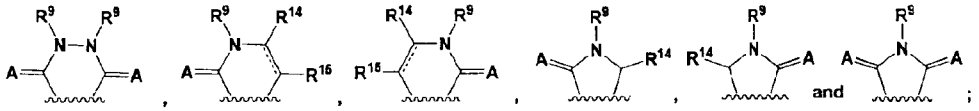


Ib

wherein:

R^1, R^2, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, $C_{1\text{-}9}$ alkyl, halide, $-CF_3$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_nOR^9$, $-(C_{1\text{-}9}\text{ alkyl})_nSR^9$, $-(C_{1\text{-}9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1\text{-}9}\text{ alkyl})_nSO_2R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1\text{-}9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1\text{-}9}\text{ alkyl})_nC(=A)R^9$;

alternatively, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

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each R^9 is independently selected from the group consisting of H, C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{alkyl})_n$carbocyclyl, $-(C_{1-9}\text{alkyl})_n$heterocyclyl, $-(C_{1-9}\text{alkyl})_n$aryl and $-(C_{1-9}\text{alkyl})_n$heteroaryl;

alternatively, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl;

each R^{10} is independently selected from the group consisting of C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{alkyl})_n$carbocyclyl, $-(C_{1-9}\text{alkyl})_n$heterocyclyl, $-(C_{1-9}\text{alkyl})_n$aryl and $-(C_{1-9}\text{alkyl})_n$heteroaryl;

each R^{11} is independently selected from the group consisting of $-OR^9$ and R^9;

each R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9}alkyl, halide, $-CF_3$, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-(C_{1-9}\text{alkyl})_nOR^9$, $-(C_{1-9}\text{alkyl})_nSR^9$, $-(C_{1-9}\text{alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{alkyl})_nSO_2R^9$, $-(C_{1-9}\text{alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{alkyl})_nC(=A)R^9$;

R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9}alkyl, halide, $-CF_3$, $-(C_{1-9}\text{alkyl})_n$carbocyclylR^{12}, $-(C_{1-9}\text{alkyl})_n$heterocyclylR^{12}, $-(C_{1-9}\text{alkyl})_n$arylR^{12}, $-(C_{1-9}\text{alkyl})_n$heteroarylR^{12}, $-(C_{1-9}\text{alkyl})_nOR^9$, $-(C_{1-9}\text{alkyl})_nSR^9$, $-(C_{1-9}\text{alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{alkyl})_nSO_2R^9$, $-(C_{1-9}\text{alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{alkyl})_nC(=A)R^9$;

alternatively, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine;

each A is independently selected from the group consisting of O, S and NR^{11};

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Y^3 and Y^4 are independently selected from the group consisting of carbon and nitrogen with the proviso that at least one of Y^3 and Y^4 are nitrogen;

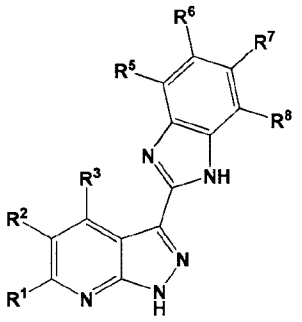
Y^1 and Y^2 are C;

when Y^3 is nitrogen then R^7 is absent;

when Y^4 is nitrogen then R^8 is absent; and

each n is 0 or 1.

[0014b] In a more particular embodiment, there is provided a compound or pharmaceutically acceptable salt thereof having the structure of formula **Ia**:



Ia

wherein:

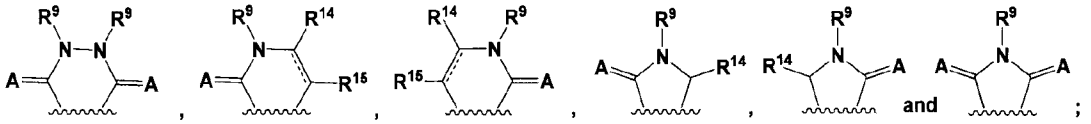
R^1, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, $C_{1\text{-}9}$ alkyl, halide, $-CF_3$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1\text{-}9}\text{ alkyl})_nOR^9$, $-(C_{1\text{-}9}\text{ alkyl})_nSR^9$, $-(C_{1\text{-}9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1\text{-}9}\text{ alkyl})_nSO_2R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1\text{-}9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1\text{-}9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1\text{-}9}\text{ alkyl})_nC(=A)R^9$;

if R^1 and R^3 are H then R^2 is independently selected from the group consisting of $-C(=O)NH(C_{1\text{-}9}\text{ alkyl}R^9)$, $-C(=S)NH(C_{1\text{-}9}\text{ alkyl}R^9)$, $-C(=O)N(R^{10})_2$, $-C(=S)N(R^{10})_2$, $-C(=NR^{11})N(R^9)_2$,

-(C_{1-9} alkyl)$_n$carbocyclylR^{13}, -(C_{1-9} alkyl)$_n$heterocyclylR^{13}, -(C_{1-9} alkyl)$_n$arylR^{13} and -(C_{1-9} alkyl)$_n$heteroarylR^{13};

if R^1 and R^3 are not both H then R^2 is independently selected from the group consisting of H, C_{1-9} alkyl, halide, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclylR^{12}, -(C_{1-9} alkyl)$_n$heterocyclylR^{12}, -(C_{1-9} alkyl)$_n$arylR^{12}, -(C_{1-9} alkyl)$_n$heteroarylR^{12}, -(C_{1-9} alkyl)$_n$OR^9, -(C_{1-9} alkyl)$_n$SR^9, -(C_{1-9} alkyl)$_n$S(=O)R^{10}, -(C_{1-9} alkyl)$_n$SO_2R^9, -(C_{1-9} alkyl)$_n$N(R^9)SO_2R^9, -(C_{1-9} alkyl)$_n$SO_2N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)N(R^9)$_2$, -(C_{1-9} alkyl)$_n$C(=A)N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)R^9, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)CH(R^9)$_2$, -NO_2, -CN, -(C_{1-9} alkyl)$_n$CO_2R^9 and -(C_{1-9} alkyl)$_n$C(=A)R^9;

alternatively, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^9 is independently selected from the group consisting of H, C_{1-9} alkyl, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

alternatively, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl;

each R^{10} is independently selected from the group consisting of C_{1-9} alkyl, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclyl, -(C_{1-9} alkyl)$_n$heterocyclyl, -(C_{1-9} alkyl)$_n$aryl and -(C_{1-9} alkyl)$_n$heteroaryl;

each R^{11} is independently selected from the group consisting of –OR^9 and R^9;

each R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, -CF_3, carbocyclyl, heterocyclyl, aryl, heteroaryl, -(C_{1-9} alkyl)$_n$OR^9, -(C_{1-9} alkyl)$_n$SR^9, -(C_{1-9} alkyl)$_n$S(=O)R^{10}, -(C_{1-9} alkyl)$_n$SO_2R^9, -(C_{1-9} alkyl)$_n$N(R^9)SO_2R^9,

$-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl)$_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

R^{13} is 1-5 substituents each selected from the group consisting of $-N(R^9)C(=A)N(R^9)_2$, $-C(=A)N(R^9)_2$, $-N(R^9)C(=A)R^9$, $-N(R^9)C(=A)CH(R^9)_2$, $-N(R^9)SO_2R^9$ and $-SO_2(C_{1-9}\text{ alkyl})$;

R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}$ alkyl)$_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

alternatively, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine;

each A is independently selected from the group consisting of O, S and NR^{11};

each n is 0 or 1.

[0015] Some embodiments of the present invention include pharmaceutical compositions comprising a compound of general formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, or excipient.

[0016] Other embodiments disclosed herein include methods of inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins by administering to a subject affected by a disorder or disease in which aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, cell cycling and mutations in Wnt signaling components, a compound according to formula (I) or a pharmaceutically acceptable salt thereof. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct a genetic disorder due to mutations in Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, osteoarthritis, polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-ameliasyndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

[0017] Some embodiments of the present invention include methods to prepare a compound of general formula (I).

[0018] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Compositions and methods for inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins would be of tremendous benefit. Certain embodiments provide such compositions and methods.

[0020] Some embodiments relate to a method for treating a disease such as cancers, diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, osteoarthritis, polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

[0021] In some embodiments, pharmaceutical compositions are provided that are effective for treatment of a disease of an animal, *e.g.*, a mammal, caused by the pathological activation or mutations of the Wnt pathway. The composition includes a pharmaceutically acceptable carrier and a Wnt pathway inhibitor as described herein.

Definitions

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0023] In this specification and in the claims, the following terms have the meanings as defined. As used herein, "alkyl" means a branched, or straight chain chemical group containing only carbon and hydrogen, such as methyl, isopropyl,

isobutyl, sec-butyl and pentyl. Alkyl groups can either be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, or other functionality that may be suitably blocked, if necessary for purposes of the invention, with a protecting group. Alkyl groups can be saturated or unsaturated (e.g., containing -C=C- or -C≡C- subunits), at one or several positions. Typically, alkyl groups will comprise 1 to 9 carbon atoms, preferably 1 to 6, and more preferably 1 to 4 carbon atoms.

[0024] As used herein, "carbocyclyl" means a cyclic ring system containing only carbon atoms in the ring system backbone, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexenyl. Carbocyclyls may include multiple fused rings. Carbocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. Carbocyclyl groups can either be unsubstituted or substituted with one or more substituents, e.g., alkyl, halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, or other functionality that may be suitably blocked, if necessary for purposes of the invention, with a protecting group. Typically, carbocyclyl groups will comprise 3 to 10 carbon atoms, preferably 3 to 6.

[0025] As used herein, "lower alkyl" means a subset of alkyl, and thus is a hydrocarbon substituent, which is linear, or branched. Preferred lower alkyls are of 1 to about 4 carbons, and may be branched or linear. Examples of lower alkyl include butyl, propyl, isopropyl, ethyl, and methyl. Likewise, radicals using the terminology "lower" refer to radicals preferably with 1 to about 4 carbons in the alkyl portion of the radical.

[0026] As used herein, "amido" means a H-CON- or alkyl-CON-, carbocyclyl-CON-, aryl-CON-, heteroaryl-CON- or heterocyclyl-CON group wherein the alkyl, carbocyclyl, aryl or heterocyclyl group is as herein described.

[0027] As used herein, "aryl" means an aromatic radical having a single-ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) with only carbon atoms present in the ring backbone. Aryl groups can either be unsubstituted or substituted with one or more substituents, e.g., alkyl, amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, and other substituents. A preferred carbocyclic aryl is phenyl.

[0028] As used herein, the term "heteroaryl" means an aromatic radical having one or more heteroatom(s) (e.g., N, O, or S) in the ring backbone and may include a single ring (e.g., pyridine) or multiple condensed rings (e.g., quinoline). Heteroaryl groups can either be unsubstituted or substituted with one or more substituents, e.g., amino, cyano, hydroxyl, lower alkyl, haloalkyl, alkoxy, nitro, halo, mercapto, and other substituents. Examples of heteroaryl include thienyl, pyrridyl, furyl, oxazolyl, oxadiazolyl, pyrollyl, imidazolyl, triazolyl, thiodiazolyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl and others.

[0029] In these definitions it is clearly contemplated that substitution on the aryl and heteroaryl rings is within the scope of certain embodiments. Where substitution occurs, the radical is called substituted aryl or substituted heteroaryl. Preferably one to three and more preferably one or two substituents occur on the aryl or heteroaryl ring. Though many substituents will be useful, preferred substituents include those commonly found in aryl or heteroaryl compounds, such as alkyl, cycloalkyl, hydroxy, alkoxy, cyano, halo, haloalkyl, mercapto and the like.

[0030] As used herein, "amide" includes both RNR'CO- (in the case of R = alkyl, alkaminocarbonyl-) and RCONR'- (in the case of R = alkyl, alkyl carbonylamino-).

[0031] As used herein, the term "ester" includes both ROCO- (in the case of R = alkyl, alkoxycarbonyl-) and RCOO- (in the case of R = alkyl, alkylcarbonyloxy-).

[0032] As used herein, "acyl" means an H-CO- or alkyl-CO-, carbocyclyl-CO-, aryl-CO-, heteroaryl-CO- or heterocyclyl-CO- group wherein the alkyl, carbocyclyl, aryl or heterocyclyl group is as herein described. Preferred acyls contain a lower alkyl. Exemplary alkyl acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, t-butylacetyl, butanoyl and palmitoyl.

[0033] As used herein, "halo or halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro, bromo and fluoro are preferred halides. The term "halo" also contemplates terms sometimes referred to as "halogen", or "halide".

[0034] As used herein, "haloalkyl" means a hydrocarbon substituent, which is linear or branched or cyclic alkyl, alkenyl or alkynyl substituted with chloro, bromo, fluoro or iodo atom(s). Most preferred of these are fluoroalkyls, wherein one or more of the hydrogen atoms have been substituted by fluoro. Preferred haloalkyls are of 1 to

about 3 carbons in length, more preferred haloalkyls are 1 to about 2 carbons, and most preferred are 1 carbon in length. The skilled artisan will recognize then that as used herein, "haloalkylene" means a diradical variant of haloalkyl, such diradicals may act as spacers between radicals, other atoms, or between the parent ring and another functional group.

[0035] As used herein, "heterocyclyl" means a cyclic ring system comprising at least one heteroatom in the ring system backbone. Heterocyclyls may include multiple fused rings. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. Heterocyclyls may be substituted or unsubstituted with one or more substituents, e.g., alkyl, halogen, alkoxy, acyloxy, amino, amido, cyano, nitro, hydroxyl, mercapto, carboxy, carbonyl, benzyloxy, aryl, heteroaryl, and other substituents, and are attached to other groups via any available valence, preferably any available carbon or nitrogen. More preferred heterocycles are of 5-7 members. In six membered monocyclic heterocycles, the heteroatom(s) are selected from one up to three of O, N or S, and wherein when the heterocycle is five membered, preferably it has one or two heteroatoms selected from O, N, or S.

[0036] As used herein, "substituted amino" means an amino radical which is substituted by one or two alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl groups, wherein the alkyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0037] As used herein, "substituted thiol" means RS- group wherein R is an alkyl, an aryl, heteroaryl or a heterocyclyl group, wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0038] As used herein, "sulfonyl" means an alkylSO_2, arylSO_2, heteroarylSO_2, carbocyclylSO_2, or heterocyclyl-SO_2 group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl are defined as above.

[0039] As used herein, "sulfamido" means an alkyl-N-$S(O)_2$N-, aryl-N$S(O)_2$N-, heteroaryl-N$S(O)_2$N-, carbocyclyl-N$S(O)_2$N or heterocyclyl-N$S(O)_2$N- group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0040] As used herein, "sulfonamido" means an alkyl-$S(O)_2N$-, aryl-$S(O)_2N$-, heteroaryl-$S(O)_2N$-, carbocyclyl-$S(O)_2N$- or heterocyclyl-$S(O)_2N$- group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0041] As used herein, "ureido" means an alkyl-NCON-, aryl-NCON-, heteroaryl-NCON- , carbocyclyl-NCON- or heterocyclyl-NCON- group wherein the alkyl, carbocyclyl, aryl, heteroaryl or heterocyclyl group is as herein described.

[0042] As used herein, when two groups are indicated to be "linked" or "bonded" to form a "ring," it is to be understood that a bond is formed between the two groups and may involve replacement of a hydrogen atom on one or both groups with the bond, thereby forming a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring. The skilled artisan will recognize that such rings can and are readily formed by routine chemical reactions, and it is within the purview of the skilled artisan to both envision such rings and the methods of their formations. Preferred are rings having from 3-7 members, more preferably 5 or 6 members. As used herein the term "ring" or "rings" when formed by the combination of two radicals refers to heterocyclic, carbocyclic, aryl, or heteroaryl rings.

[0043] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically, the artisan recognizes that such structures are only a very small portion of a sample of such compound(s). Such compounds are clearly contemplated within the scope of this invention, though such resonance forms or tautomers are not represented herein.

[0044] The compounds provided herein may encompass various stereochemical forms. The compounds also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[0045] The term "administration" or "administering" refers to a method of giving a dosage of a compound or pharmaceutical composition to a vertebrate or invertebrate, including a mammal, a bird, a fish, or an amphibian, where the method is,

e.g., intrarespiratory, topical, oral, intravenous, intraperitoneal, intramuscular, buccal, rectal, sublingual. The preferred method of administration can vary depending on various factors, *e.g.*, the components of the pharmaceutical composition, the site of the disease, the disease involved, and the severity of the disease.

[0046] A "diagnostic" as used herein is a compound, method, system, or device that assists in the identification and characterization of a health or disease state. The diagnostic can be used in standard assays as is known in the art.

[0047] The term "mammal" is used in its usual biological sense. Thus, it specifically includes humans, cattle, horses, dogs, and cats, but also includes many other species.

[0048] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, *e.g.*, in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, *e.g.*, in Gilman *et al.* (Eds.) (2006); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 11th Ed., The McGraw-Hill Companies.

[0049] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds of the preferred embodiments and, which are not biologically or otherwise undesirable. In many cases, the compounds of the preferred embodiments are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid,

propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987.

[0050] "Solvate" refers to the compound formed by the interaction of a solvent and a Wnt pathway inhibitor, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0051] "Subject" as used herein, means a human or a non-human mammal, *e.g.*, a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, *e.g.*, a chicken, as well as any other vertebrate or invertebrate.

[0052] By "therapeutically effective amount" or "pharmaceutically effective amount" is typically one which is sufficient to achieve the desired effect and may vary according to the nature and severity of the disease condition, and the potency of the compound. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of an active disease. This amount can further depend upon the patient's height, weight, sex, age and medical history.

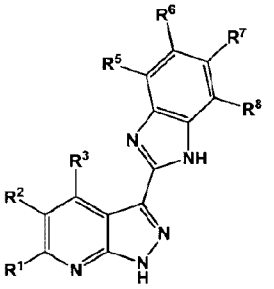
[0053] A therapeutic effect relieves, to some extent, one or more of the symptoms of the disease, and includes curing a disease. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease may exist even after a cure is obtained (such as extensive tissue damage).

[0054] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for therapeutic purposes. The term "therapeutic treatment" refers to administering treatment to a patient already suffering from a disease thus causing a therapeutically beneficial effect, such as ameliorating existing symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, postponing or preventing the further development of a disorder and/or reducing the severity of symptoms that will or are expected to develop.

Compounds

[0055] The compounds and compositions described herein can be used as anti-proliferative agents, e.g., anti-cancer and anti-angiogenesis agents, and as inhibitors of the Wnt signaling pathway, e.g., for treating diseases or disorders associated with aberrant Wnt signaling. In addition, the compounds can be used as inhibitors of one or more kinases, kinase receptors, or kinase complexes (e.g., VEGF, CHK-1, CLK, HIPK, Abl, JAK and/or CDK complexes). Such compounds and compositions are also useful for controlling cellular proliferation, differentiation, and/or apoptosis.

[0056] Some embodiments of the present invention include compounds, salts, pharmaceutically acceptable salts or pro-drugs thereof of formula (**Ia**):



Ia

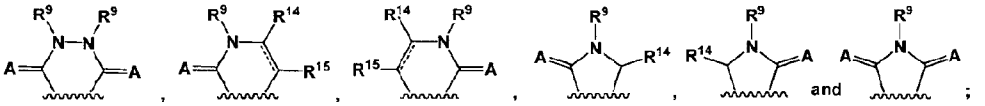
[0057] In some embodiments, R^1, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, -

$(C_{1-9}$ alkyl$)_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nC(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)R^9$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}$ alkyl$)_nCO_2R^9$ and $-(C_{1-9}$ alkyl$)_nC(=A)R^9$.

[0058] In some embodiments, if R^1 and R^3 are H then R^2 is independently selected from the group consisting of $-C(=O)NH(C_{1-9}$ alkyl$R^9)$, $-C(=S)NH(C_{1-9}$ alkyl$R^9)$, $-C(=O)N(R^{10})_2$, $-C(=S)N(R^{10})_2$, $-C(=NR^{11})N(R^9)_2$, $-(C_{1-9}$ alkyl$)_n$carbocyclylR^{13}, $-(C_{1-9}$ alkyl$)_n$heterocyclylR^{13}, $-(C_{1-9}$ alkyl$)_n$arylR^{13} and $-(C_{1-9}$ alkyl$)_n$heteroarylR^{13}.

[0059] In some embodiments, if R^1 and R^3 are not both H then R^2 is independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclylR^{12}, $-(C_{1-9}$ alkyl$)_n$heterocyclylR^{12}, $-(C_{1-9}$ alkyl$)_n$arylR^{12}, $-(C_{1-9}$ alkyl$)_n$heteroarylR^{12}, $-(C_{1-9}$ alkyl$)_nOR^9$, $-(C_{1-9}$ alkyl$)_nSR^9$, $-(C_{1-9}$ alkyl$)_nS(=O)R^{10}$, $-(C_{1-9}$ alkyl$)_nSO_2R^9$, $-(C_{1-9}$ alkyl$)_nN(R^9)SO_2R^9$, $-(C_{1-9}$ alkyl$)_nSO_2N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nC(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)R^9$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}$ alkyl$)_nCO_2R^9$ and $-(C_{1-9}$ alkyl$)_nC(=A)R^9$.

[0060] In some embodiments, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6 or R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond.

[0061] In some embodiments, each R^9 is independently selected from the group consisting of H, $-C_{1-9}$ alkyl, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclyl, $-(C_{1-9}$ alkyl$)_n$heterocyclyl, $-(C_{1-9}$ alkyl$)_n$aryl and $-(C_{1-9}$ alkyl$)_n$heteroaryl.

[0062] In some embodiments, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl.

[0063] In some embodiments, each R^{10} is independently selected from the group consisting of $-C_{1-9}$ alkyl, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclyl, $-(C_{1-9}$ alkyl$)_n$heterocyclyl, $-(C_{1-9}$ alkyl$)_n$aryl and $-(C_{1-9}$ alkyl$)_n$heteroaryl.

[0064] In some embodiments, each R^{11} is independently selected from the group consisting of $-OR^9$ and R^9.

[0065] In some embodiments, each R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[0066] In some embodiments, R^{13} is 1-5 substituents each selected from the group consisting of $-N(R^9)C(=A)N(R^9)_2$, $-C(=A)N(R^9)_2$, $-N(R^9)C(=A)R^9$, $-N(R^9)C(=A)CH(R^9)_2$, $-N(R^9)SO_2R^9$ and $-SO_2(C_{1-9}\text{ alkyl})$.

[0067] In some embodiments, R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[0068] In some embodiments, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine.

[0069] In some embodiments, each A is independently selected from O, S and NR^{11}.

[0070] In some embodiments, each n is 0 or 1.

[0071] In some embodiments, n is 0.

[0072] In some embodiments, n is 1.

[0073] In some embodiments, A is O.

[0074] In some embodiments, R^1 and R^3 are H and R^2 is selected from the group consisting of $-\text{carbocyclyl}R^{13}$, $-\text{heterocyclyl}R^{13}$, $-\text{aryl}R^{13}$ and $-\text{heteroaryl}R^{13}$.

[0075] In some embodiments, R^2 is $-\text{heteroaryl}R^{13}$.

[0076] In some embodiments, the heteroaryl is pyridine.

[0077] In some embodiments, R^{13} is selected from the group consisting of -$NHC(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$NHC(=O)CH(R^9)_2$, -$NHC(=O)R^9$, -$NHC(=O)CH(R^9)_2$ and -$NHSO_2R^9$.

[0078] In some embodiments, R^9 is selected from the group consisting of H, -C_{1-4} alkyl, carbocyclyl and -heterocyclyl.

[0079] In some embodiments, R^6, R^7 and R^8 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$NHC(=O)CH(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$.

[0080] In some embodiments, R^5 is selected from the group consisting of -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

[0081] In some embodiments, R^{12} is selected from the group consisting of H and halide.

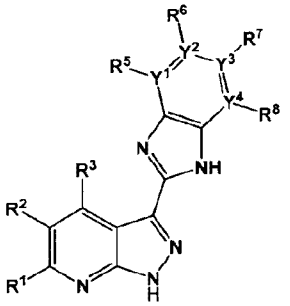
[0082] In some embodiments, the heteroaryl is pyridine.

[0083] In some embodiments, R^5 is selected from the group consisting of H, -$C(=O)N(R^9)_2$ and -CN.

[0084] In some embodiments, R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[0085] Pharmaceutically acceptable salts of all of the above embodiments are also contemplated.

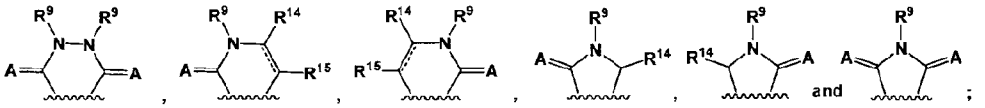
[0086] Some embodiments of the present invention include compounds, salts, pharmaceutically acceptable salts or pro-drugs thereof of formula **(Ib)**:



Ib

[0087] In some embodiments, R^1, R^2, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclylR^{12}, $-(C_{1-9}$ alkyl$)_n$heterocyclylR^{12}, $-(C_{1-9}$ alkyl$)_n$arylR^{12}, $-(C_{1-9}$ alkyl$)_n$heteroarylR^{12}, $-(C_{1-9}$ alkyl$)_nOR^9$, $-(C_{1-9}$ alkyl$)_nSR^9$, $-(C_{1-9}$ alkyl$)_nS(=O)R^{10}$, $-(C_{1-9}$ alkyl$)_nSO_2R^9$, $-(C_{1-9}$ alkyl$)_nN(R^9)SO_2R^9$, $-(C_{1-9}$ alkyl$)_nSO_2N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nC(=A)N(R^9)_2$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)R^9$, $-(C_{1-9}$ alkyl$)_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}$ alkyl$)_nCO_2R^9$ and $-(C_{1-9}$ alkyl$)_nC(=A)R^9$.

[0088] In some embodiments, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond.

[0089] In some embodiments, each R^9 is independently selected from the group consisting of H, C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclyl, $-(C_{1-9}$ alkyl$)_n$heterocyclyl, $-(C_{1-9}$ alkyl$)_n$aryl and $-(C_{1-9}$ alkyl$)_n$heteroaryl.

[0090] In some embodiments, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl.

[0091] In some embodiments, each R^{10} is independently selected from the group consisting of C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}$ alkyl$)_n$carbocyclyl, $-(C_{1-9}$ alkyl$)_n$heterocyclyl, $-(C_{1-9}$ alkyl$)_n$aryl and $-(C_{1-9}$ alkyl$)_n$heteroaryl.

[0092] In some embodiments, each R^{11} is independently selected from the group consisting of $-OR^9$ and R^9.

[0093] In some embodiments, each R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[0094] In some embodiments, R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, -CN, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[0095] In some embodiments, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine.

[0096] In some embodiments, each A is independently selected from O, S and NR^{11}.

[0097] In some embodiments, Y^1, Y^2, Y^3 and Y^4 are independently selected from the group consisting of carbon and nitrogen with the proviso that at least one of Y^1, Y^2, Y^3 and Y^4 are nitrogen.

[0098] In some embodiments, Y^1 is nitrogen and R^5 is absent.

[0099] In some embodiments, Y^2 is nitrogen and R^6 is absent.

[00100] In some embodiments, Y^3 is nitrogen and R^7 is absent.

[00101] In some embodiments, Y^4 is nitrogen and R^8 is absent.

[00102] In some embodiments, each n is 0 or 1.

[00103] In some embodiments, n is 0.

[00104] In some embodiments, n is 1.

[00105] In some embodiments, A is O.

[00106] In some embodiments, R^1 and R^3 are H and R^2 is selected from the group consisting of -carbocyclylR^{12}, -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

[00107] In some embodiments, R^2 is -heteroarylR^{12}.

[00108] In some embodiments, the heteroaryl is pyridine.

[00109] In some embodiments, R^{12} is selected from the group consisting of -$NHC(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$NHC(=O)R^9$, -$NHC(=O)CH(R^9)_2$ and -$NHSO_2R^9$.

[00110] In some embodiments, R^9 is selected from the group consisting of H, -C_{1-4} alkyl, carbocyclyl and -heterocyclyl.

[00111] In some embodiments, Y^1, Y^2 and Y^4 are carbon and Y^3 is nitrogen and R^7 is absent.

[00112] In some embodiments, R^6 and R^8 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$.

[00113] In some embodiments, R^5 is selected from the group consisting of -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

[00114] In some embodiments, R^{12} is selected from the group consisting of H and halide.

[00115] In some embodiments, the heteroaryl is pyridine.

[00116] In some embodiments, R^5 is selected from the group consisting of H, -$C(=O)N(R^9)_2$ and -CN.

[00117] In some embodiments, R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[00118] In some embodiments, Y^1, Y^2 and Y^3 are carbon and Y^4 is nitrogen and R^8 is absent.

[00119] In some embodiments, R^6 and R^7 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$.

[00120] In some embodiments, R^5 is selected from the group consisting of -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

[00121] In some embodiments, R^{12} is selected from the group consisting of H and halide.

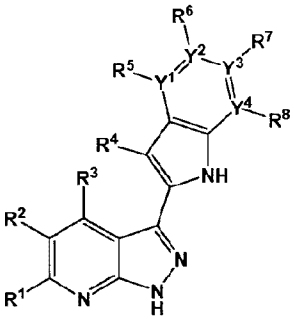
[00122] In some embodiments, the heteroaryl is pyridine.

[00123] In some embodiments, R^5 is selected from the group consisting of H, -C(=O)N(R^9)$_2$ and -CN.

[00124] In some embodiments, R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[00125] Pharmaceutically acceptable salts of the above embodiments are also contemplated.

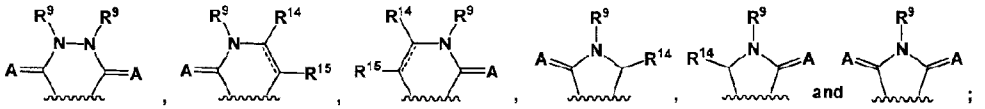
[00126] Some embodiments of the present invention include compounds, salts, pharmaceutically acceptable salts or pro-drugs thereof of formula (**Ic**):



Ic

[00127] In some embodiments, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, -CF_3, -(C_{1-9} alkyl)$_n$carbocyclylR^{12}, -(C_{1-9} alkyl)$_n$heterocyclylR^{12}, -(C_{1-9} alkyl)$_n$arylR^{12}, -(C_{1-9} alkyl)$_n$heteroarylR^{12}, -(C_{1-9} alkyl)$_n$OR^9, -(C_{1-9} alkyl)$_n$SR^9, -(C_{1-9} alkyl)$_n$S(=O)R^{10}, -(C_{1-9} alkyl)$_n$SO_2R^9, -(C_{1-9} alkyl)$_n$N(R^9)SO_2R^9, -(C_{1-9} alkyl)$_n$SO_2N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)N(R^9)$_2$, -(C_{1-9} alkyl)$_n$C(=A)N(R^9)$_2$, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)R^9, -(C_{1-9} alkyl)$_n$N(R^9)C(=A)CH(R^9)$_2$, -NO_2, -CN, -(C_{1-9} alkyl)$_n$CO_2R^9 and -(C_{1-9} alkyl)$_n$C(=A)R^9.

[00128] In some embodiments, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



and ;

wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond.

[00129] In some embodiments, each R^9 is independently selected from the group consisting of H, C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n$carbocyclyl, $-(C_{1-9}\text{ alkyl})_n$heterocyclyl, $-(C_{1-9}\text{ alkyl})_n$aryl and $-(C_{1-9}\text{ alkyl})_n$heteroaryl.

[00130] In some embodiments, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl.

[00131] In some embodiments, each R^{10} is independently selected from the group consisting of C_{1-9} alkyl, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n$carbocyclyl, $-(C_{1-9}\text{ alkyl})_n$heterocyclyl, $-(C_{1-9}\text{ alkyl})_n$aryl and $-(C_{1-9}\text{ alkyl})_n$heteroaryl.

[00132] In some embodiments, each R^{11} is independently selected from the group consisting of $-OR^9$ and R^9.

[00133] In some embodiments, each R^{12} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[00134] In some embodiments, R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n$carbocyclyl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$heterocyclyl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$aryl$R^{12}$, $-(C_{1-9}\text{ alkyl})_n$heteroaryl$R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$.

[00135] In some embodiments, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine.

[00136] In some embodiments, each A is independently selected from O, S and NR^{11}.

[00137] In some embodiments, Y^1, Y^2, Y^3 and Y^4 are independently selected from the group consisting of carbon and nitrogen.

[00138] In some embodiments, Y^1 is nitrogen and R^5 is absent.

[00139] In some embodiments, Y^2 is nitrogen and R^6 is absent.

[00140] In some embodiments, Y^3 is nitrogen and R^7 is absent.

[00141] In some embodiments, Y^4 is nitrogen and R^8 is absent.

[00142] In some embodiments, each n is 0 or 1.

[00143] In some embodiments, n is 0.

[00144] In some embodiments, n is 1.

[00145] In some embodiments, A is O.

[00146] In some embodiments, R^1 and R^3 are H and R^2 is selected from the group consisting of -carbocyclylR^{12}, -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

[00147] In some embodiments, R^2 is -heteroarylR^{12}.

[00148] In some embodiments, the heteroaryl is pyridine.

[00149] In some embodiments, R^{12} is selected from the group consisting of -$NHC(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$NHC(=O)R^9$, -$NHC(=O)CH(R^9)_2$ and -$NHSO_2R^9$.

[00150] In some embodiments, R^9 is selected from the group consisting of H, -C_{1-4} alkyl, carbocyclyl and -heterocyclyl.

[00151] In some embodiments, Y^1, Y^2, Y^3 and Y^4 are carbon, R^4, R^6, R^7 and R^8 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[00152] In some embodiments, Y^1, Y^2, Y^3 and Y^4 are carbon, R^4, R^5, R^6 and R^7 are H and R^8 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group

consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[00153] In some embodiments, Y^2, Y^3 and Y^4 are carbon, Y^1 is nitrogen, R^5 is absent, R^4, R^6 and R^7 are H and R^8 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

[00154] In some embodiments, Y^1, Y^3 and Y^4 are carbon, Y^2 is nitrogen, R^6 is absent, R^4, R^5 and R^7 are H and R^8 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

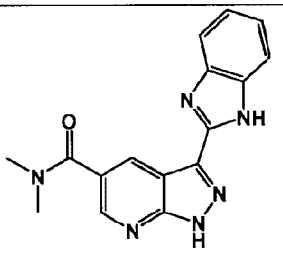
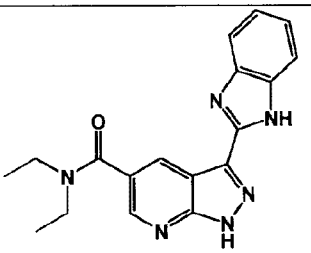
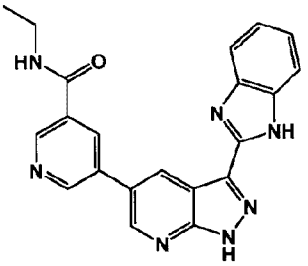
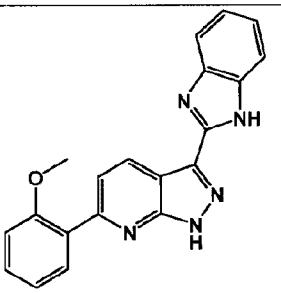
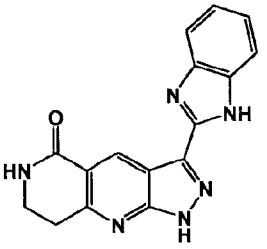
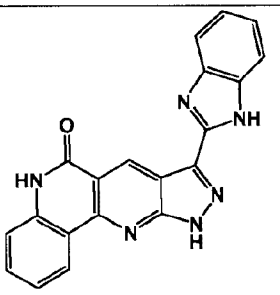
[00155] In some embodiments, Y^1, Y^2 and Y^4 are carbon, Y^3 is nitrogen, R^7 is absent, R^4, R^6 and R^8 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

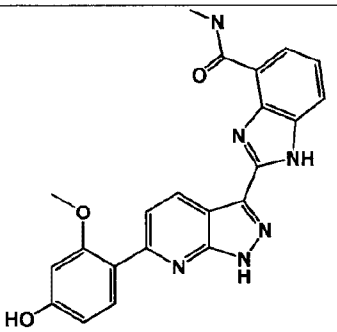
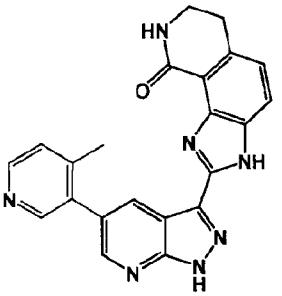
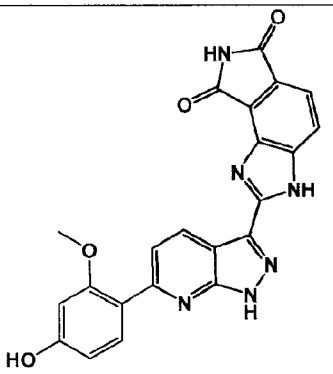
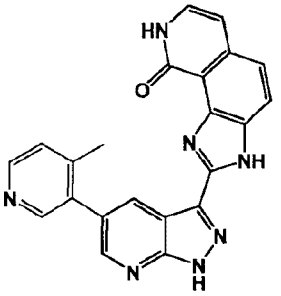
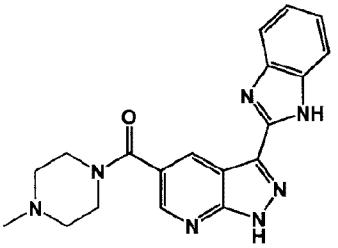
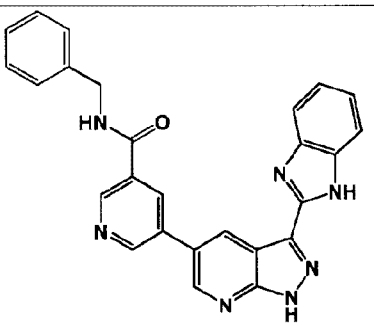
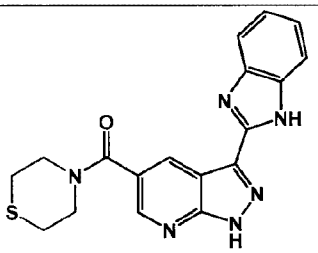
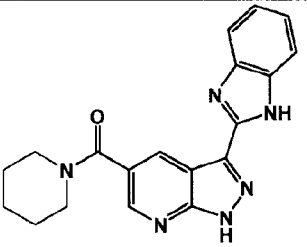
[00156] In some embodiments, Y^1, Y^2 and Y^3 are carbon, Y^4 is nitrogen, R^8 is absent, R^4, R^6 and R^7 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -$N(R^9)C(=O)N(R^9)_2$, -$C(=O)N(R^9)_2$, -$N(R^9)C(=O)R^9$, -$N(R^9)C(=O)CH(R^9)_2$, -CN, -CO_2R^9 and -$C(=O)R^9$, the heteroaryl is a pyridine, R^{12} is selected from the group consisting of H and halide, and R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

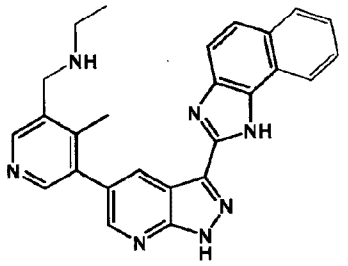
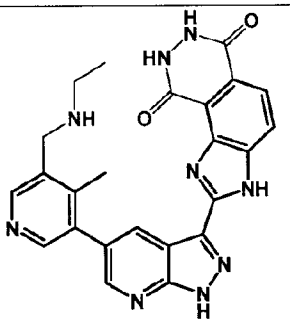
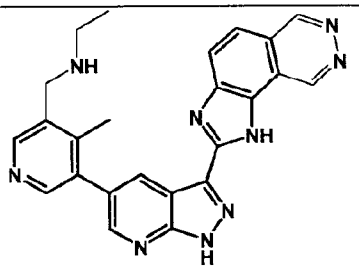
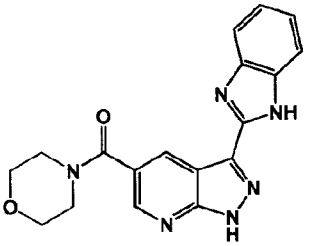
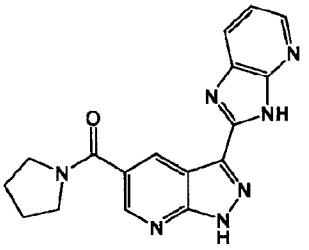
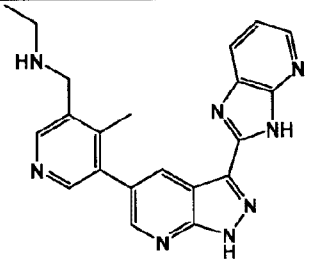
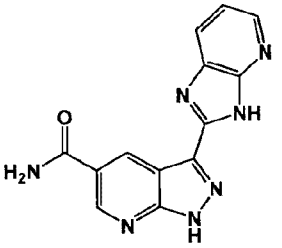
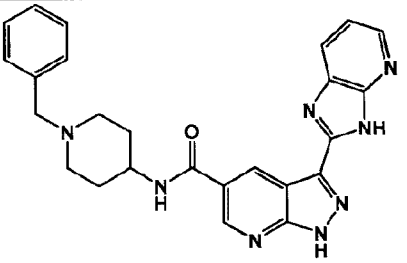
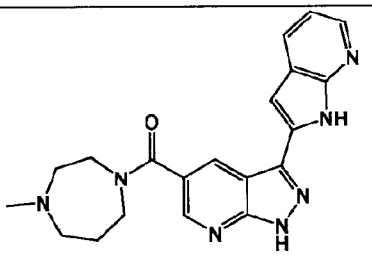
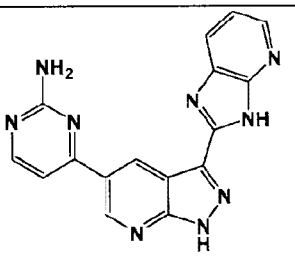
[00157] Pharmaceutically acceptable salts of the above embodiments are also contemplated.

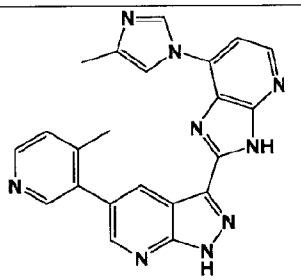
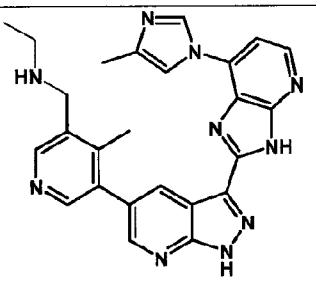
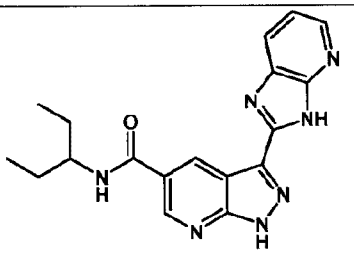
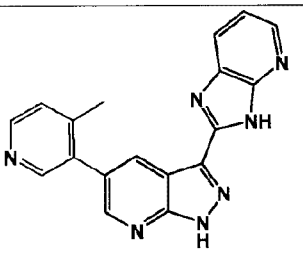
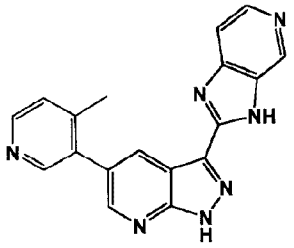
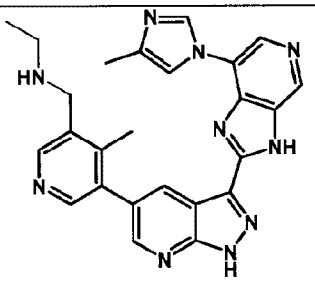
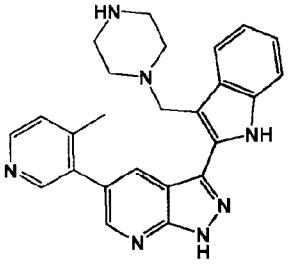
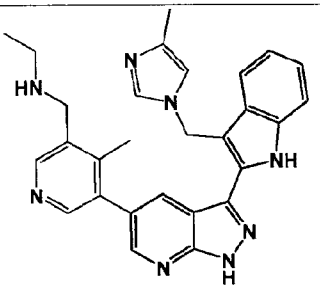
[00158] Illustrative compounds of Formula (**Ia**), (**Ib**) and (**Ic**) are shown in Table 1.

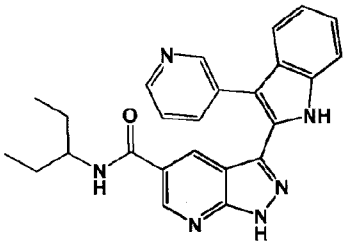
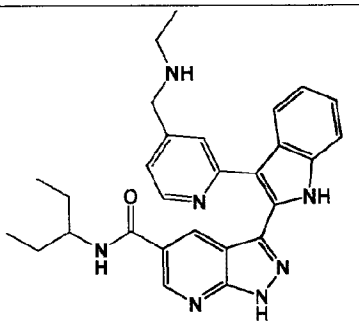
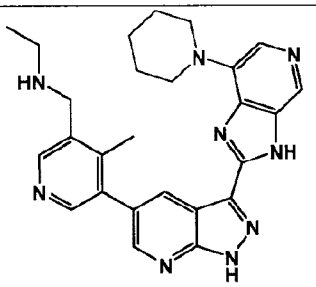
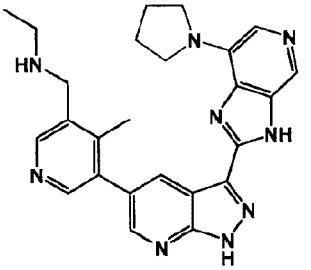
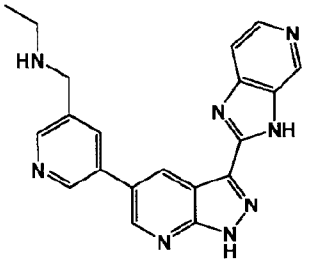
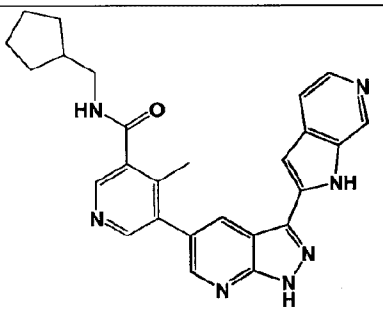
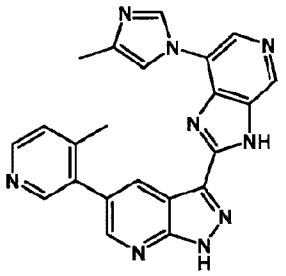
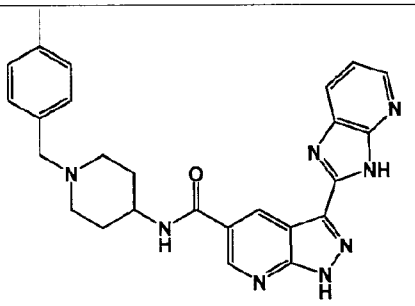
Table 1.

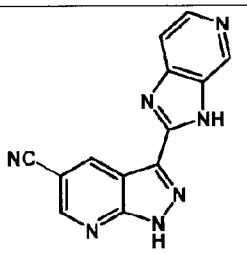
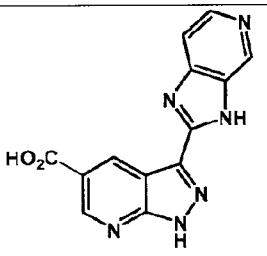
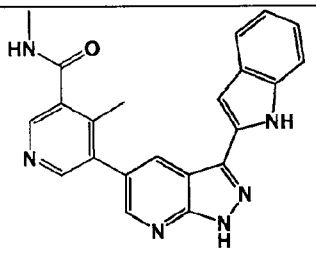
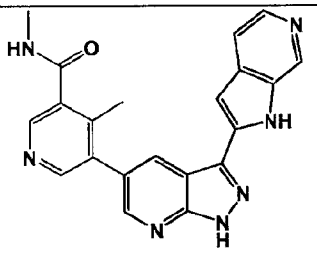
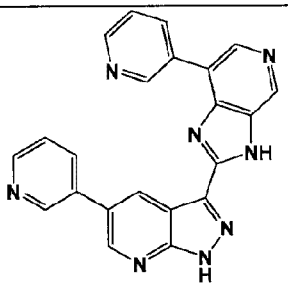
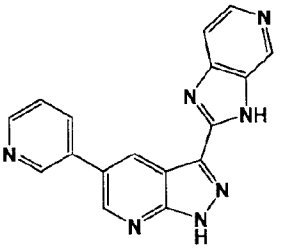
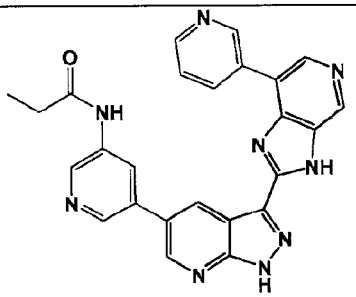
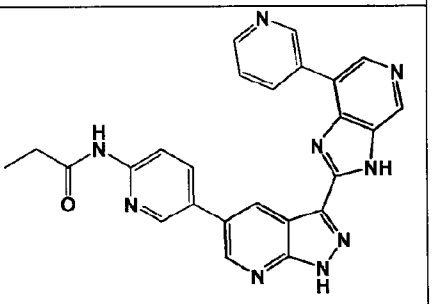
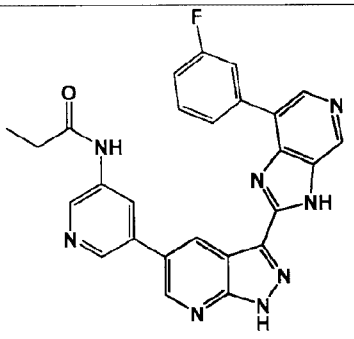
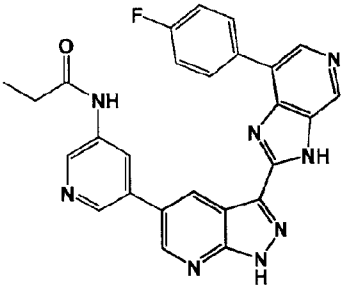
1		2	
3		4	
5		6	

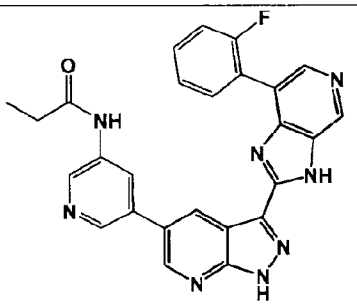
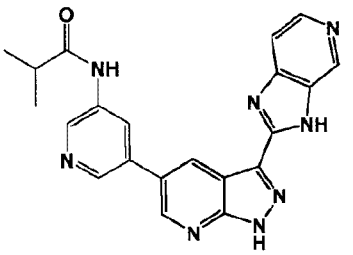
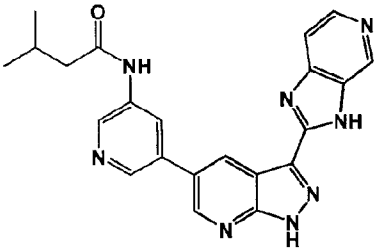
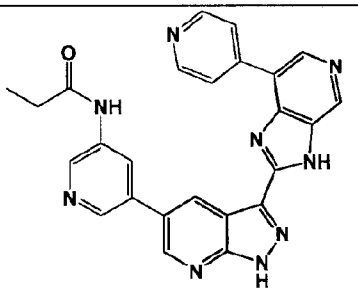
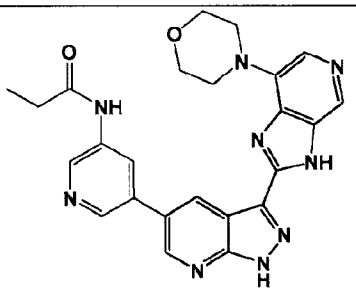
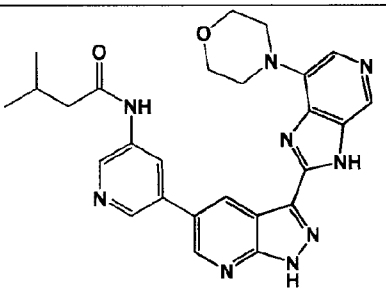
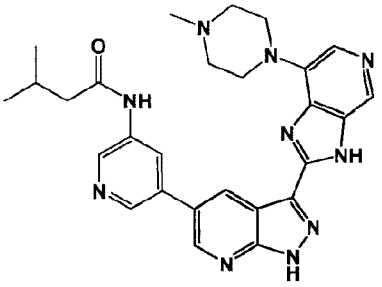
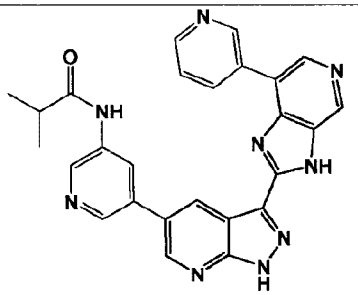
7		8	
9		10	
11		12	
13		14	

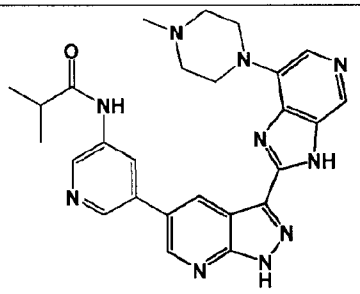
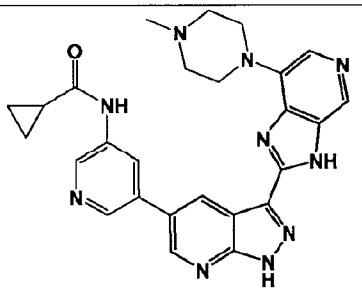
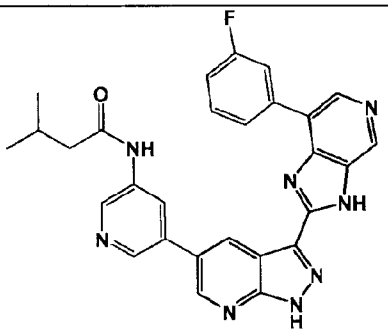
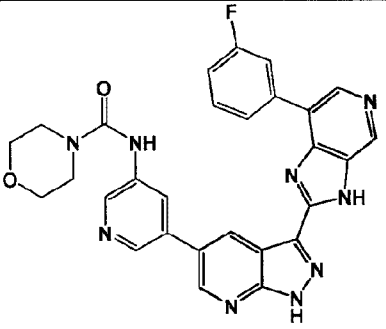
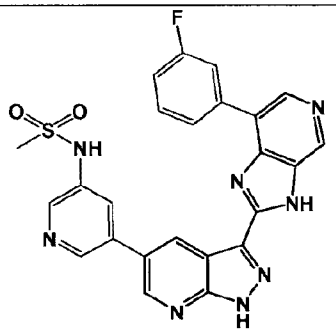
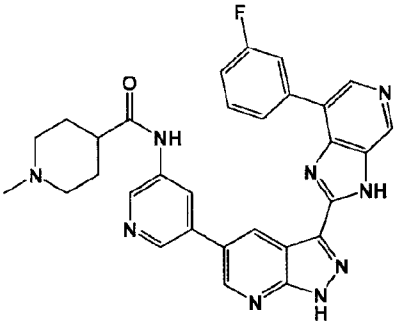
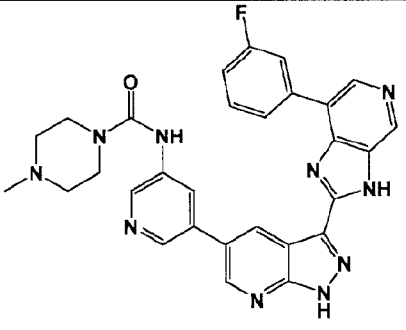
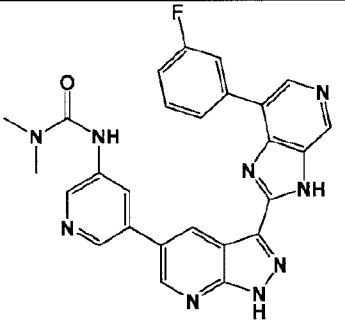
15		16	
17		18	
19		20	
21		22	
23		24	

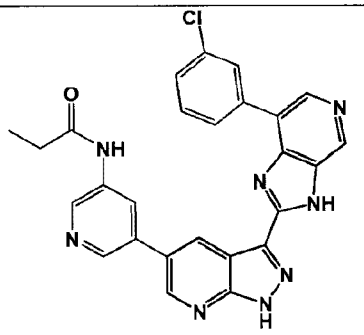
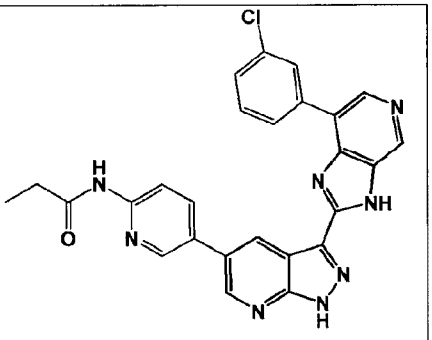
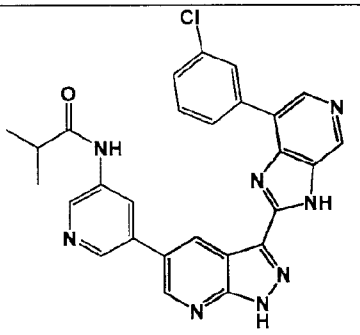
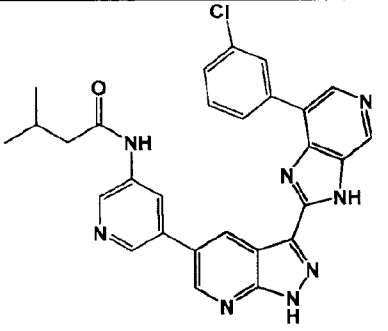
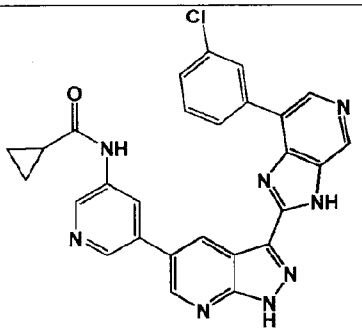
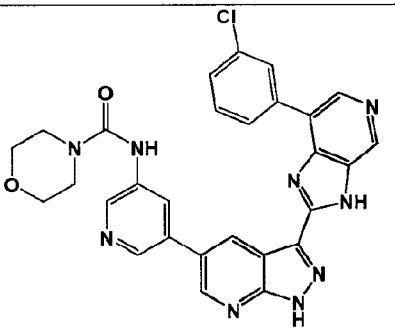
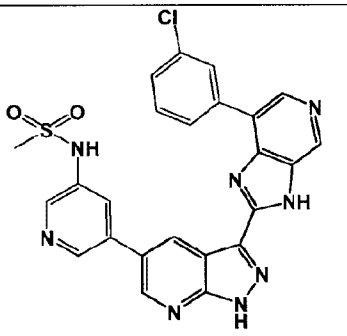
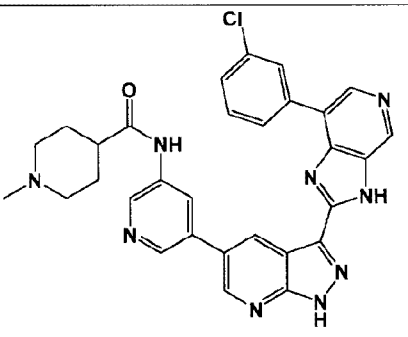
25		26	
27		28	
29		30	
31		32	

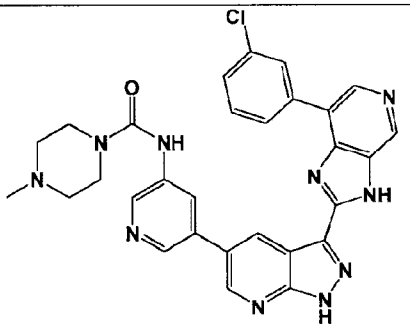
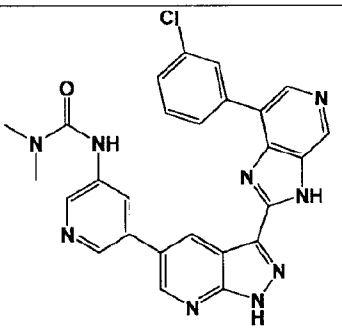
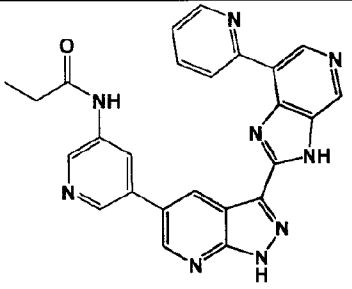
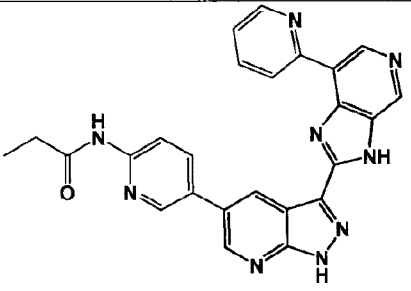
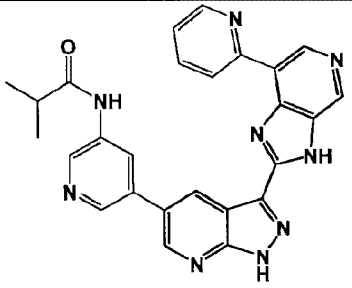
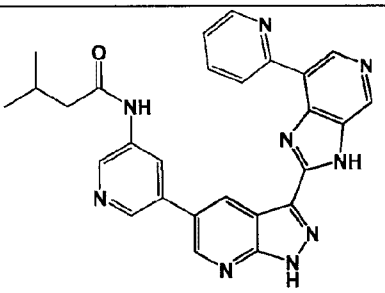
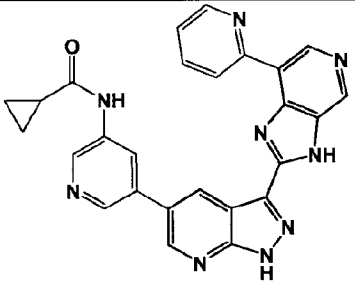
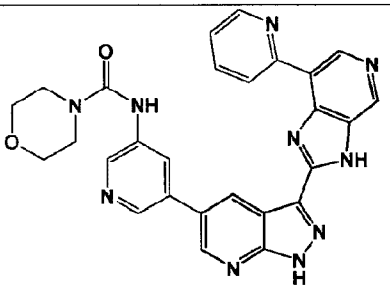
33		34	
35		36	
37		38	
39		40	

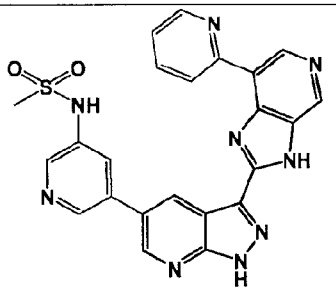
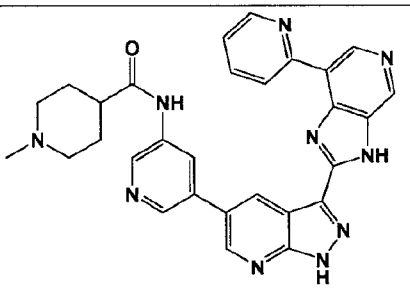
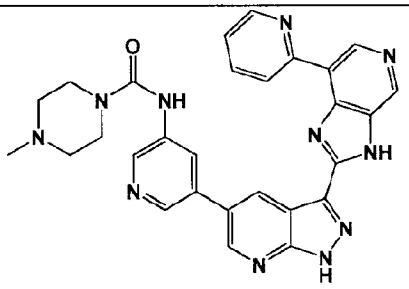
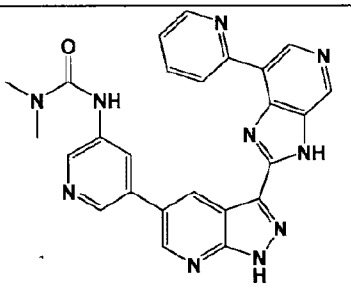
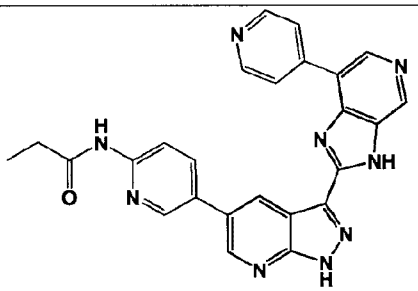
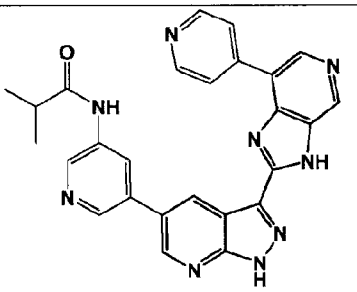
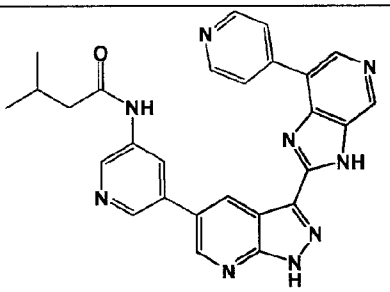
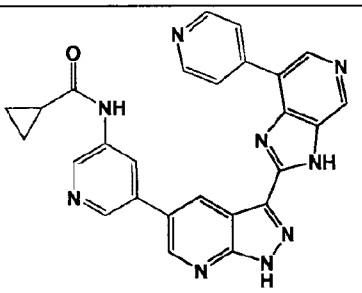
41		42	
43		44	
45		46	
47		48	
49		50	

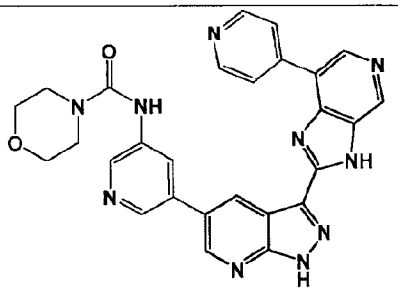
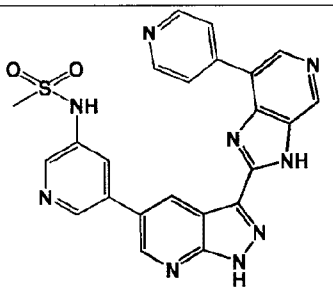
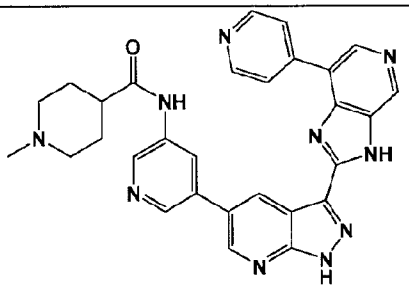
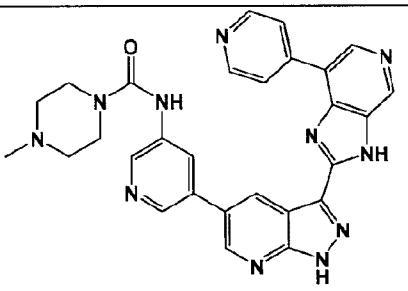
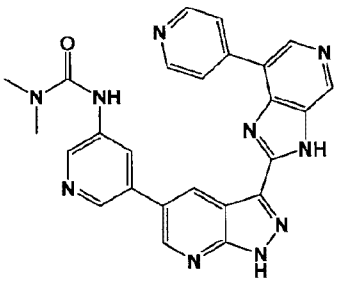
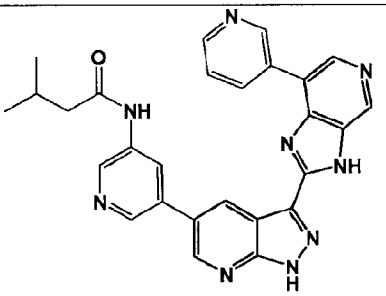
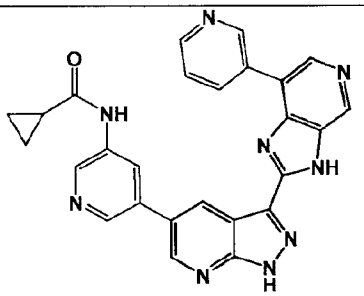
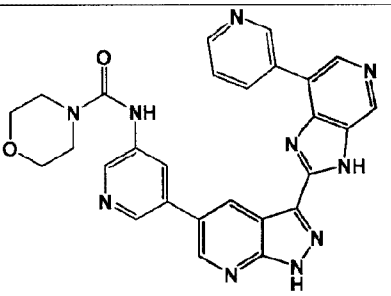
51		52	
53		54	
55		56	
57		58	

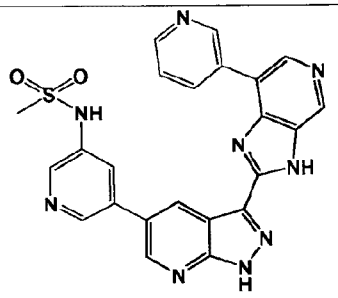
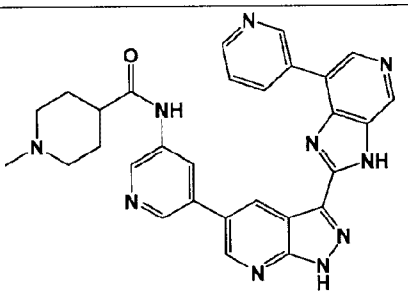
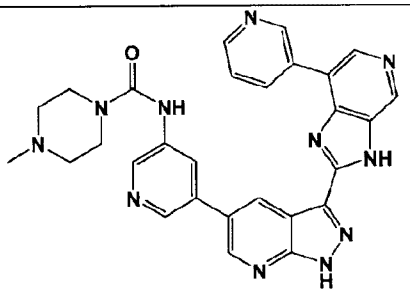
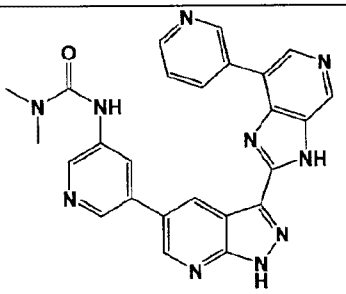
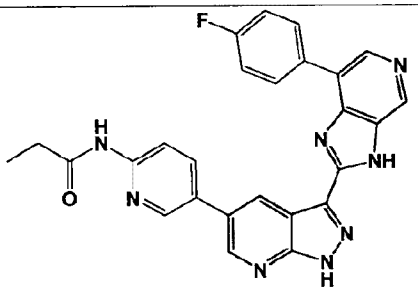
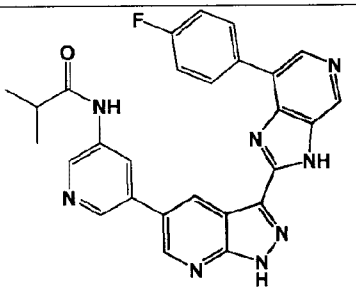
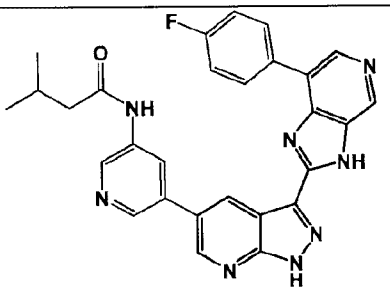
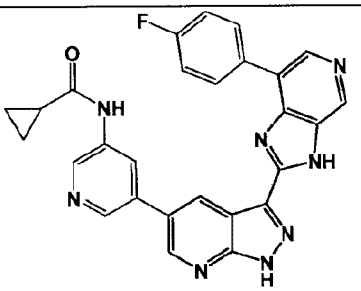
59		60	
61		62	
63		64	
65		66	

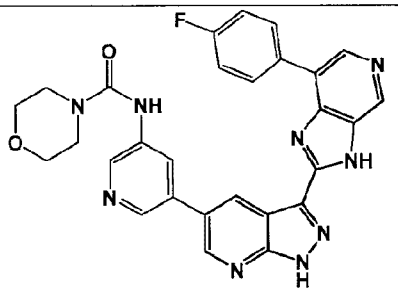
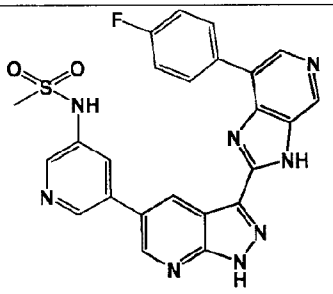
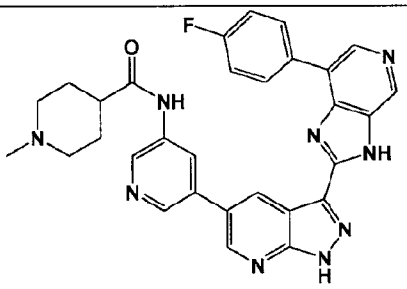
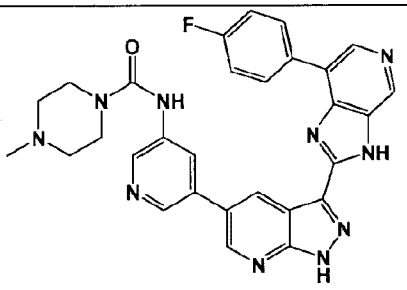
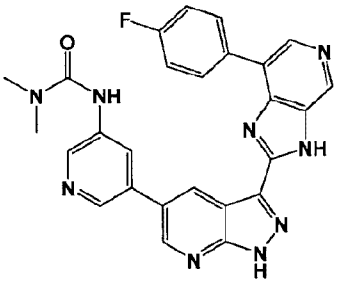
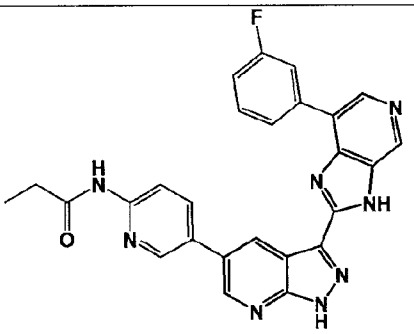
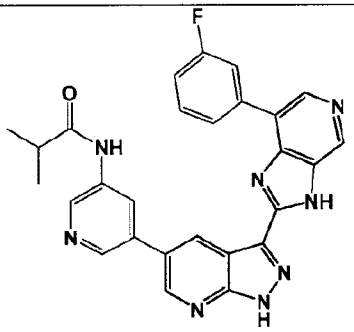
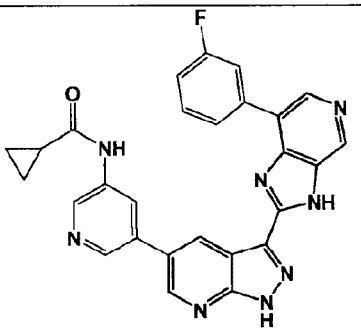
67		68	
69		70	
71		72	
73		74	

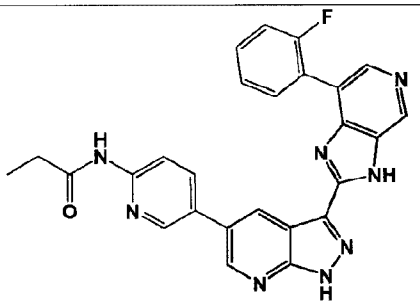
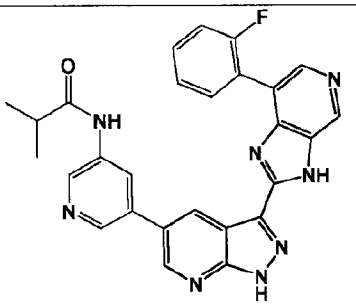
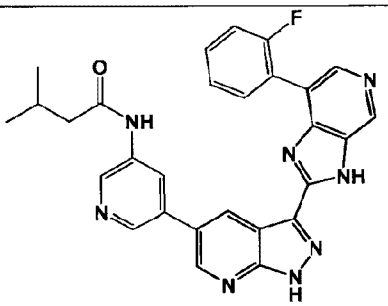
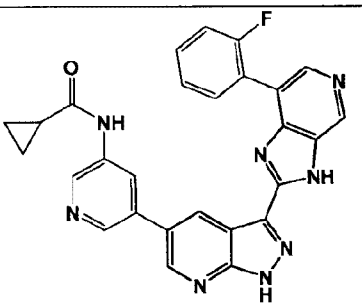
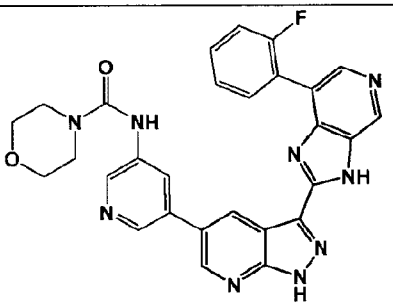
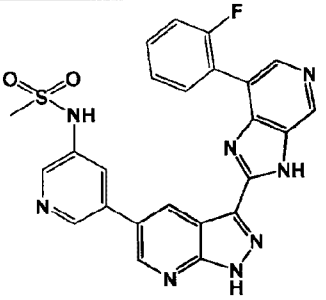
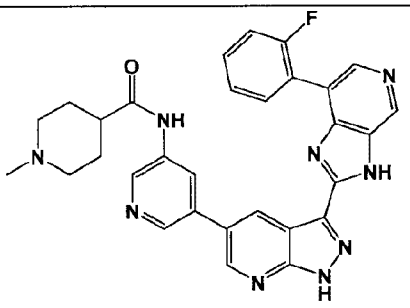
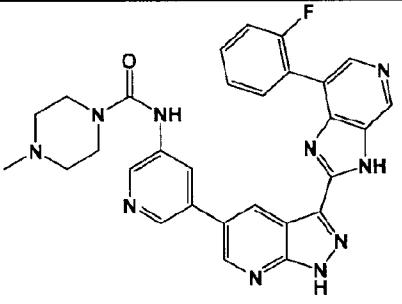
75		76	
77		78	
79		80	
81		82	

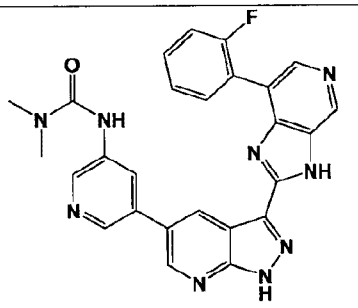
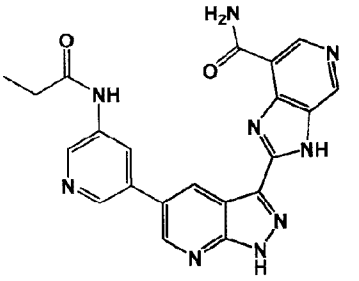
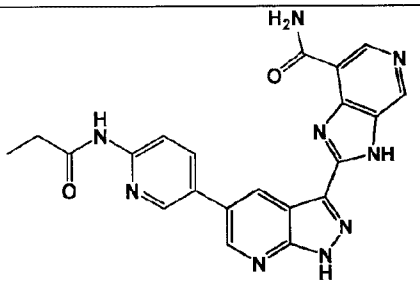
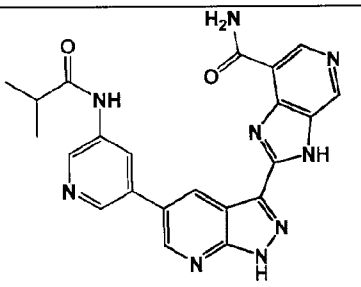
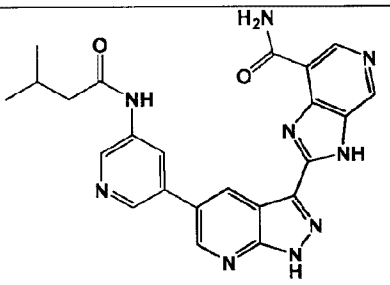
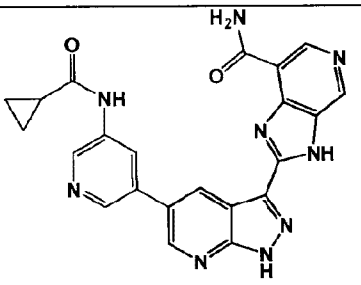
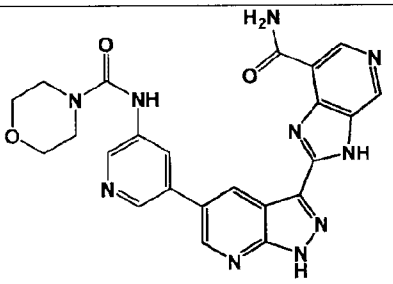
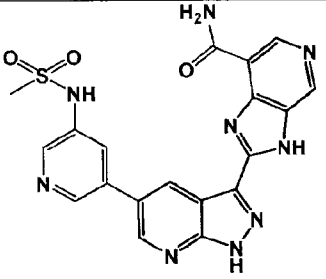
83		84	
85		86	
87		88	
89		90	

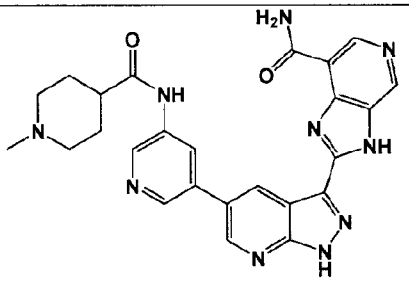
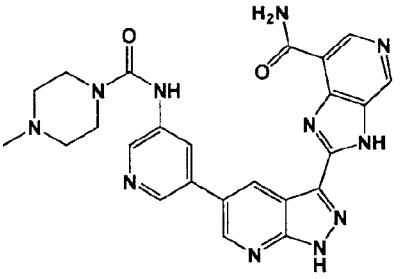
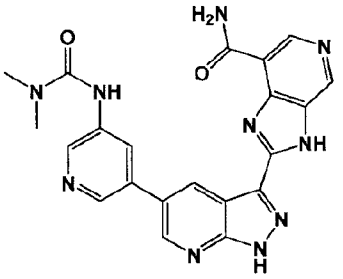
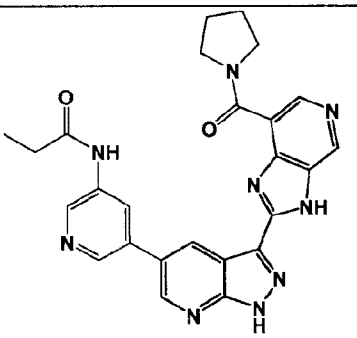
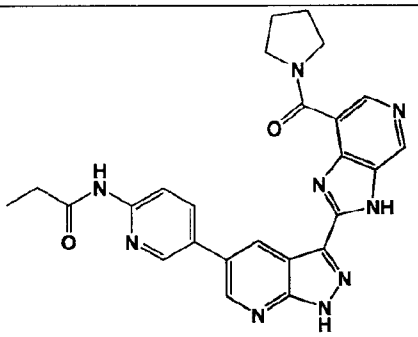
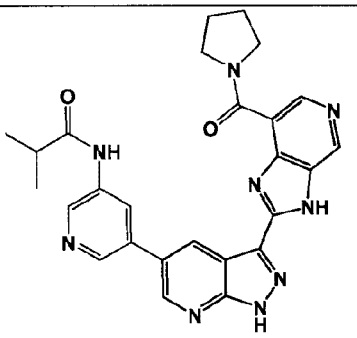
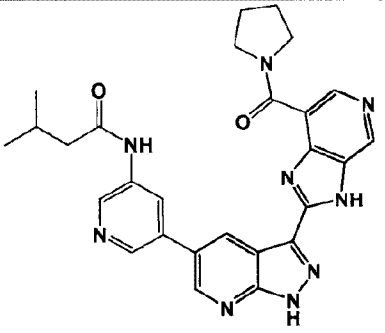
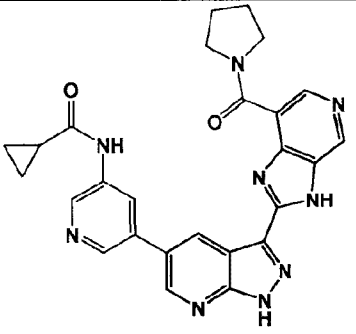
91		92	
93		94	
95		96	
97		98	

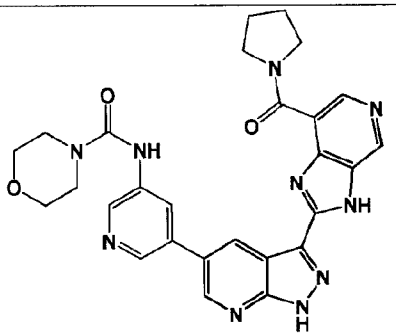
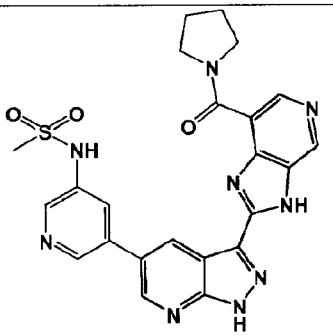
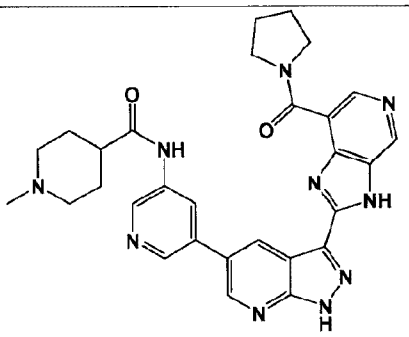
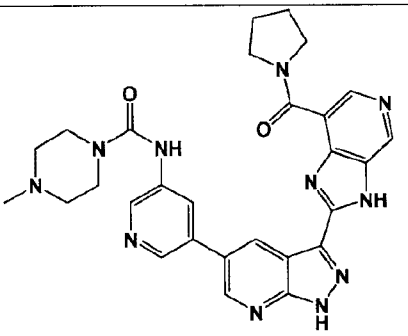
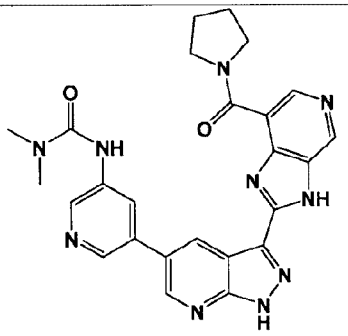
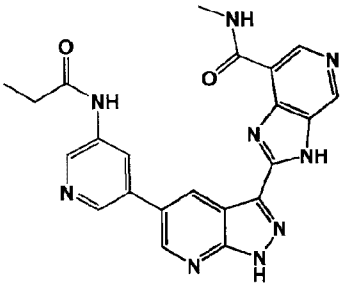
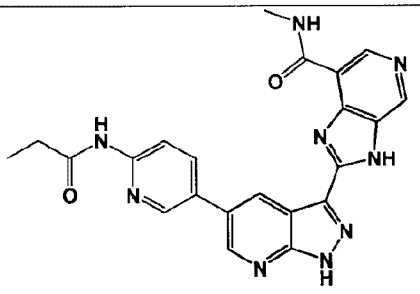
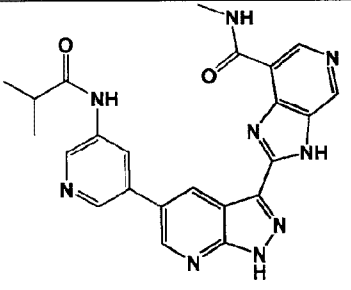
99		100	
101		102	
103		104	
105		106	

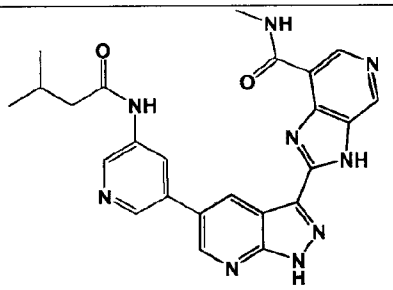
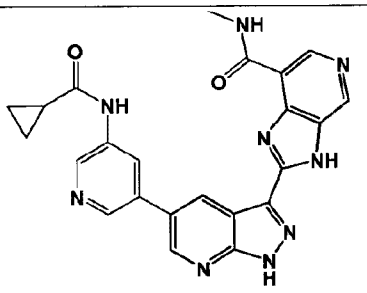
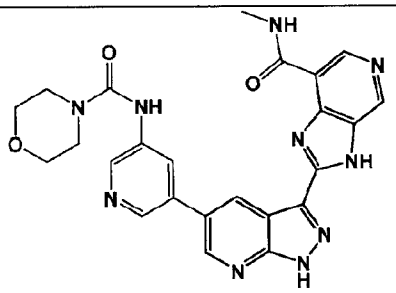
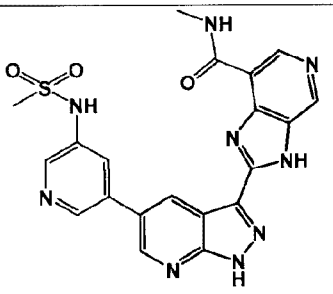
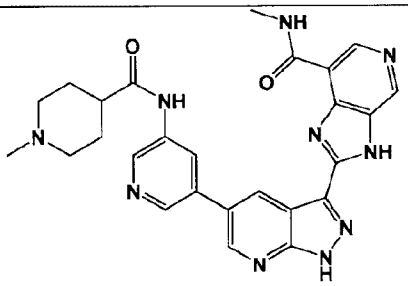
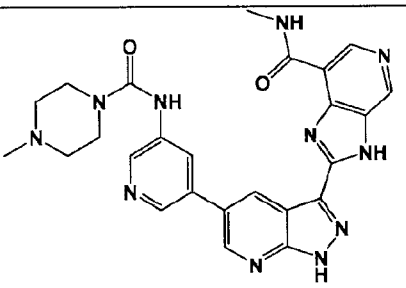
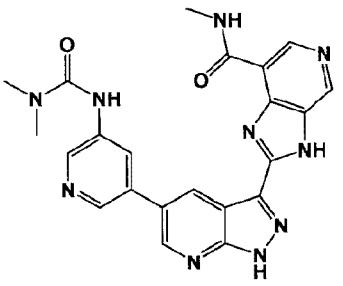
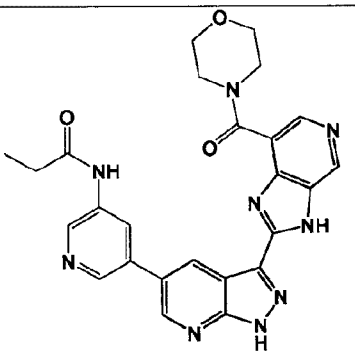
107		108	
109		110	
111		112	
113		114	

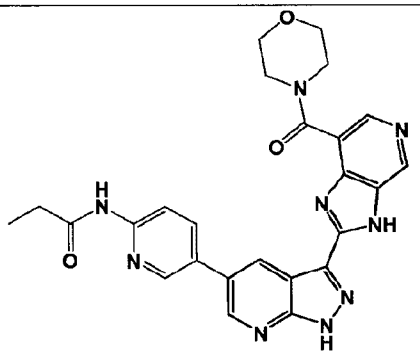
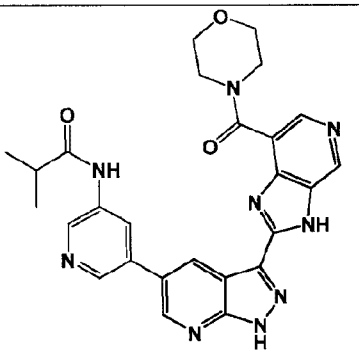
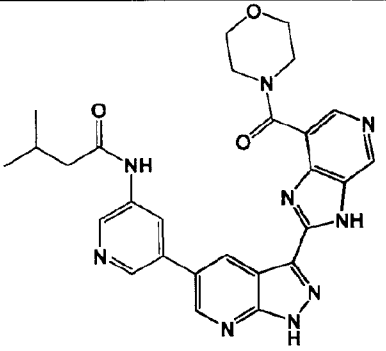
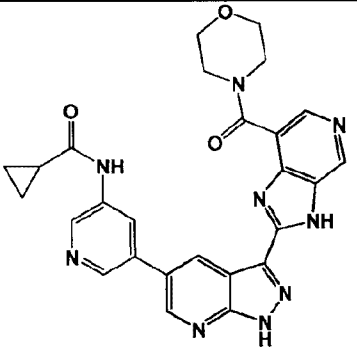
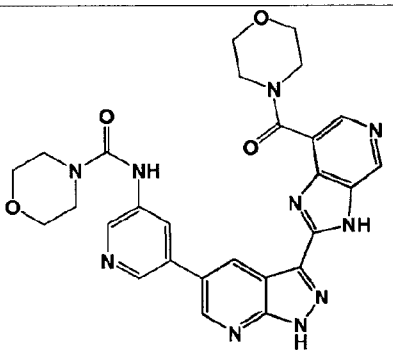
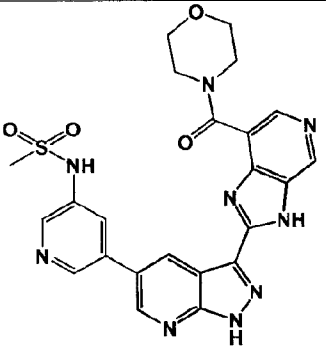
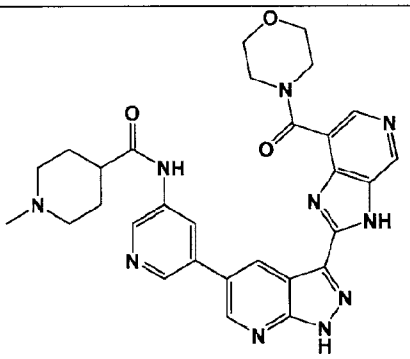
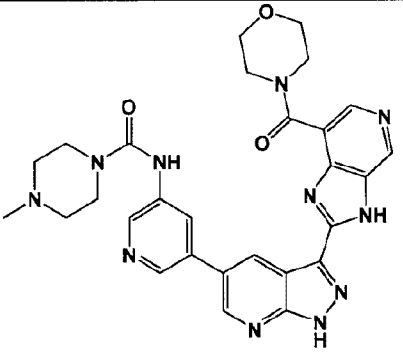
115		116	
117		118	
119		120	
121		122	

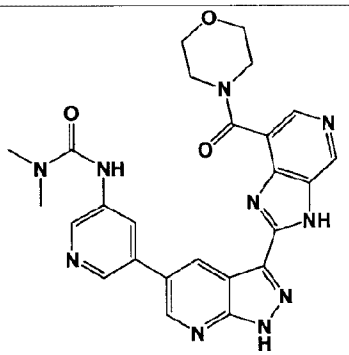
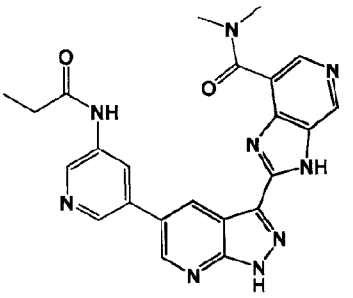
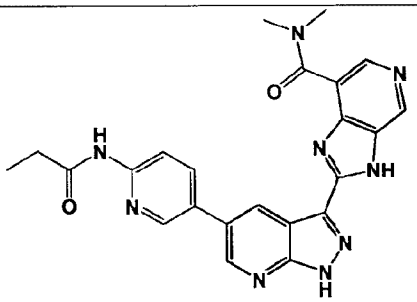
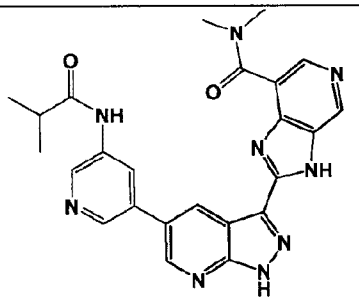
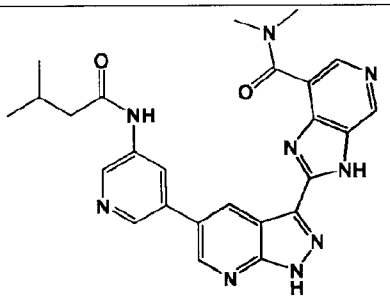
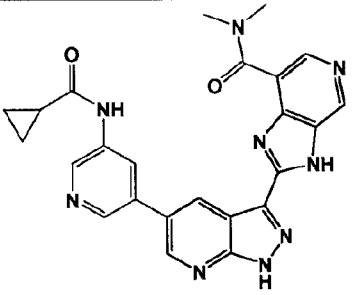
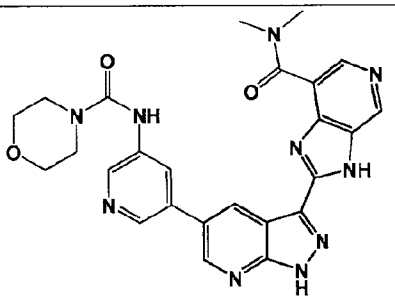
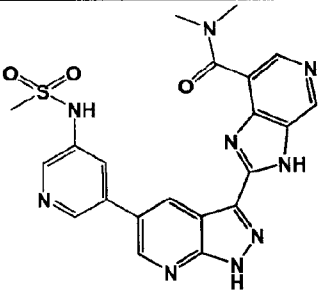
123		124	
125		126	
127		128	
129		130	

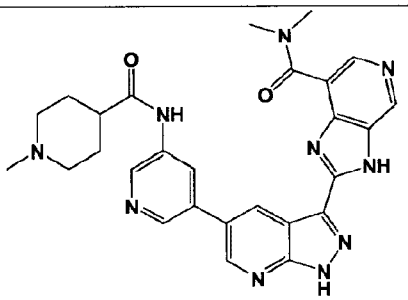
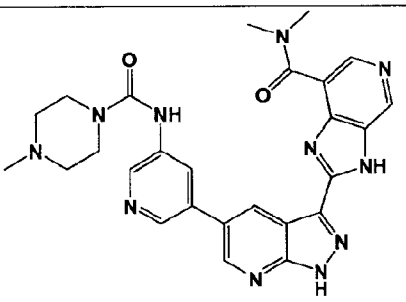
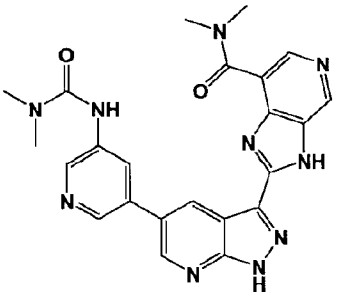
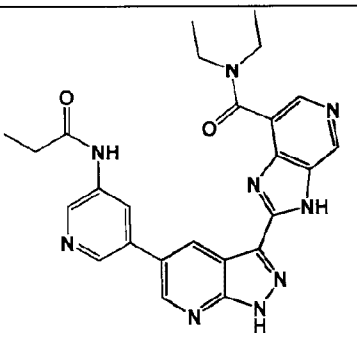
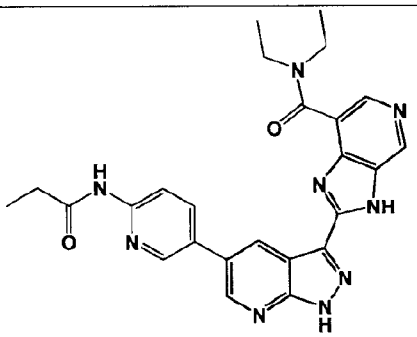
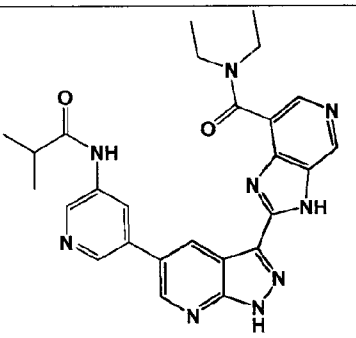
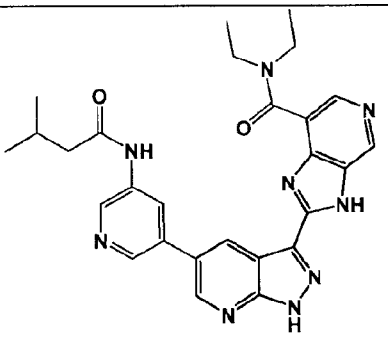
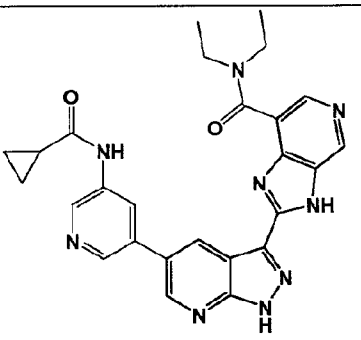
131		132	
133		134	
135		136	
137		138	

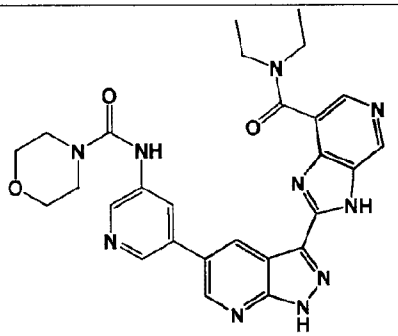
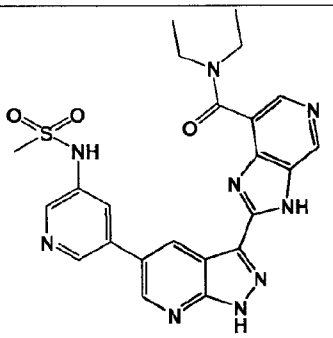
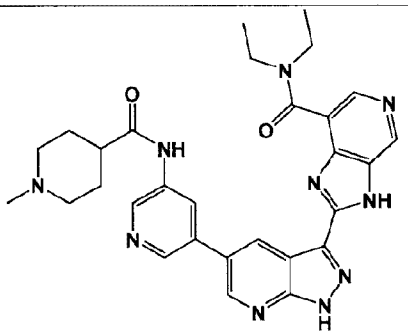
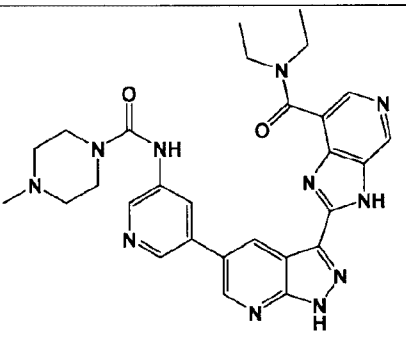
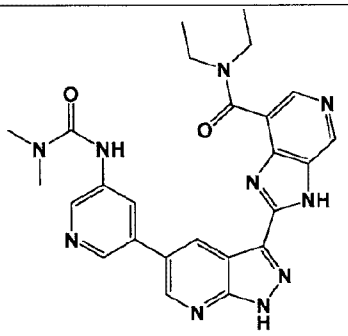
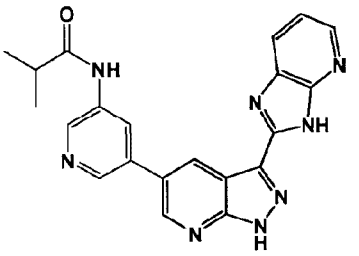
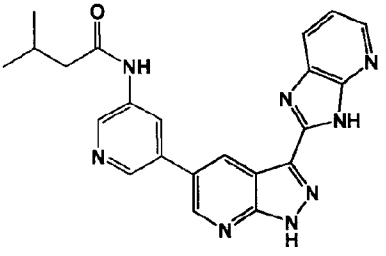
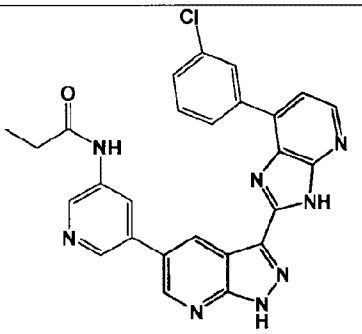
139		140	
141		142	
143		144	
145		146	

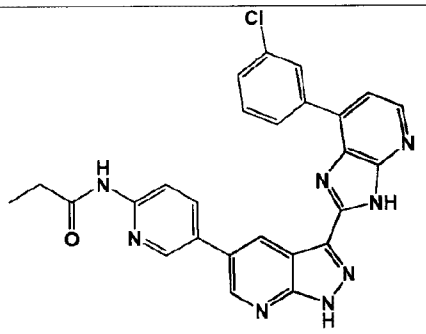
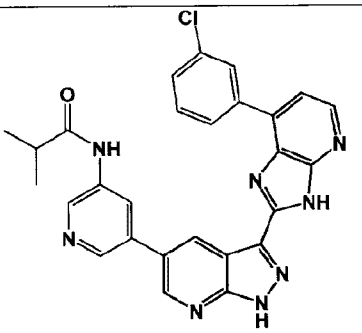
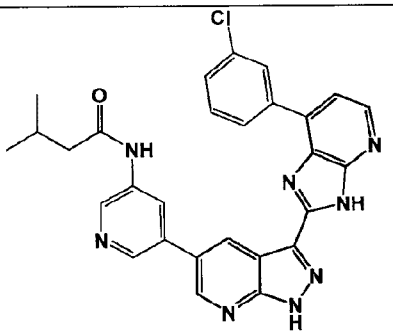
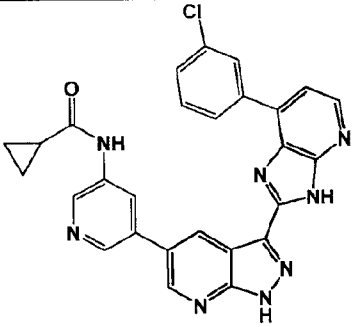
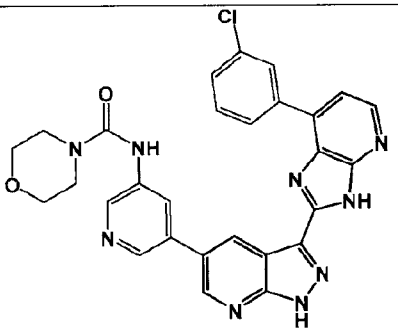
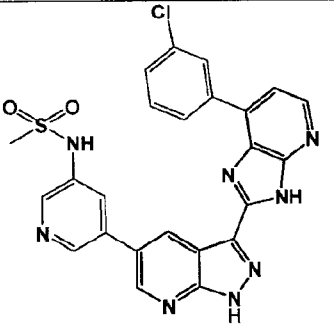
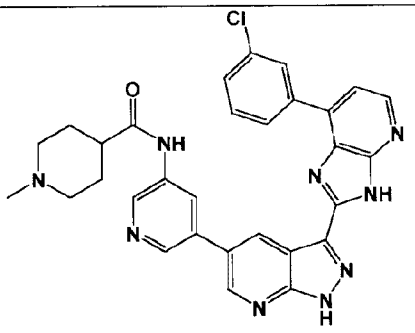
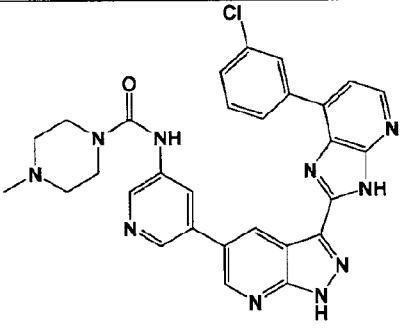
147		148	
149		150	
151		152	
153		154	

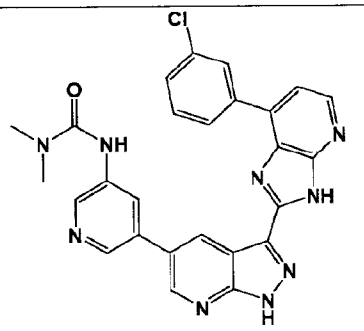
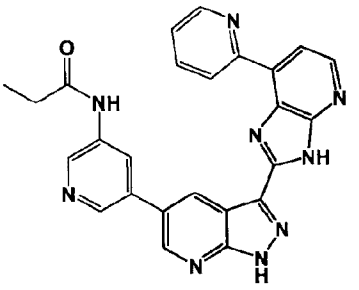
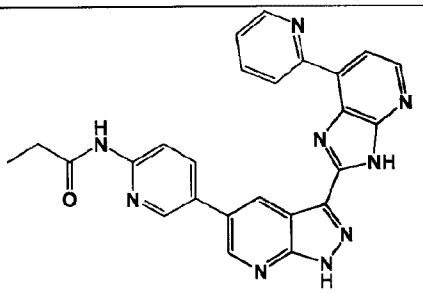
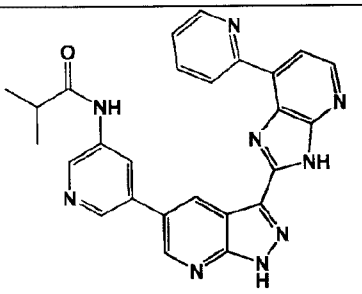
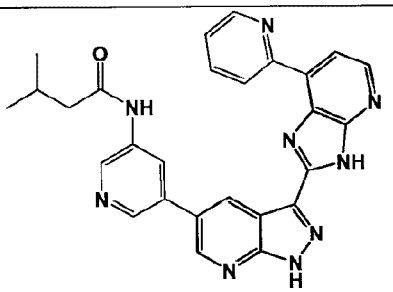
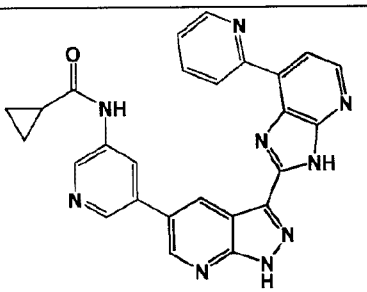
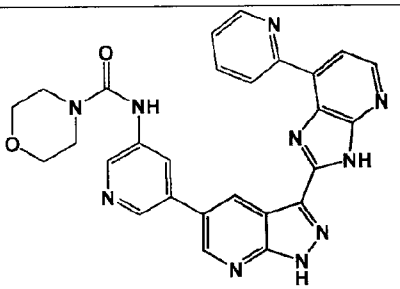
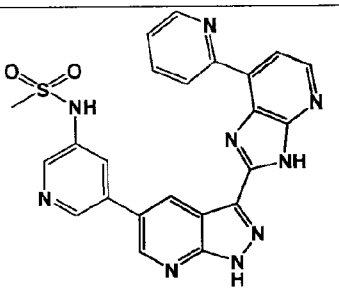
155		156	
157		158	
159		160	
161		162	

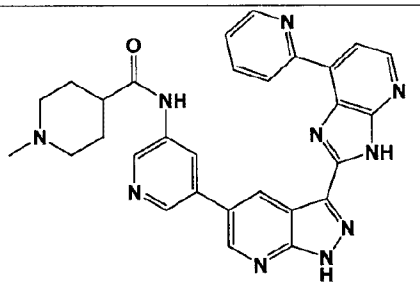
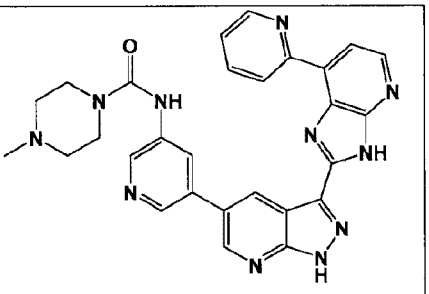
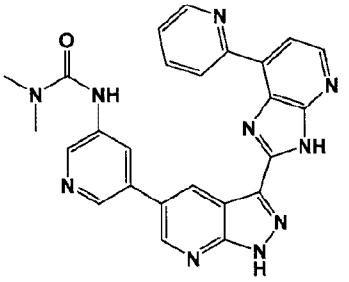
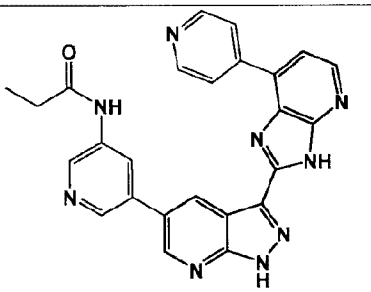
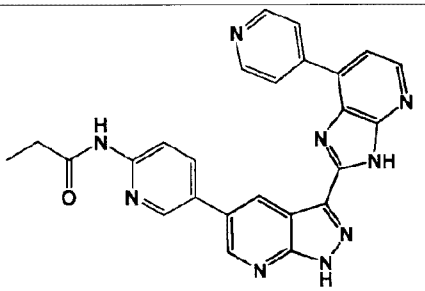
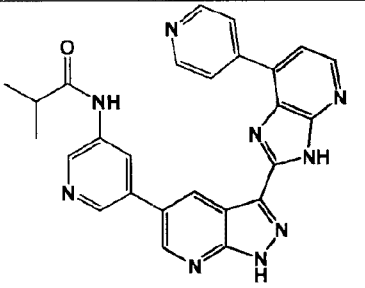
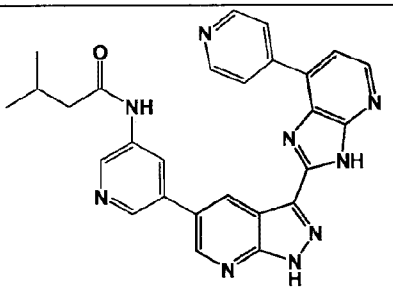
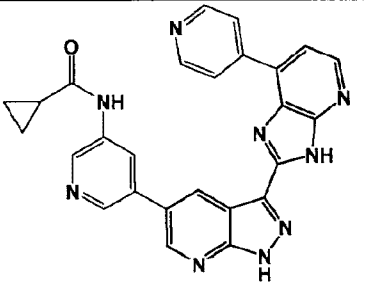
163		164	
165		166	
167		168	
169		170	

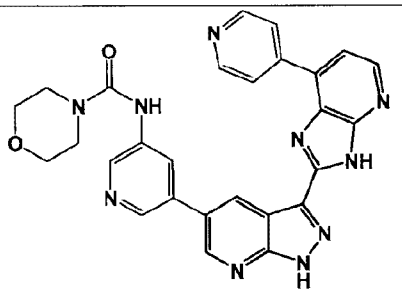
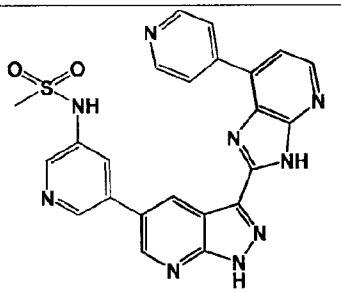
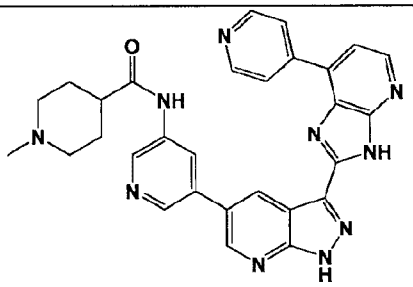
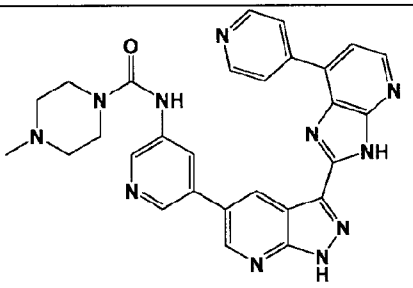
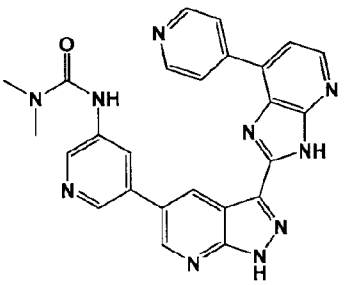
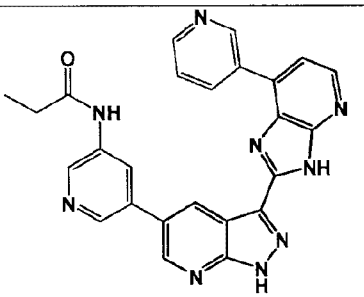
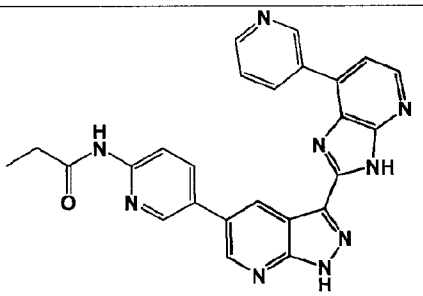
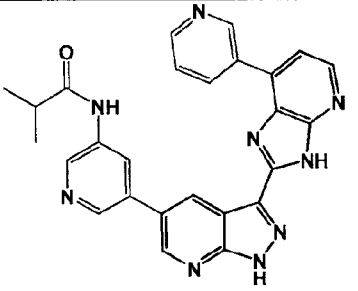
171		172	
173		174	
175		176	
177		178	

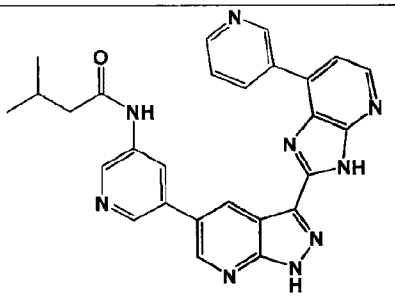
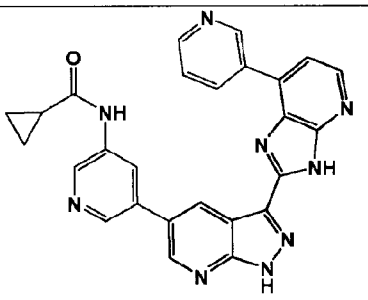
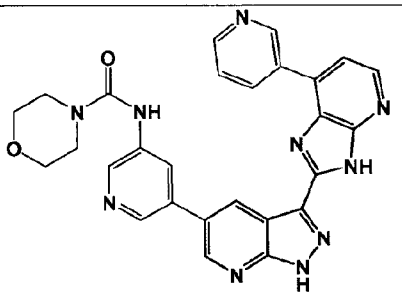
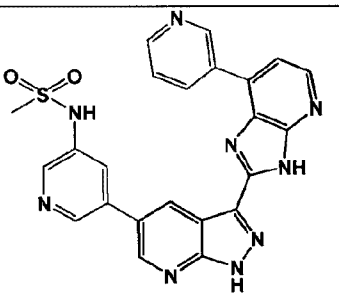
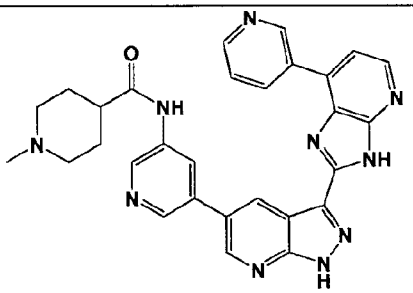
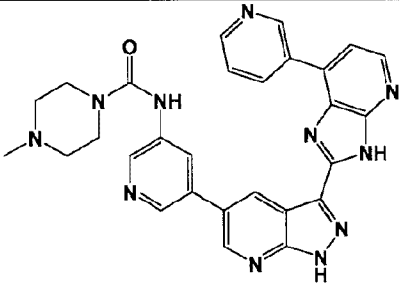
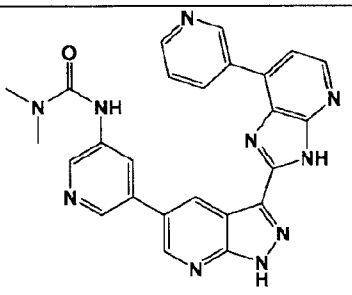
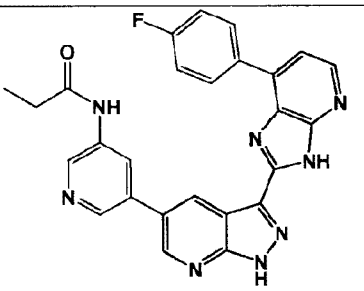
179		180	
181		182	
183		184	
185		186	

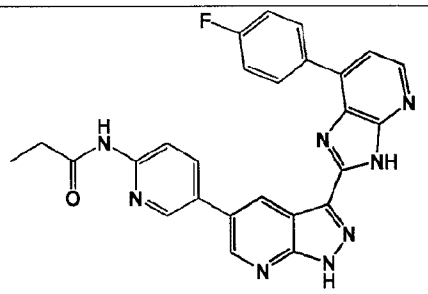
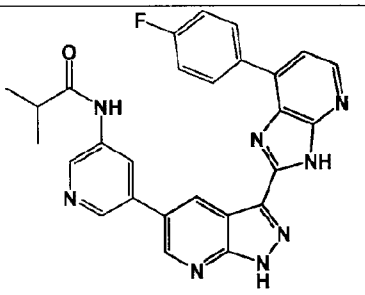
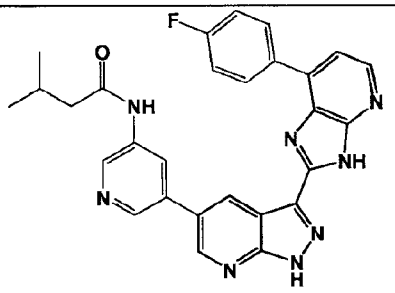
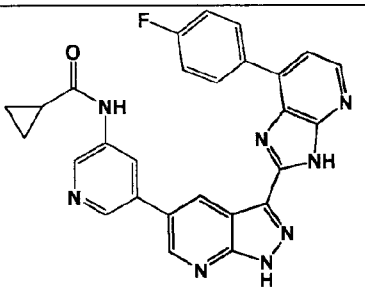
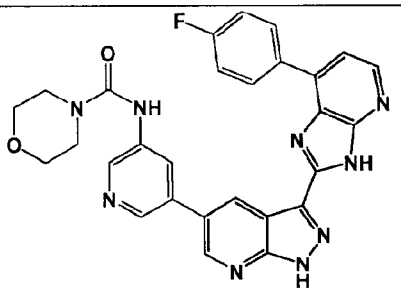
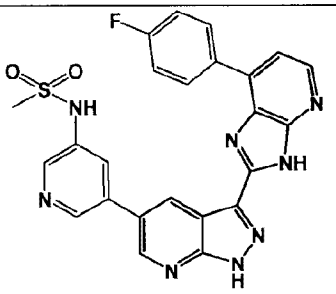
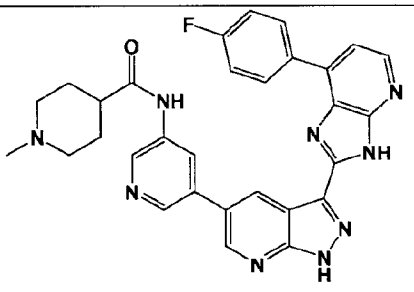
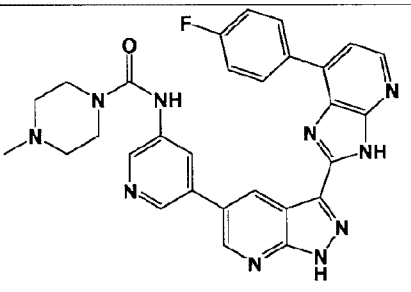
187		188	
189		190	
191		192	
193		194	

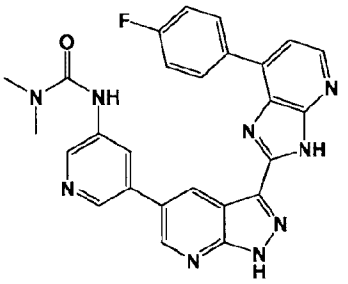
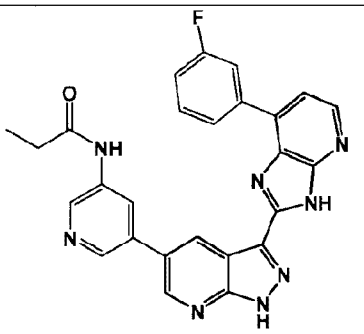
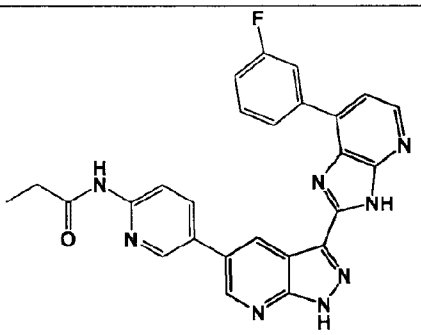
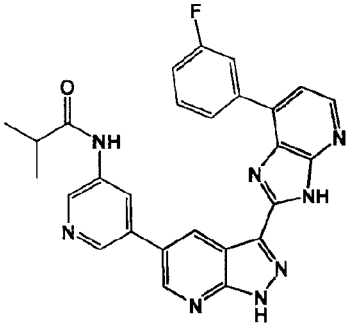
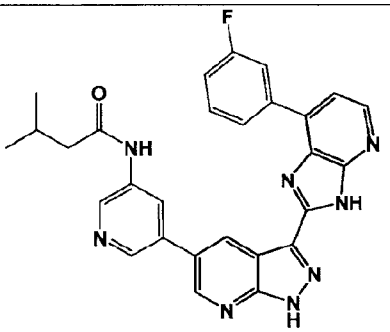
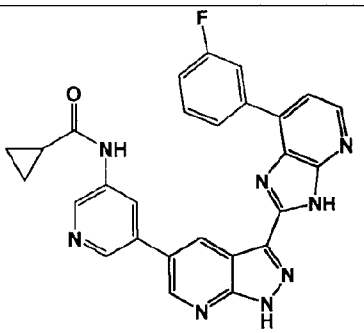
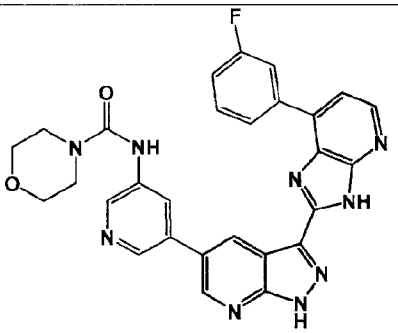
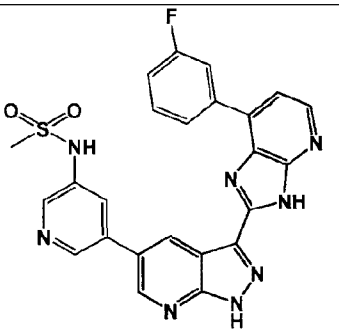
195		196	
197		198	
199		200	
201		202	

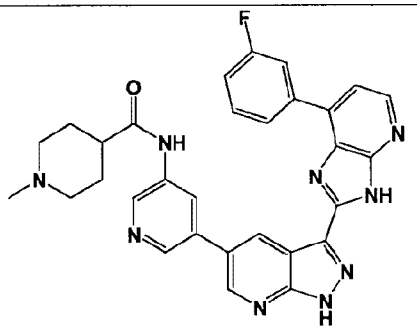
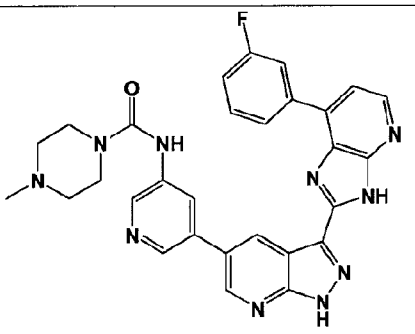
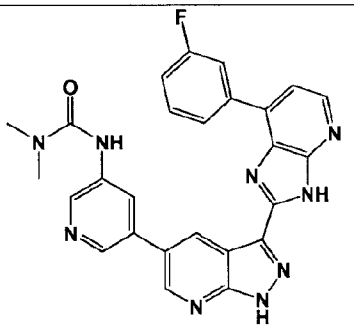
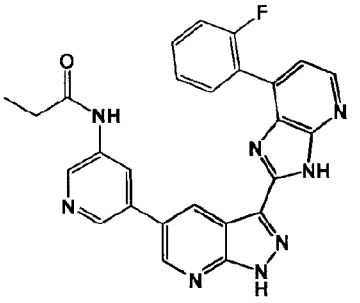
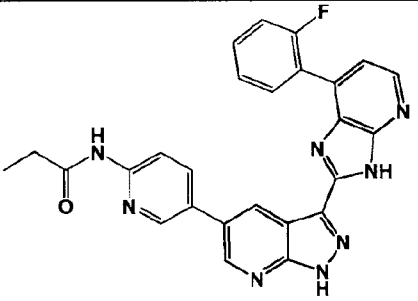
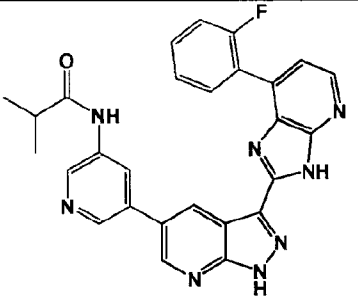
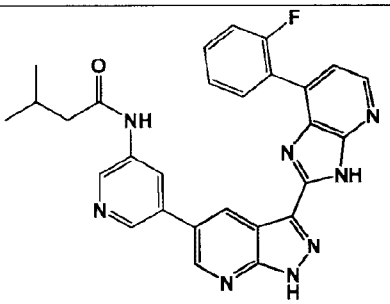
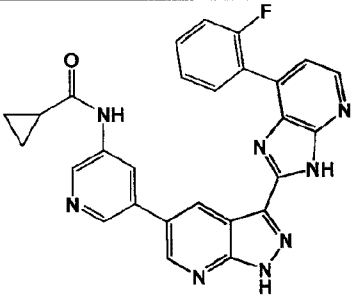
203		204	
205		206	
207		208	
209		210	

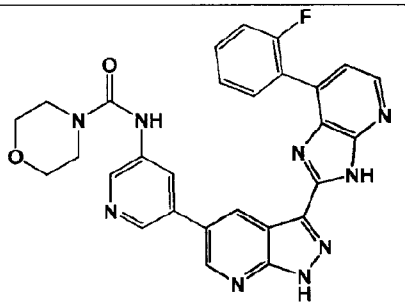
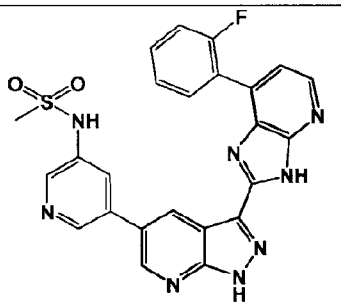
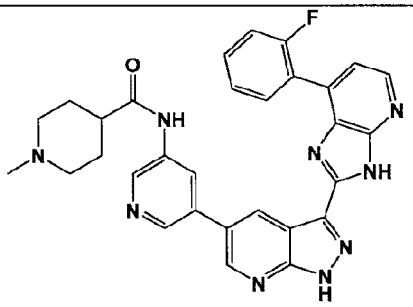
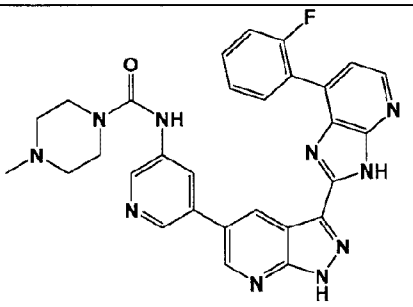
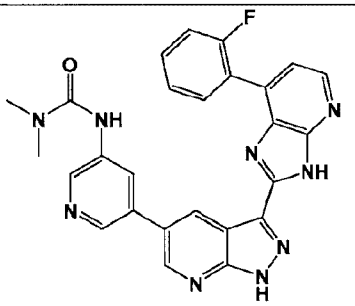
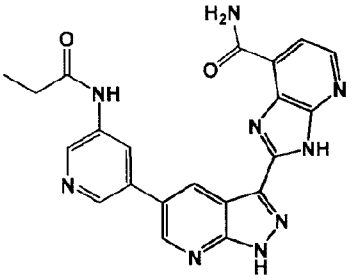
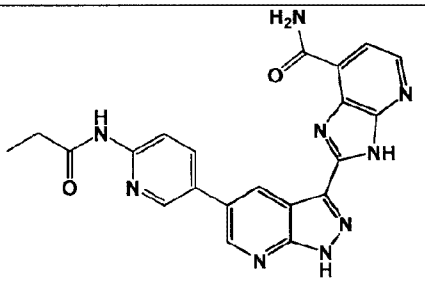
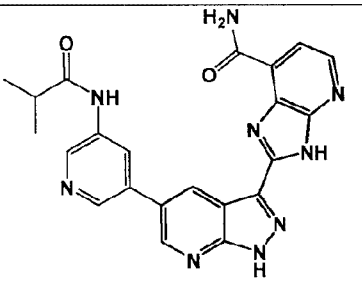
211		212	
213		214	
215		216	
217		218	

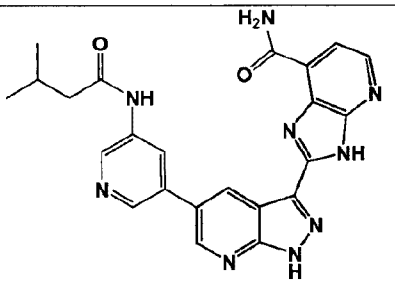
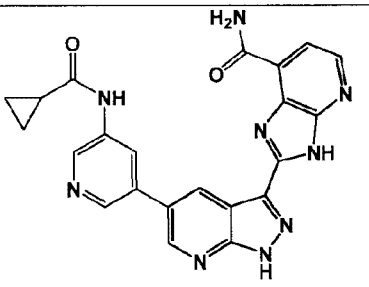
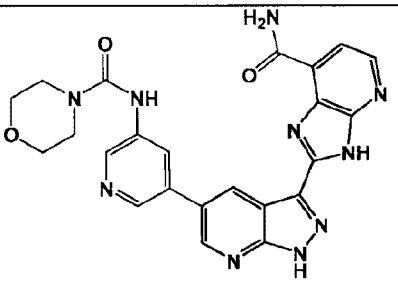
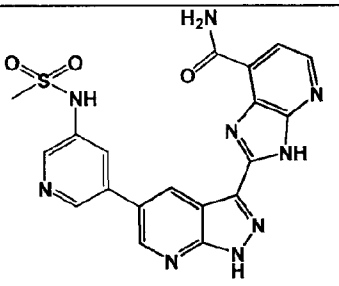
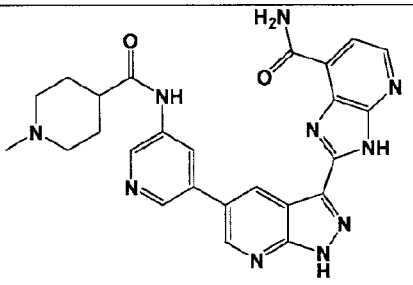
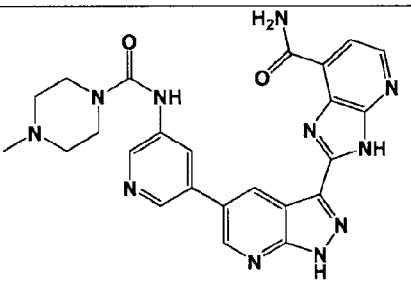
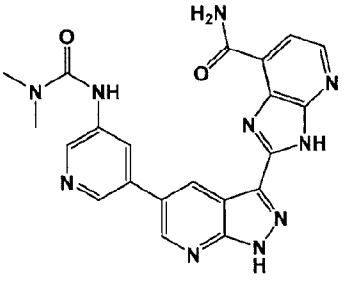
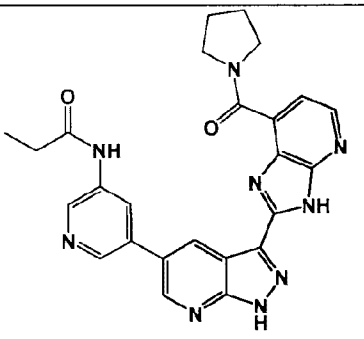
219		220	
221		222	
223		224	
225		226	

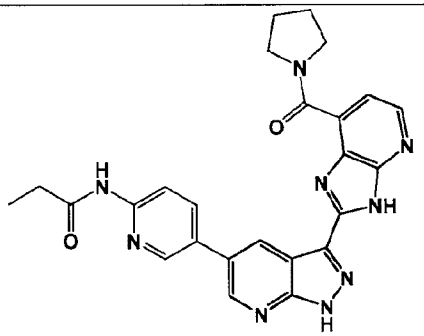
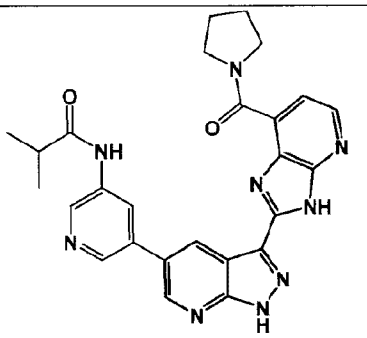
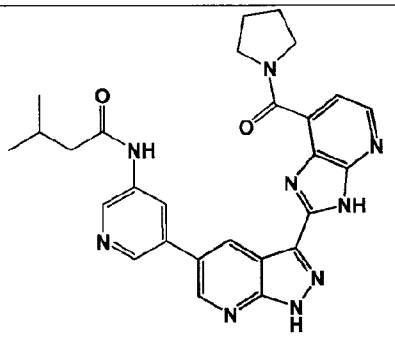
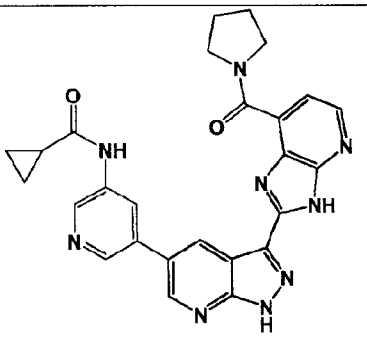
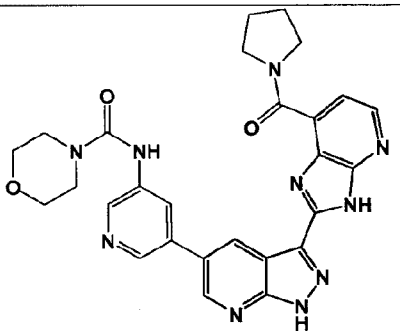
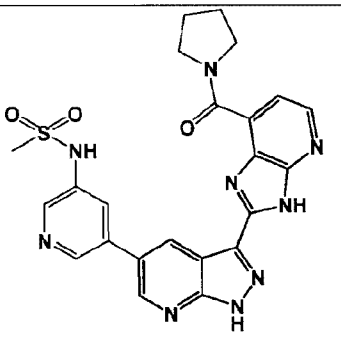
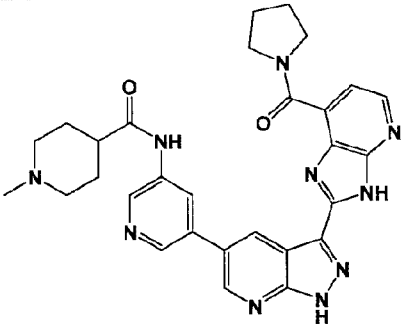
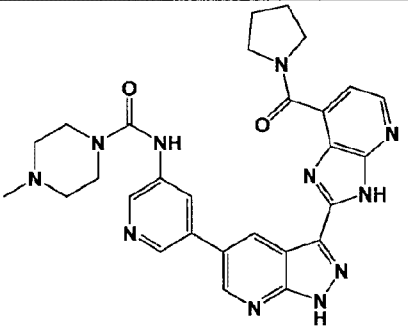
227		228	
229		230	
231		232	
233		234	

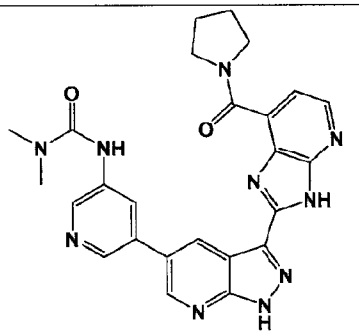
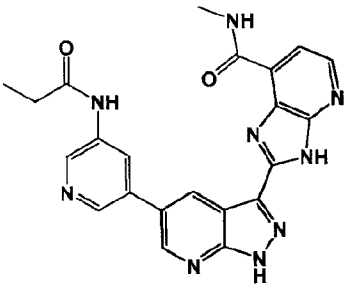
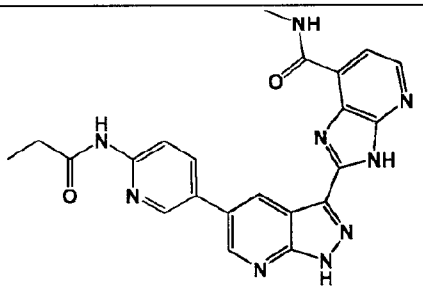
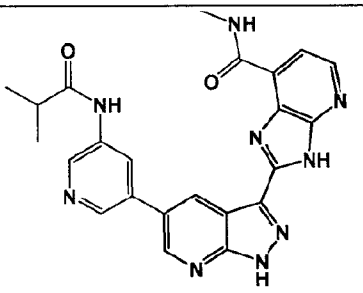
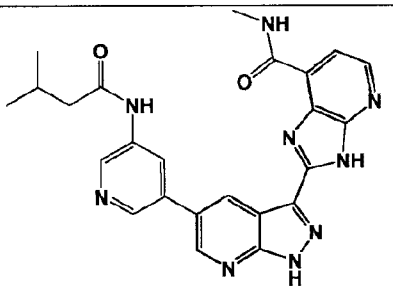
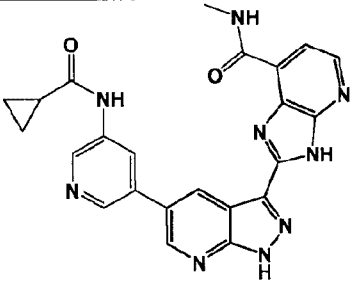
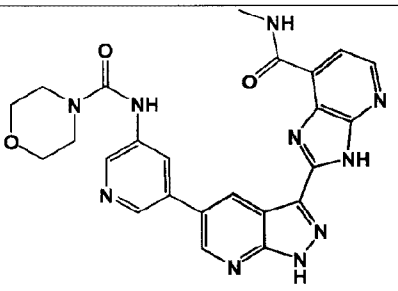
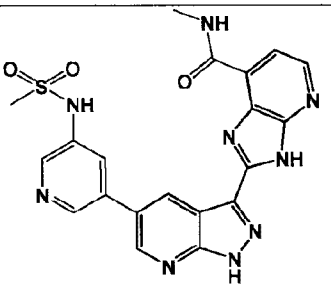
235		236	
237		238	
239		240	
241		242	

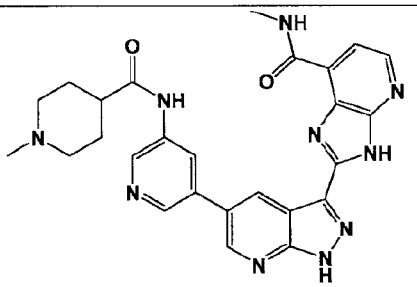
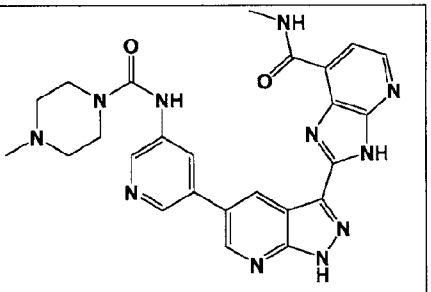
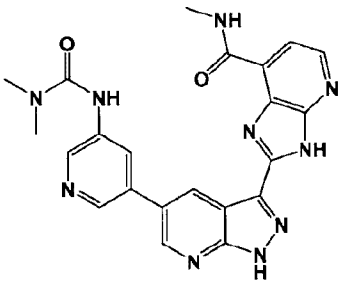
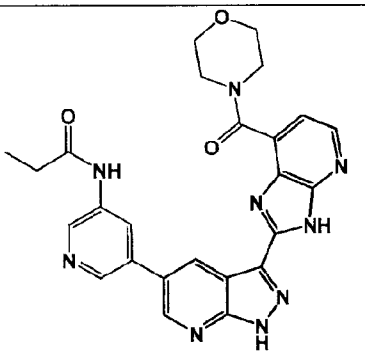
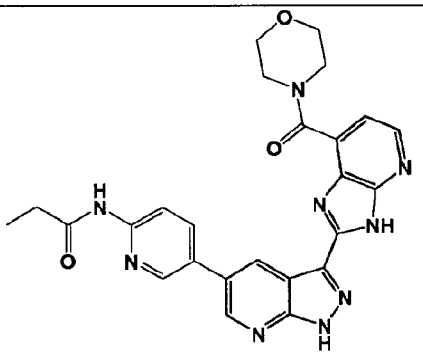
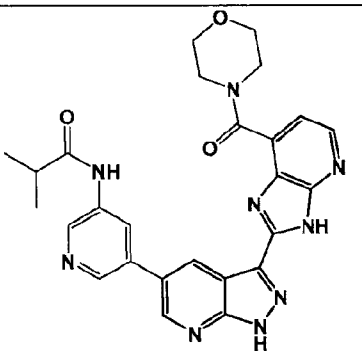
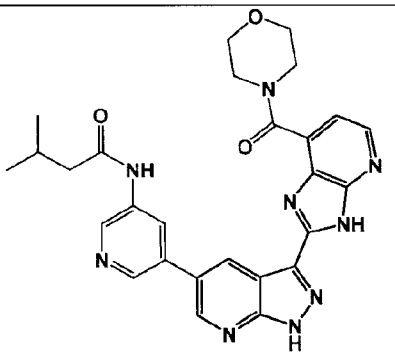
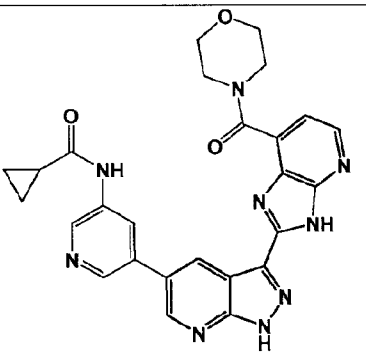
243		244	
245		246	
247		248	
249		250	

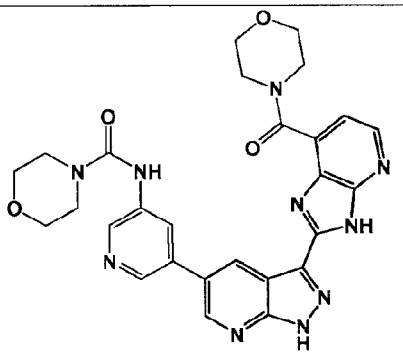
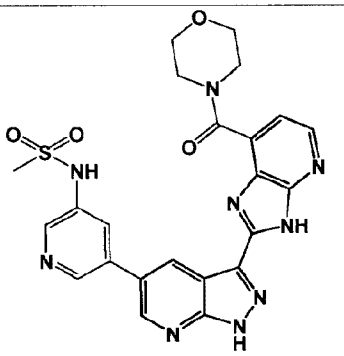
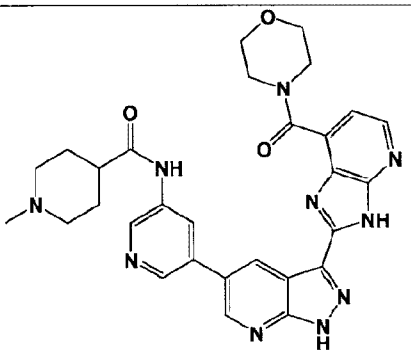
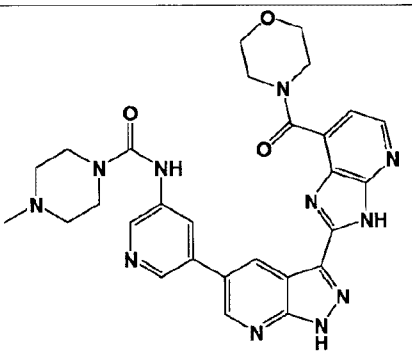
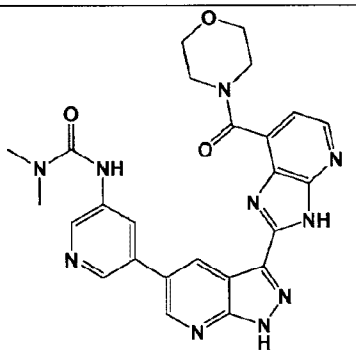
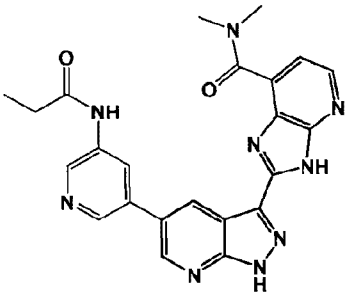
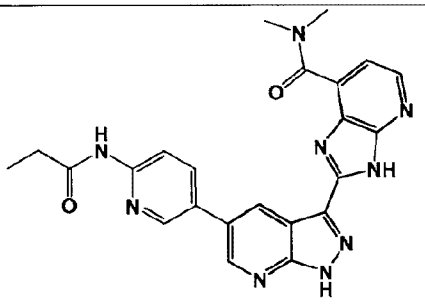
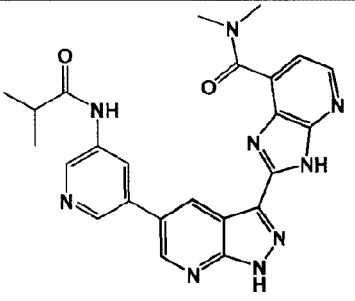
251		252	
253		254	
255		256	
257		258	

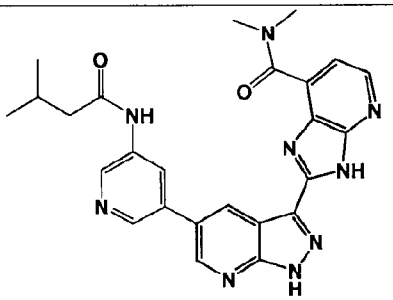
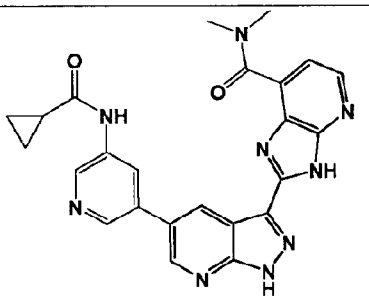
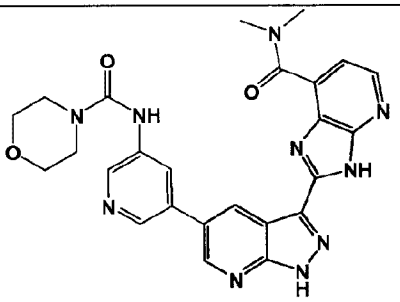
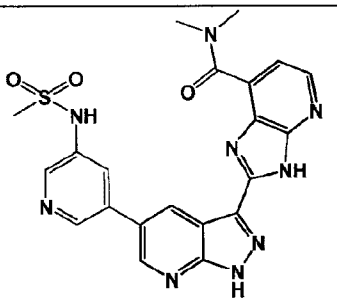
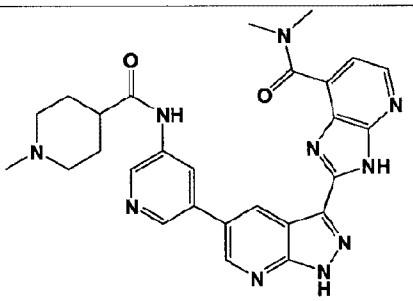
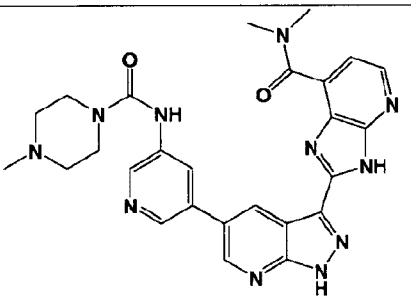
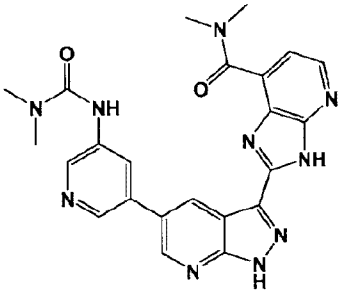
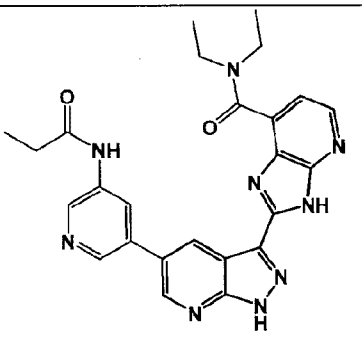
259		260	
261		262	
263		264	
265		266	

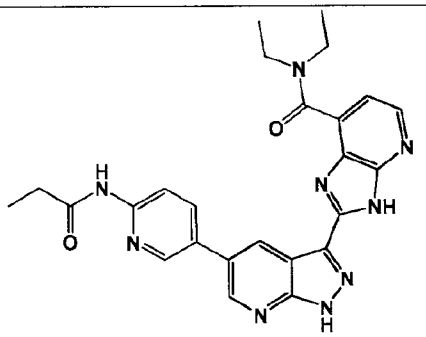
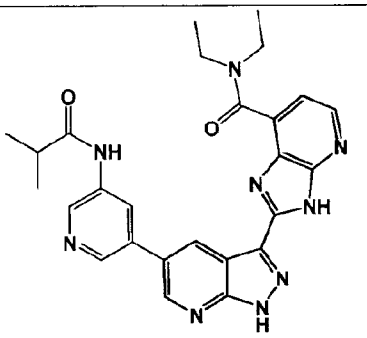
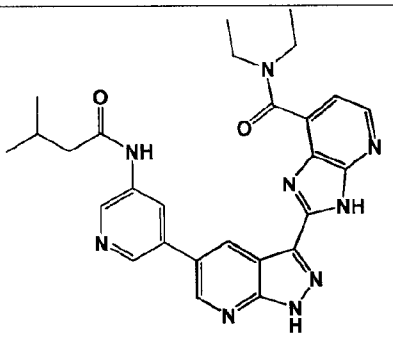
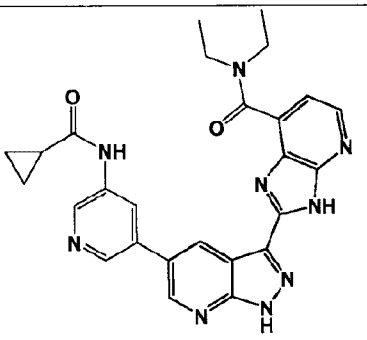
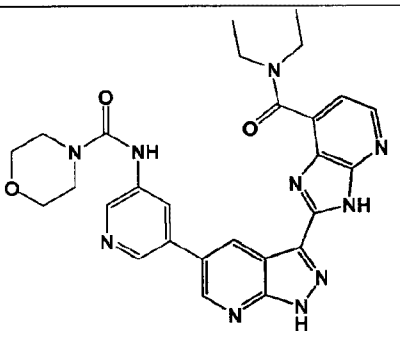
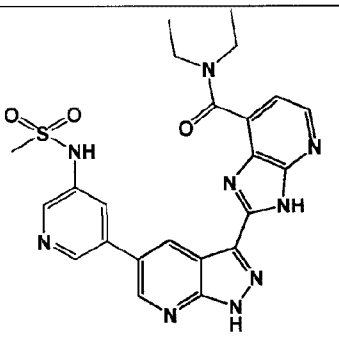
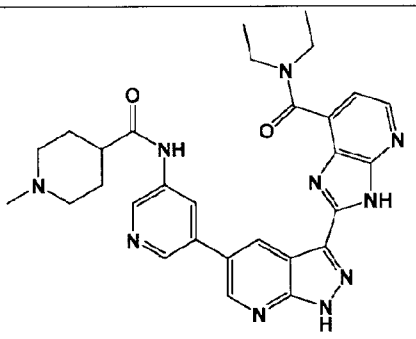
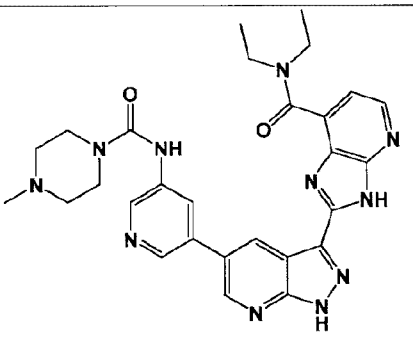
267		268	
269		270	
271		272	
273		274	

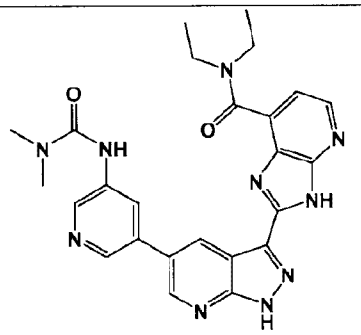
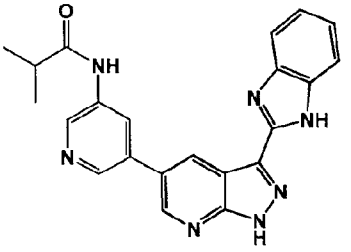
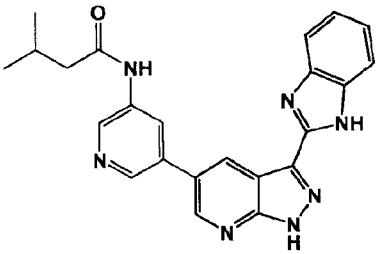
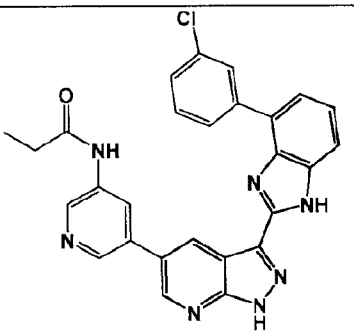
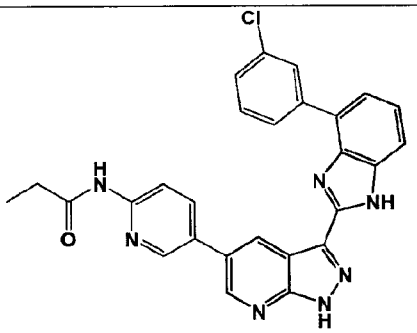
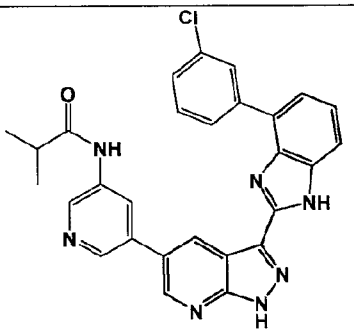
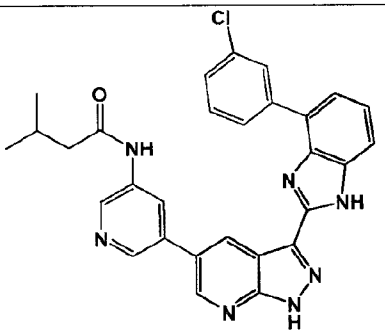
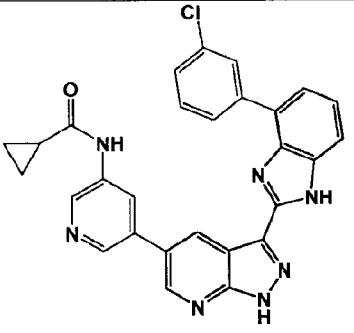
275		276	
277		278	
279		280	
281		282	

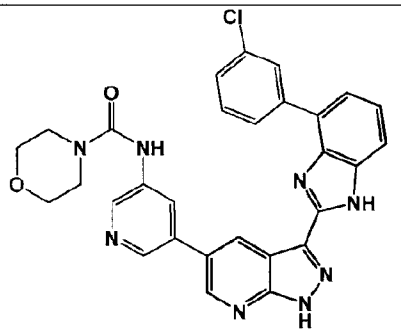
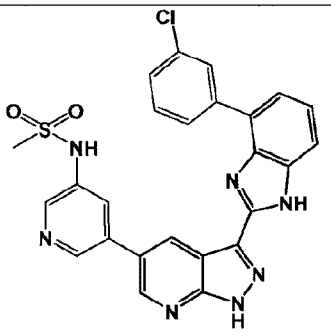
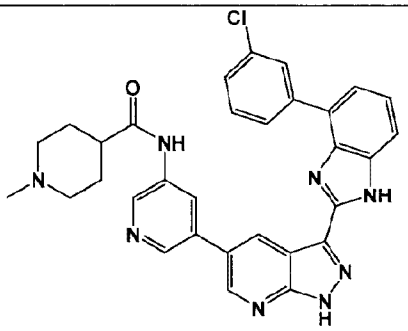
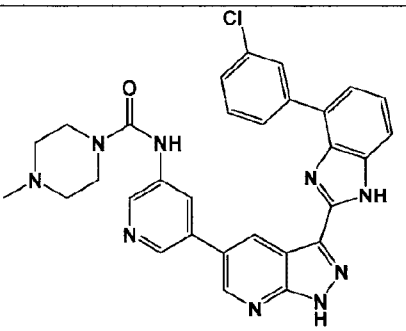
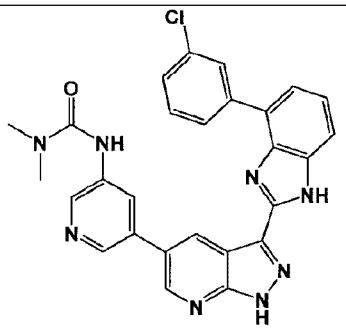
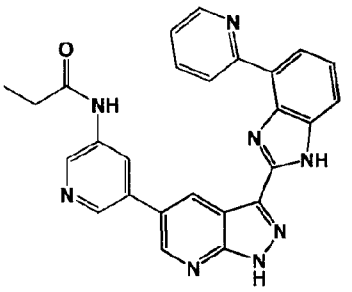
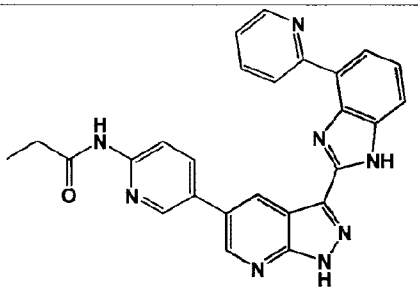
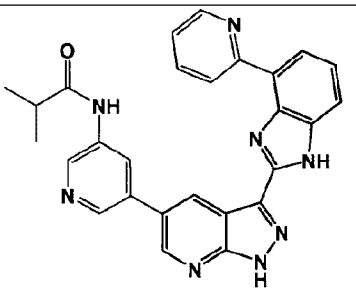
283		284	
285		286	
287		288	
289		290	

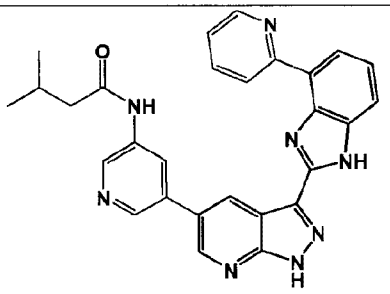
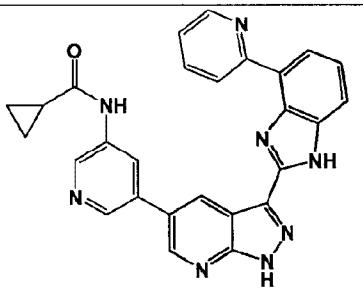
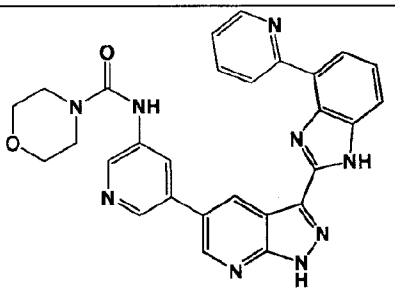
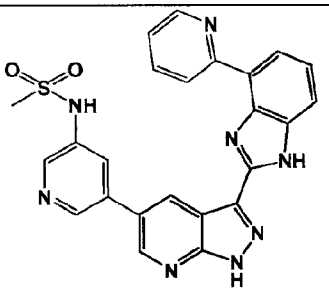
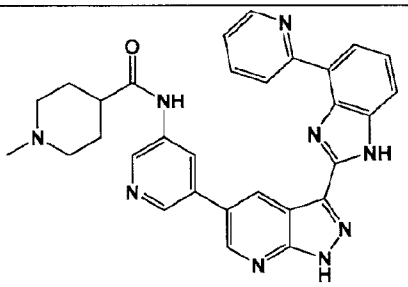
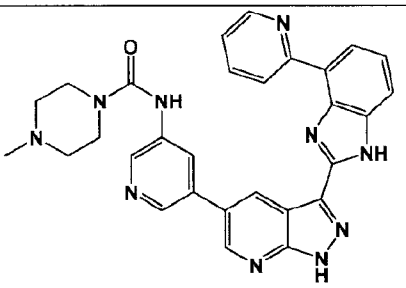
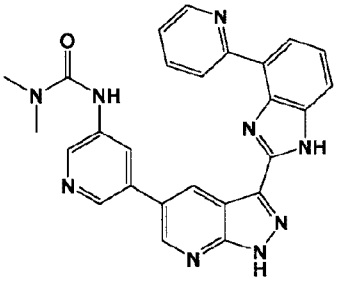
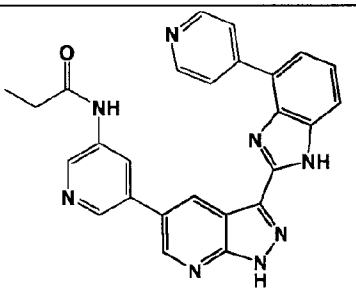
291		292	
293		294	
295		296	
297		298	

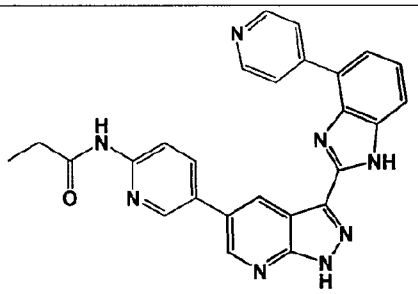
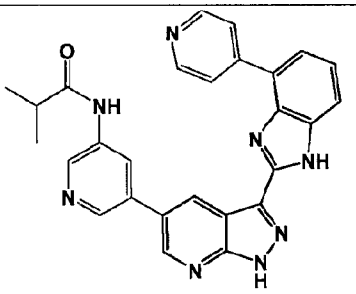
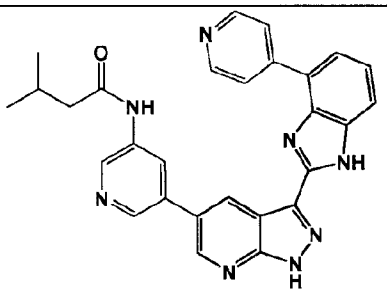
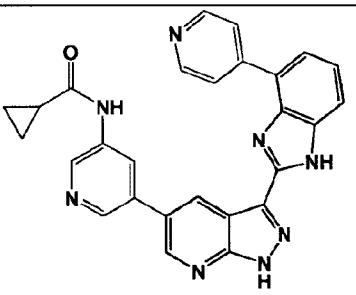
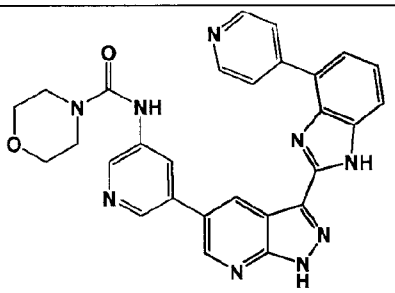
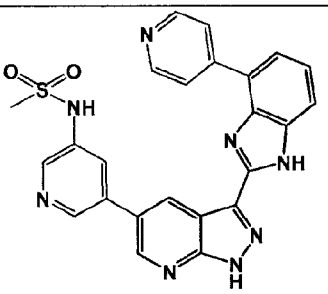
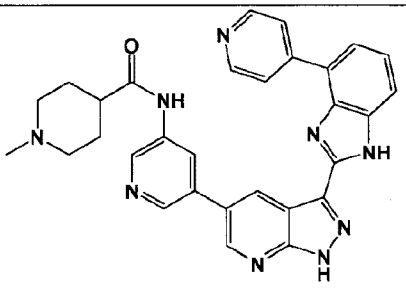
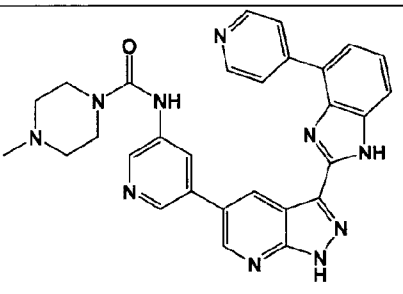
299		300	
301		302	
303		304	
305		306	

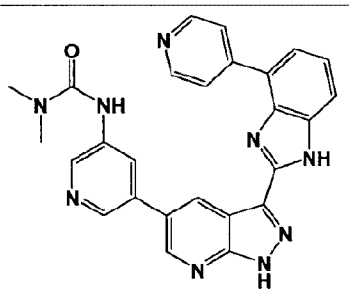
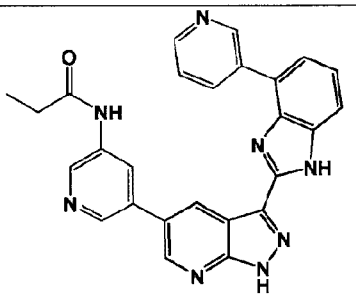
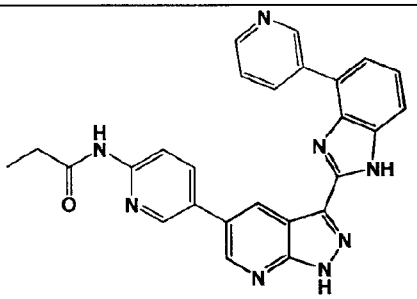
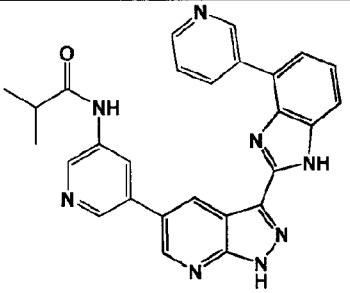
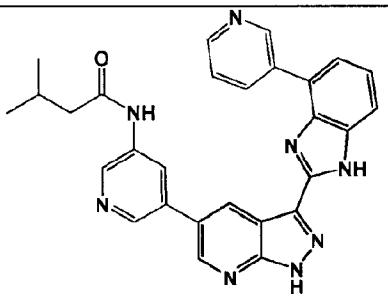
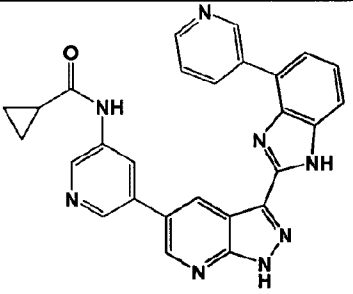
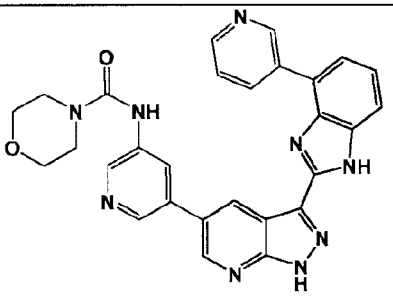
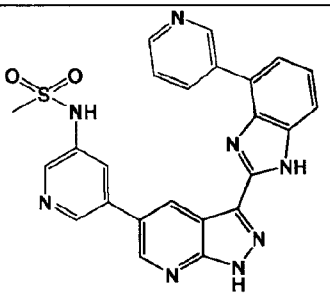
307		308	
309		310	
311		312	
313		314	

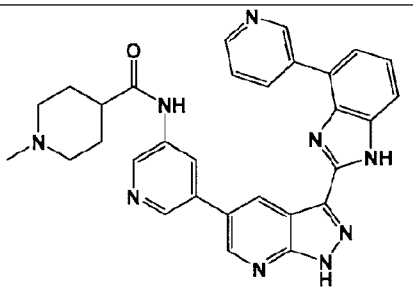
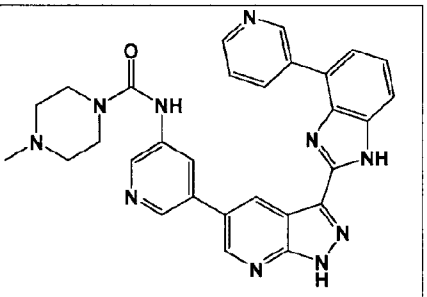
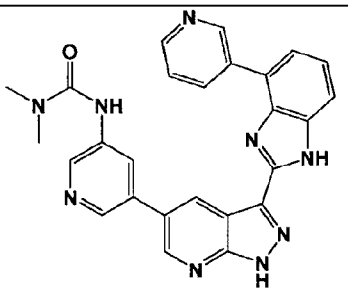
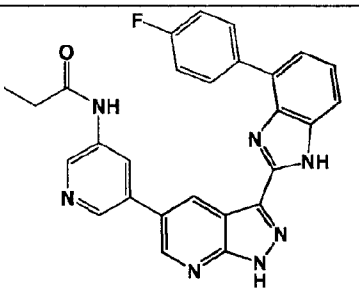
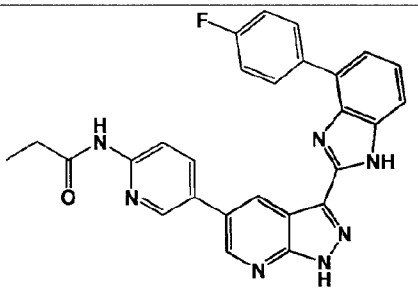
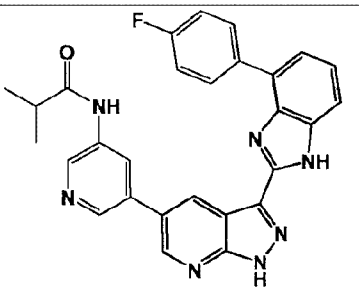
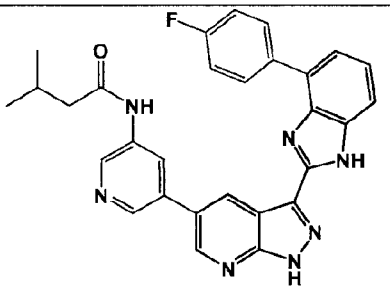
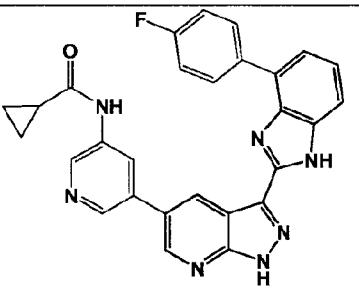
315		316	
317		318	
319		320	
321		322	

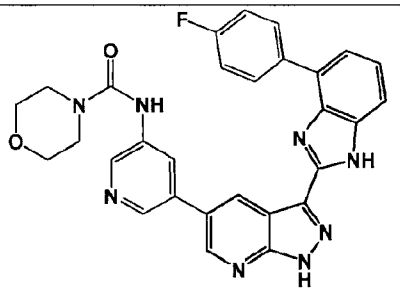
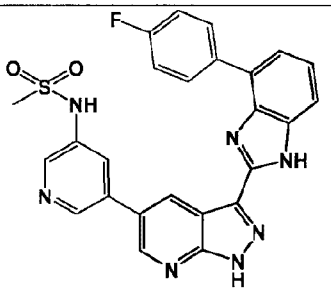
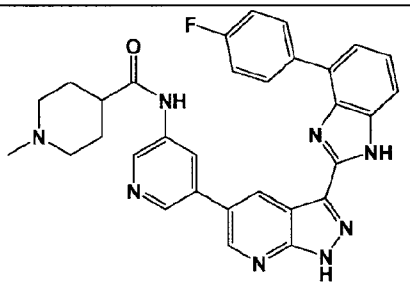
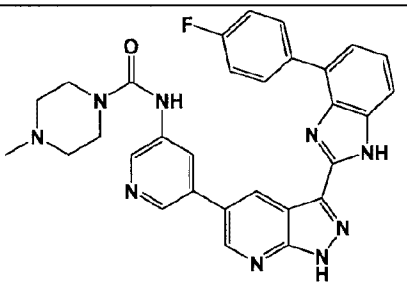
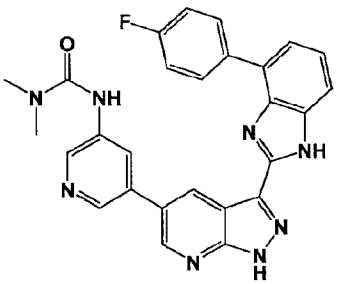
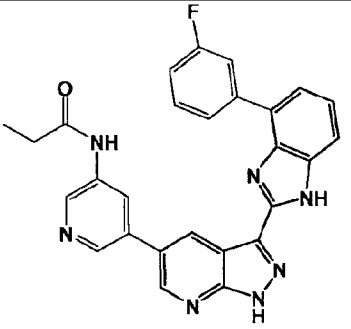
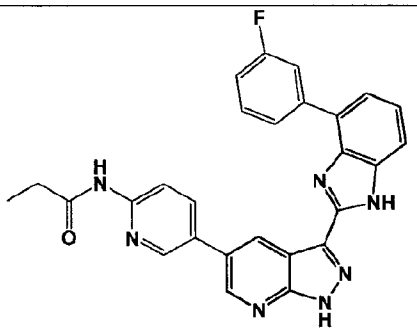
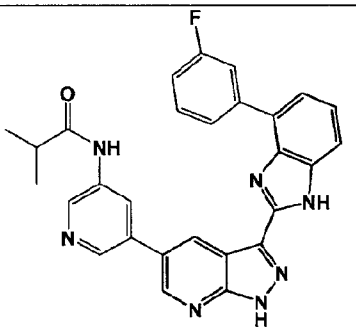
323		324	
325		326	
327		328	
329		330	

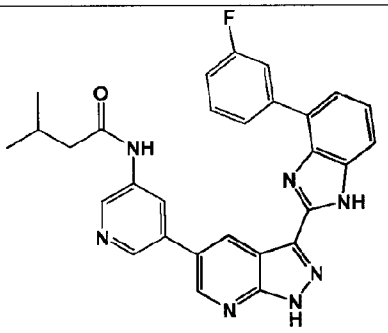
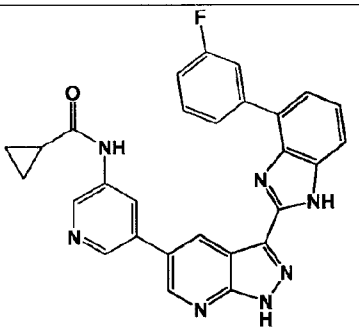
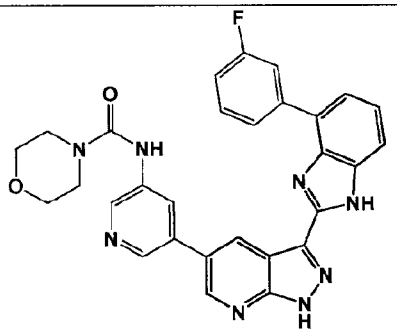
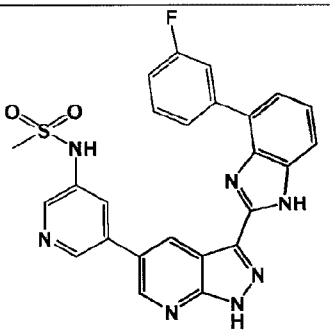
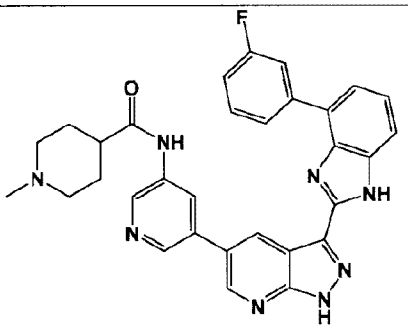
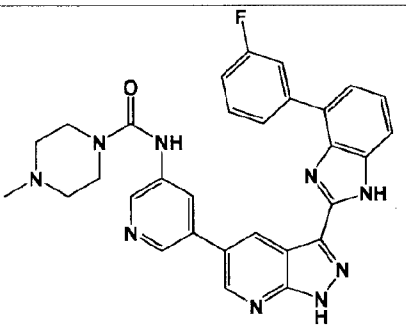
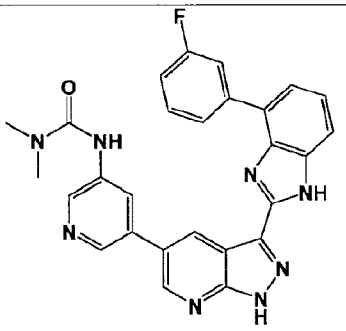
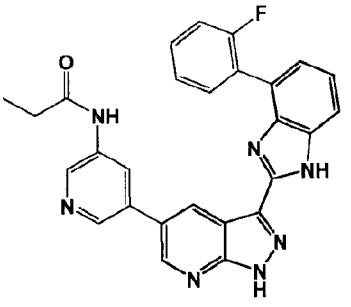
331		332	
333		334	
335		336	
337		338	

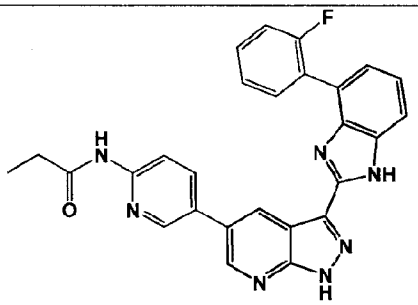
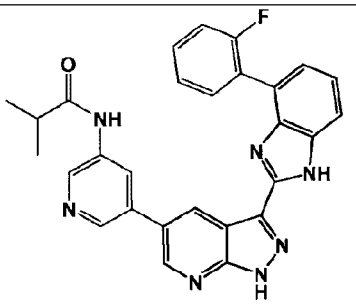
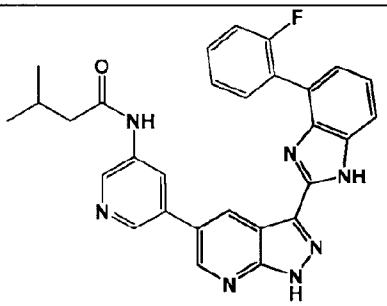
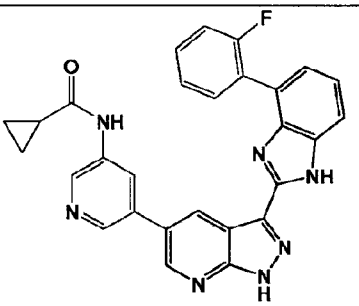
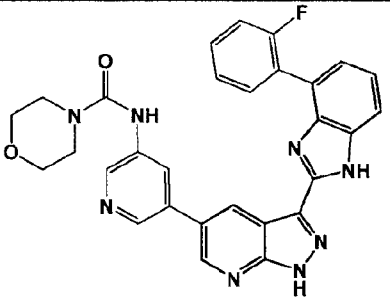
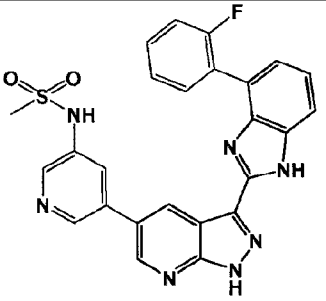
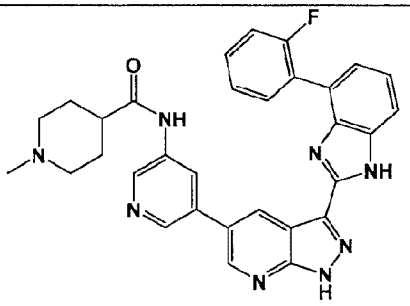
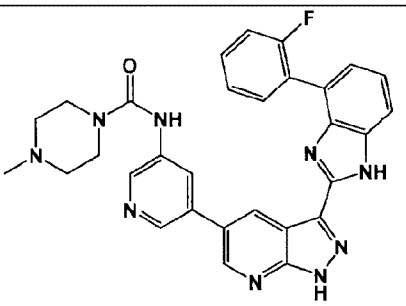
339		340	
341		342	
343		344	
345		346	

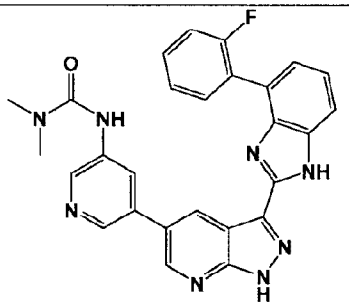
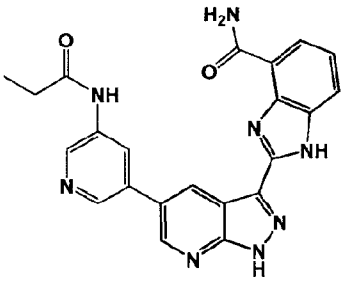
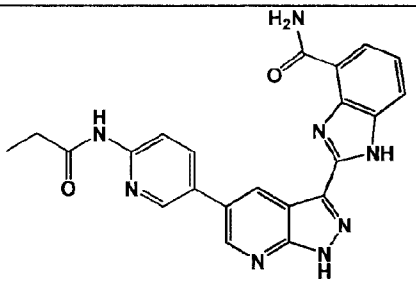
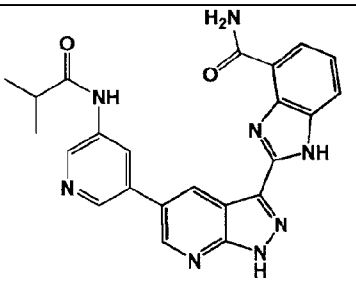
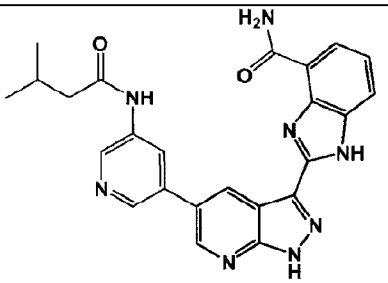
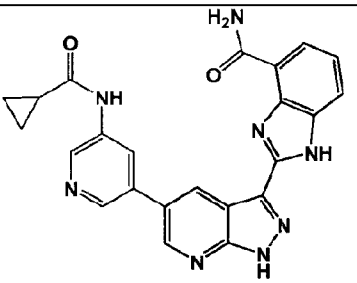
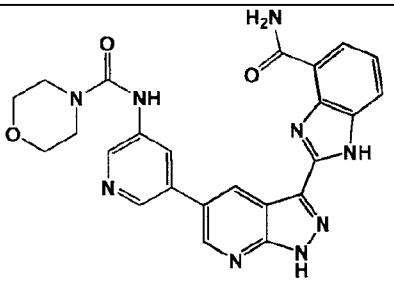
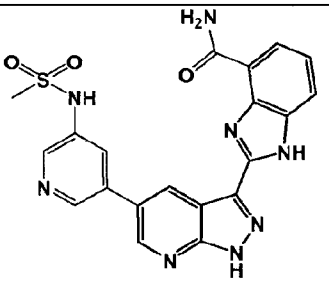
347		348	
349		350	
351		352	
353		354	

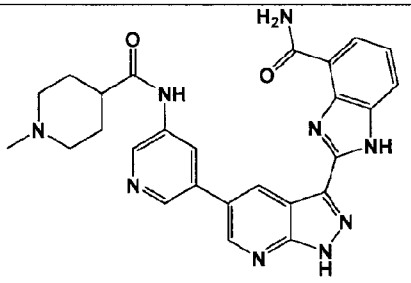
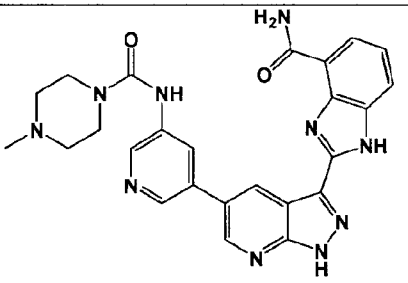
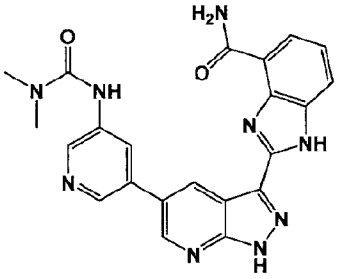
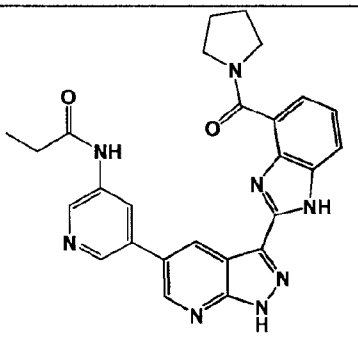
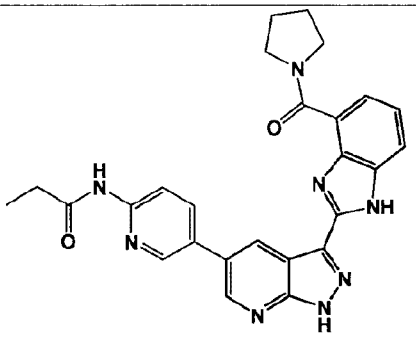
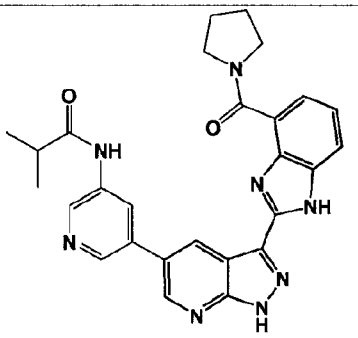
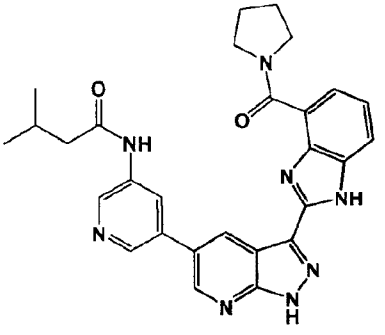
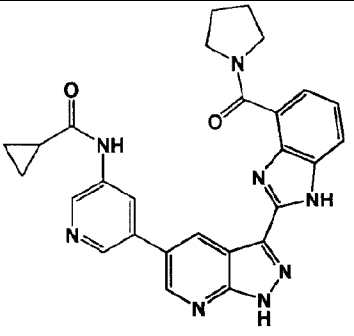
355		356	
357		358	
359		360	
361		362	

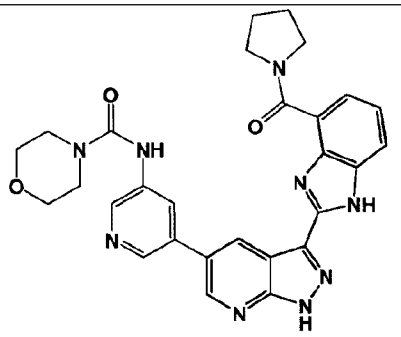
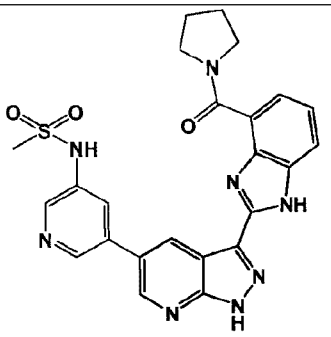
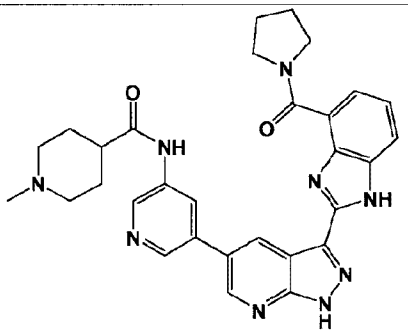
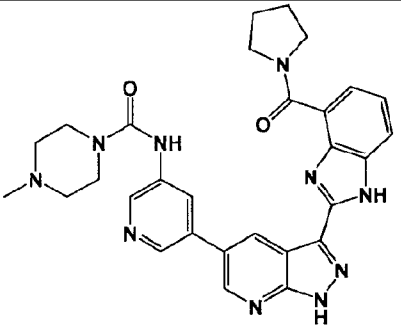
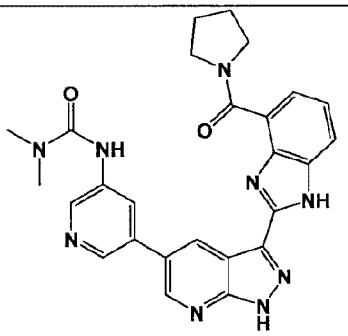
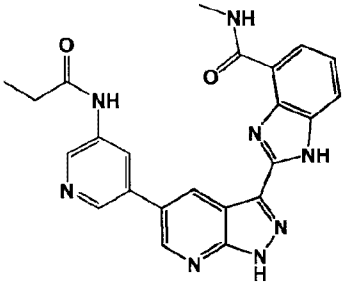
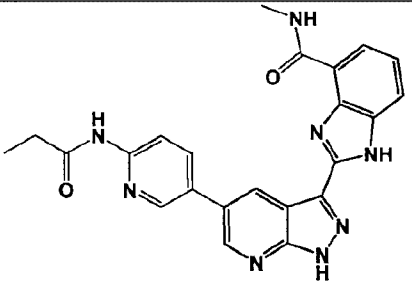
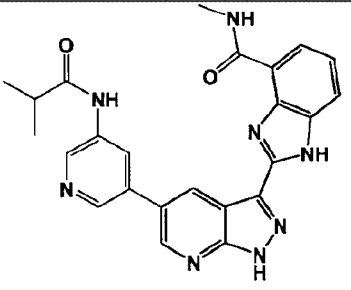
363		364	
365		366	
367		368	
369		370	

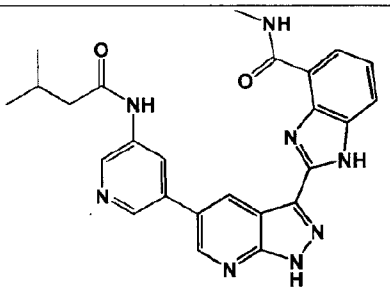
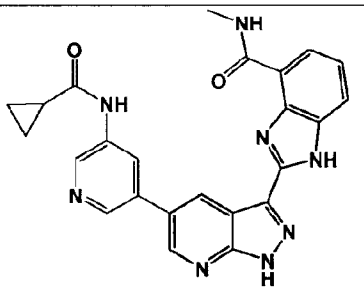
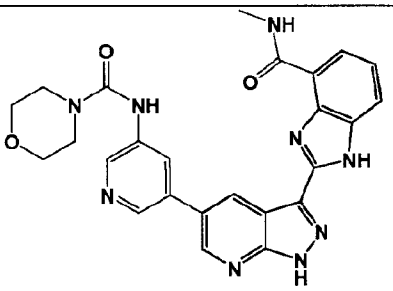
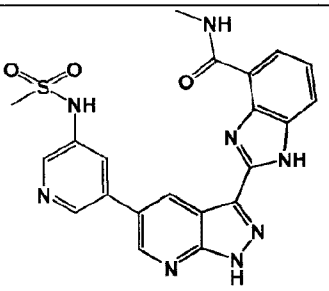
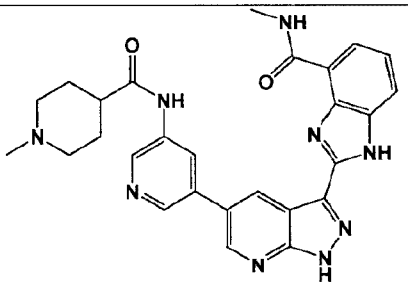
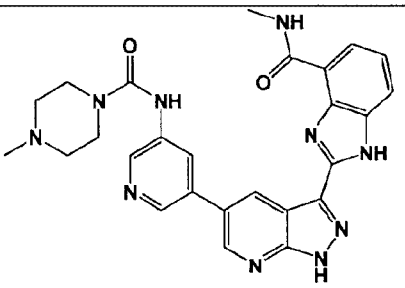
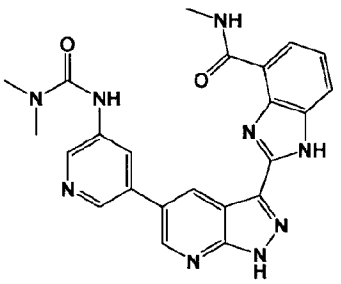
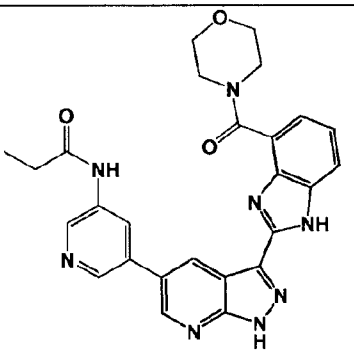
371		372	
373		374	
375		376	
377		378	

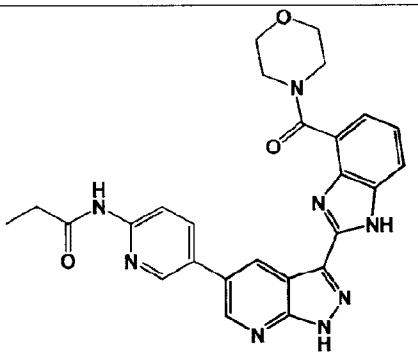
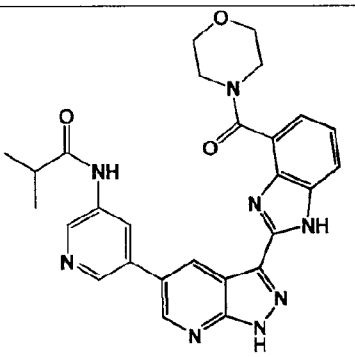
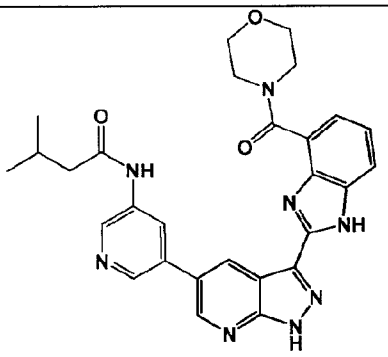
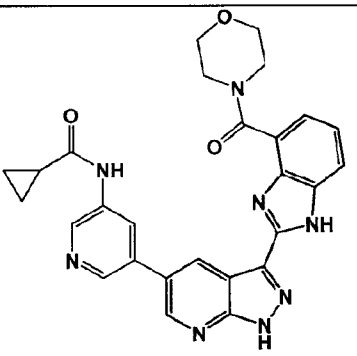
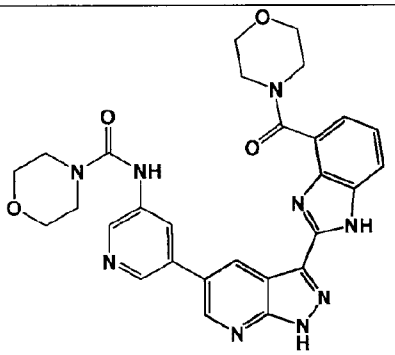
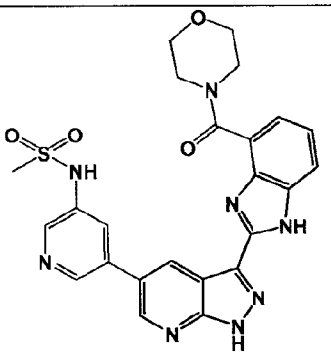
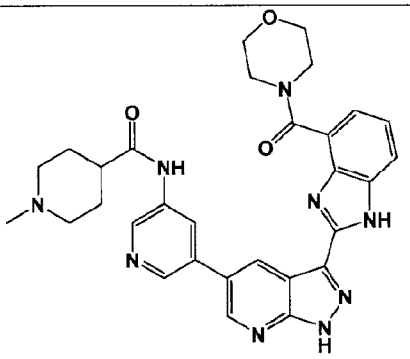
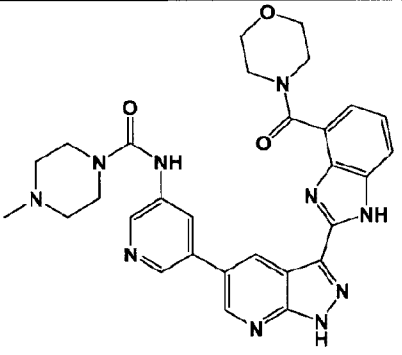
379		380	
381		382	
383		384	
385		386	

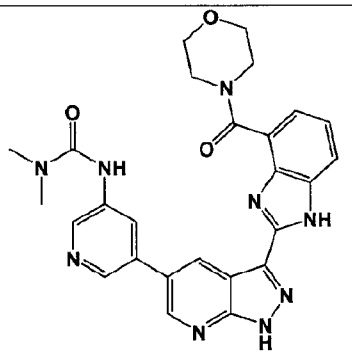
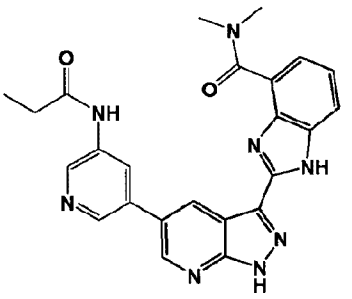
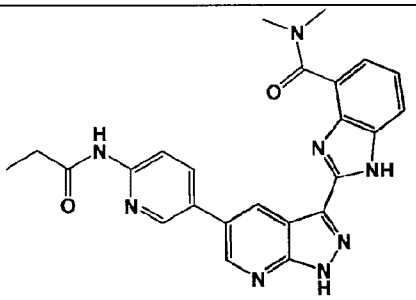
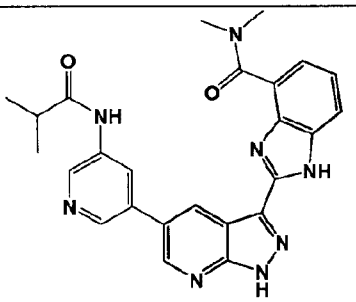
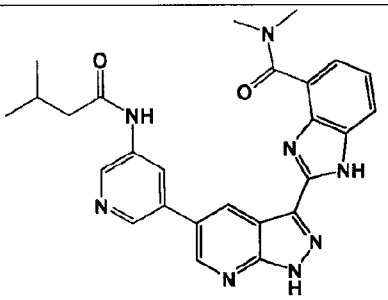
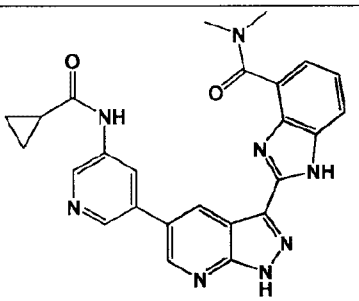
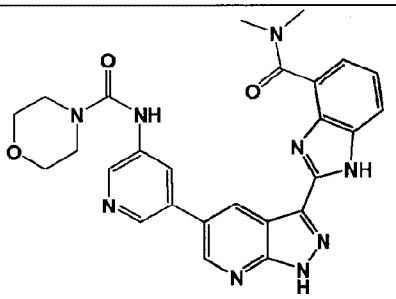
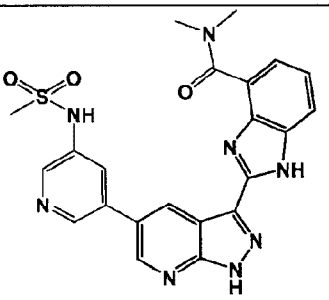
387		388	
389		390	
391		392	
393		394	

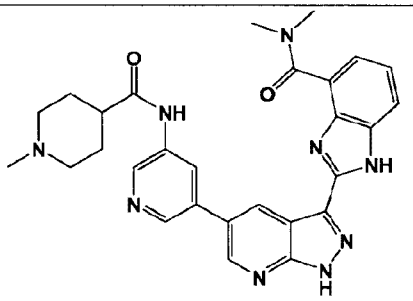
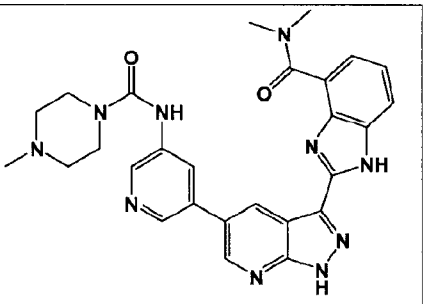
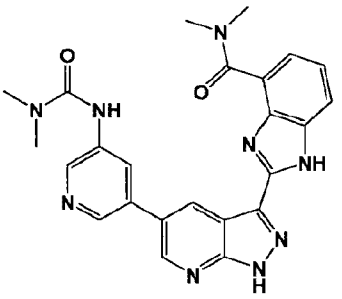
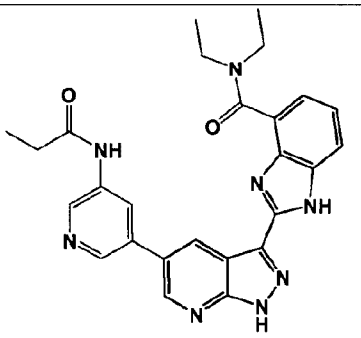
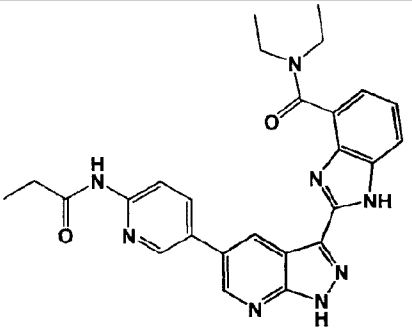
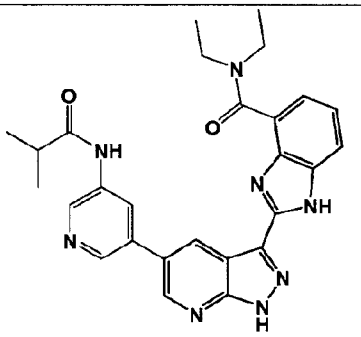
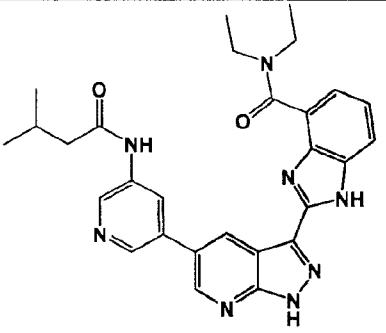
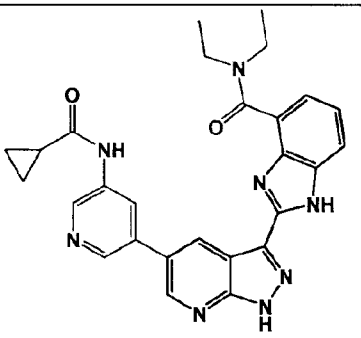
395		396	
397		398	
399		400	
401		402	

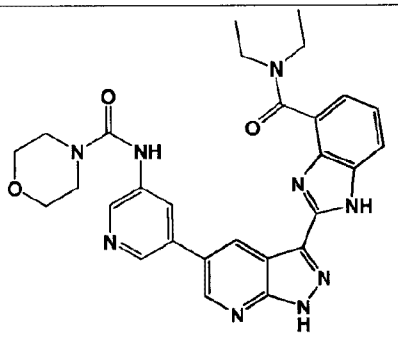
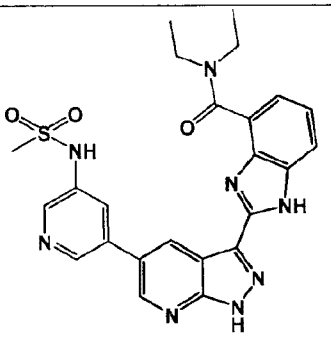
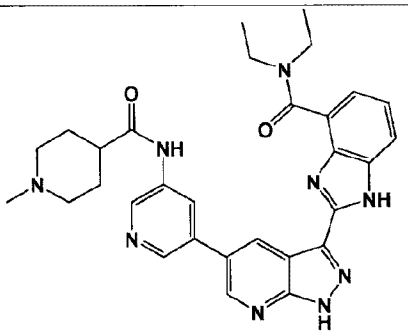
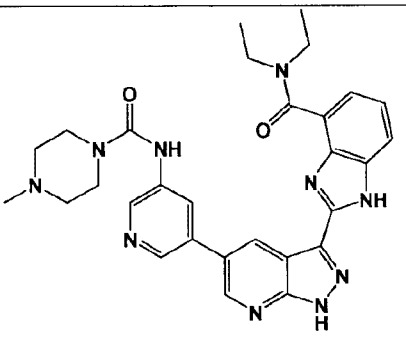
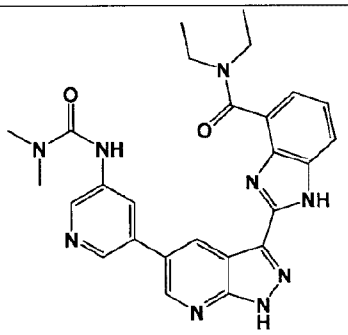
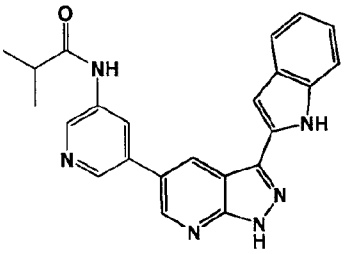
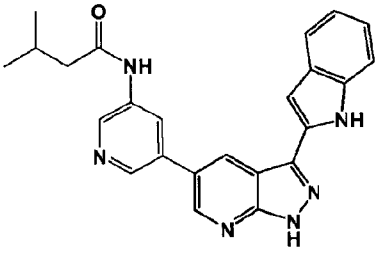
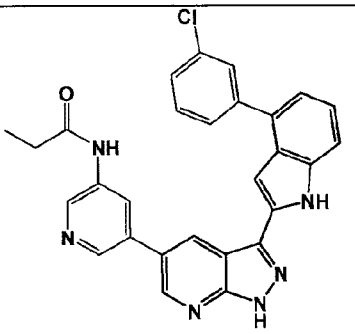
403		404	
405		406	
407		408	
409		410	

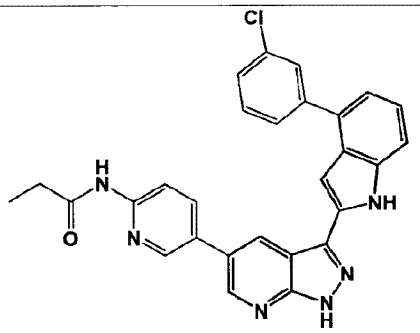
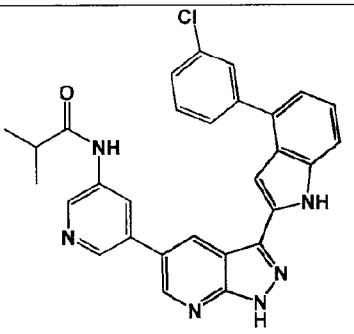
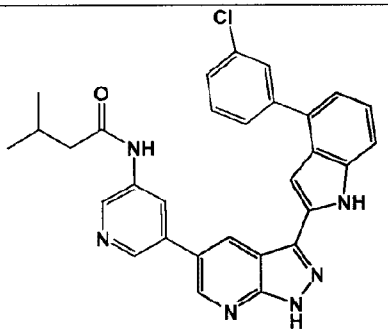
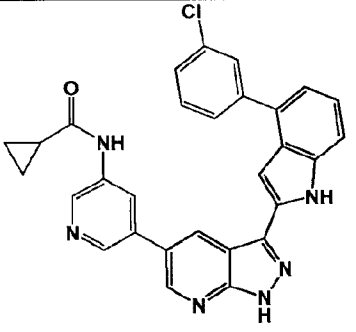
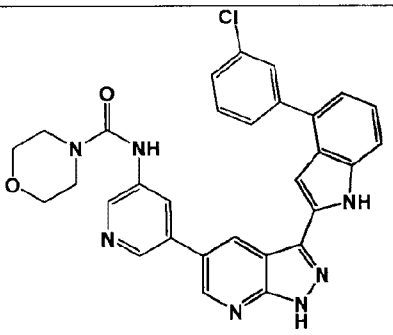
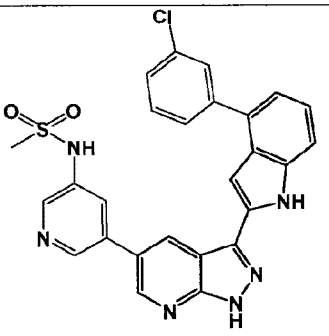
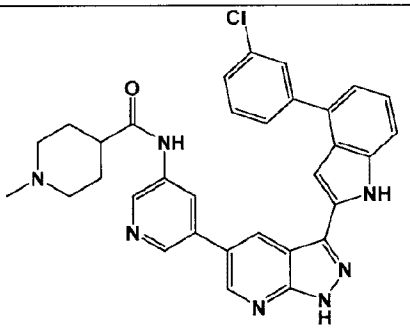
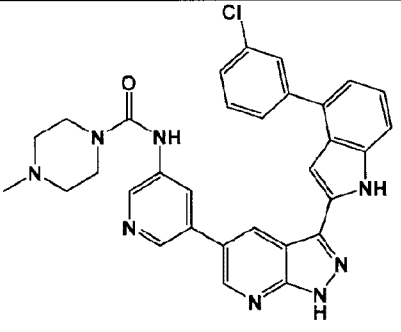
411		412	
413		414	
415		416	
417		418	

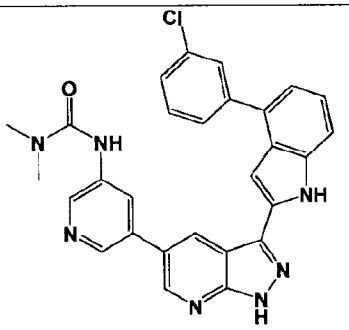
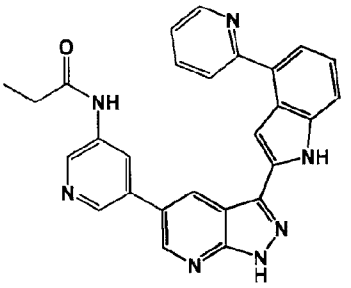
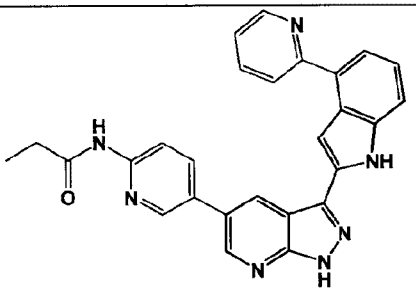
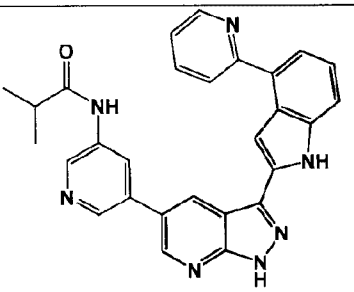
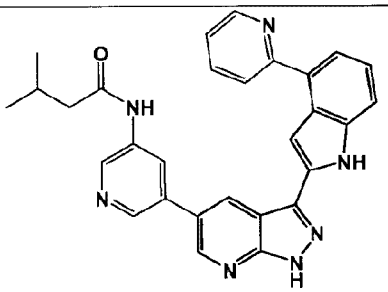
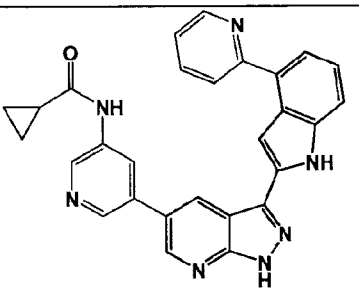
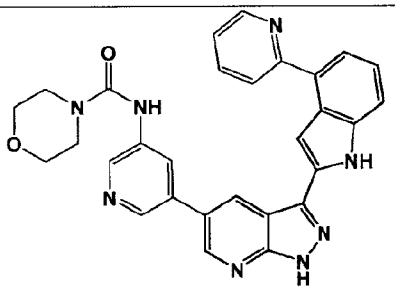
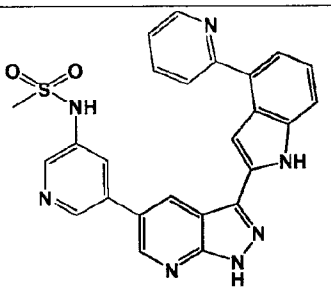
419		420	
421		422	
423		424	
425		426	

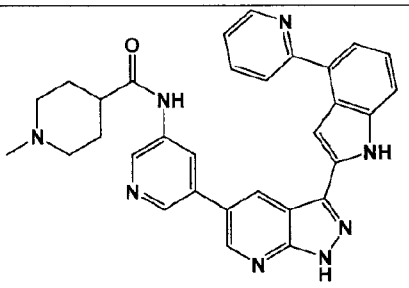
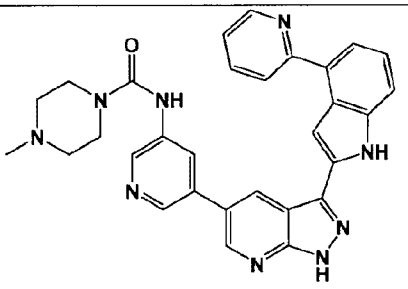
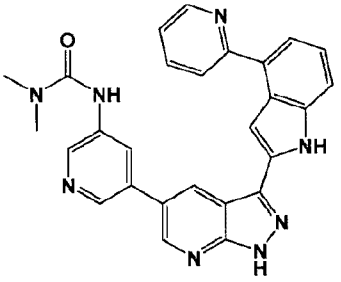
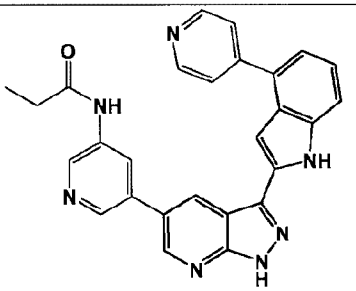
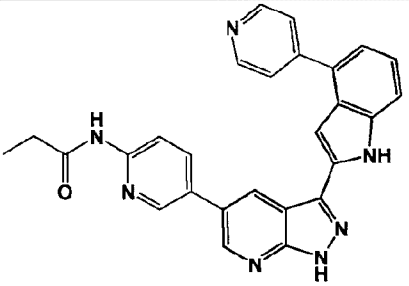
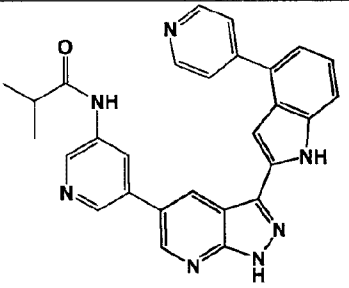
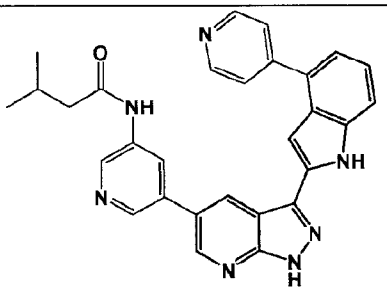
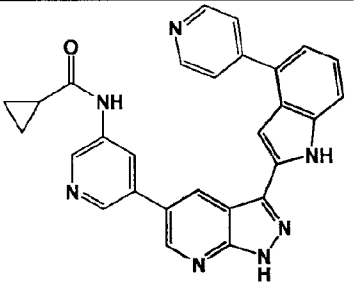
427		428	
429		430	
431		432	
433		434	

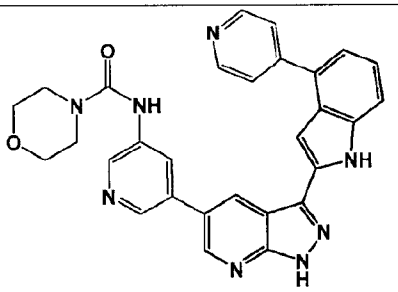
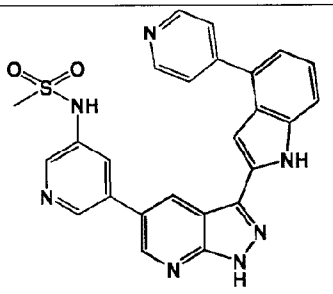
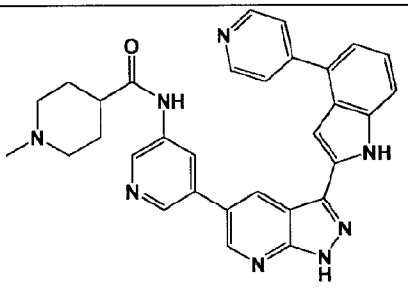
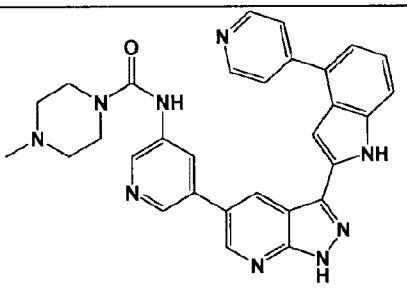
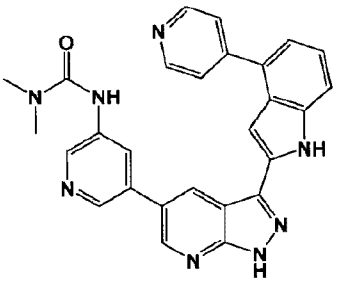
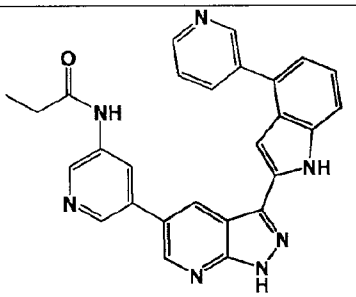
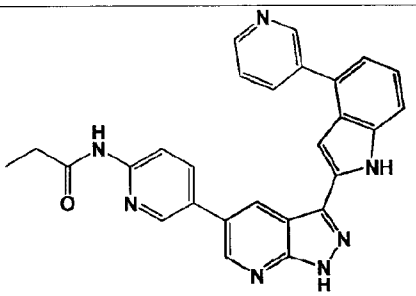
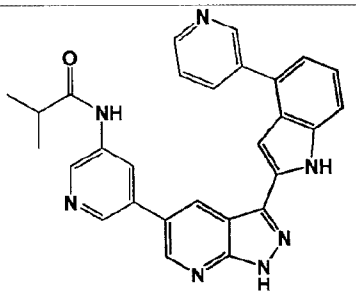
435		436	
437		438	
439		440	
441		442	

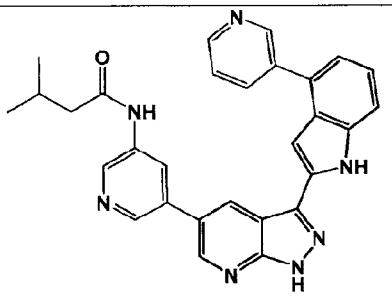
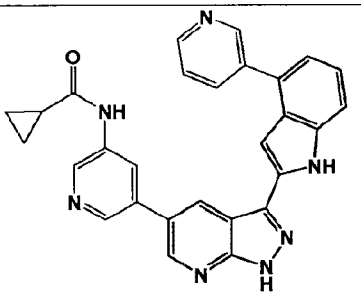
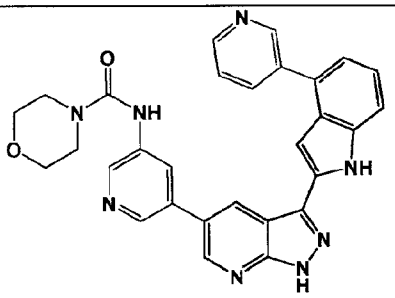
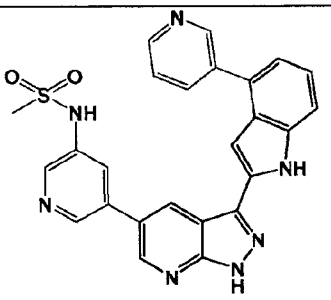
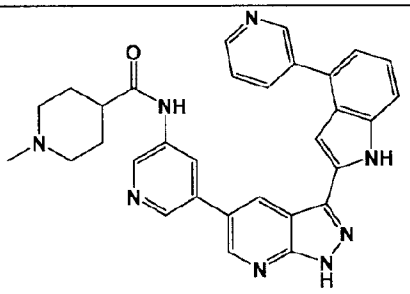
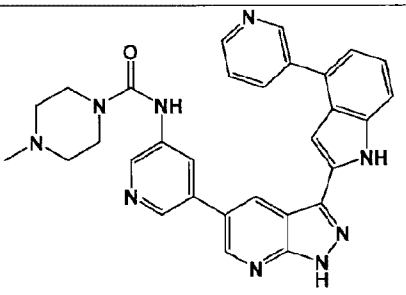
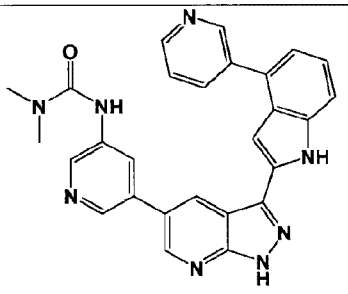
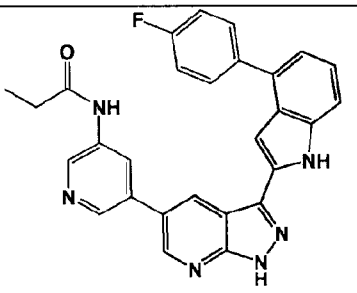
443		444	
445		446	
447		448	
449		450	

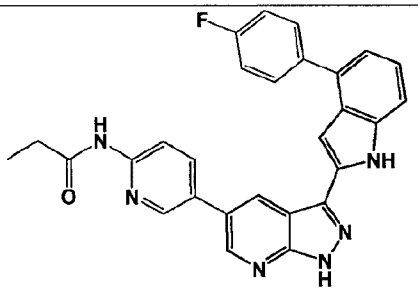
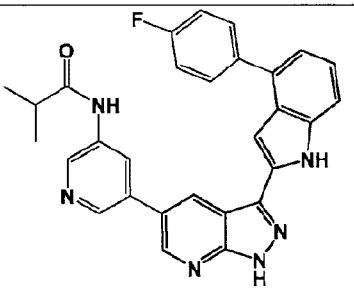
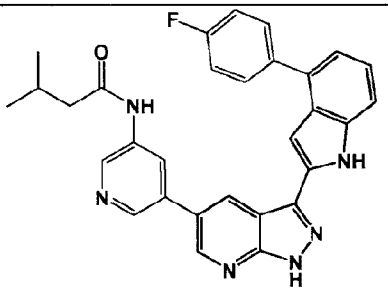
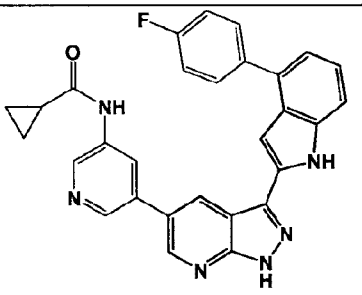
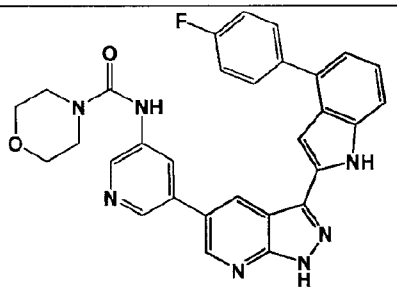
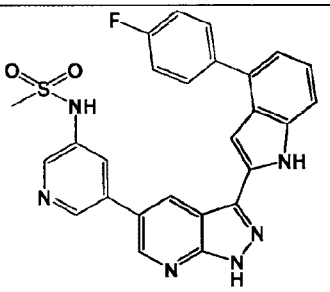
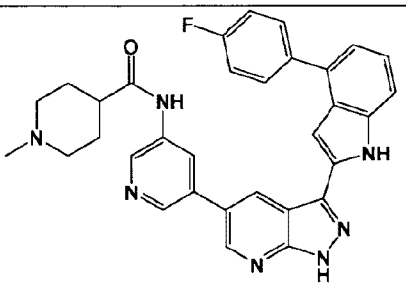
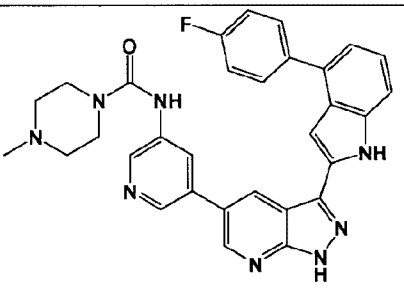
451		452	
453		454	
455		456	
457		458	

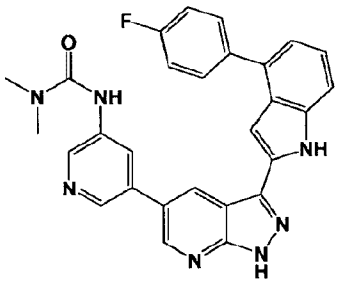
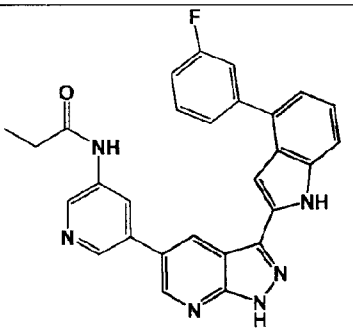
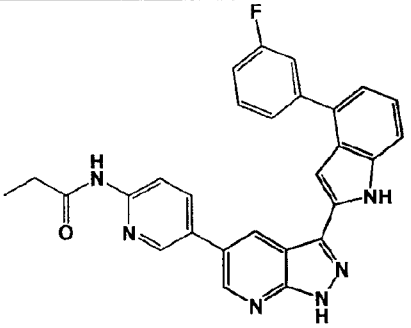
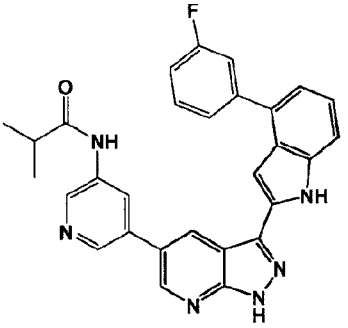
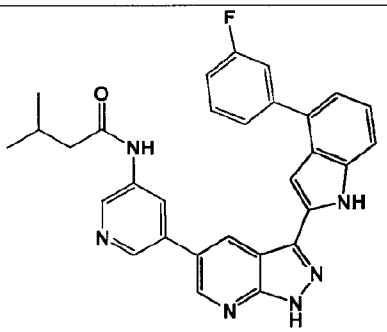
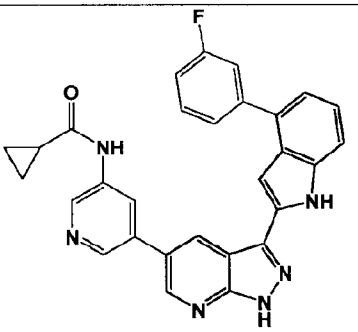
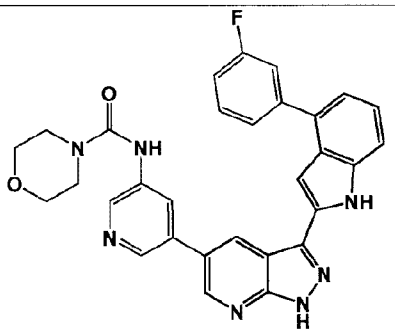
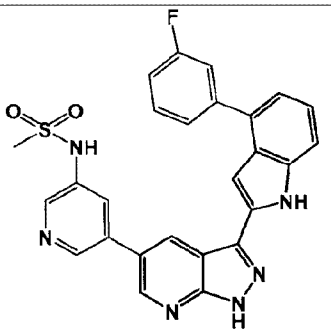
459		460	
461		462	
463		464	
465		466	

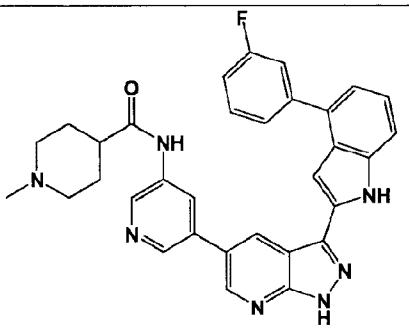
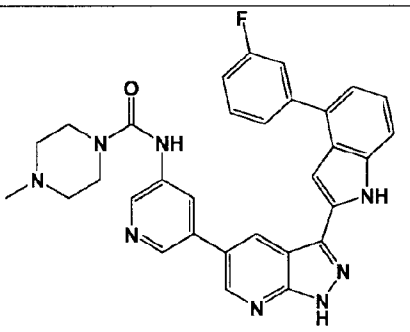
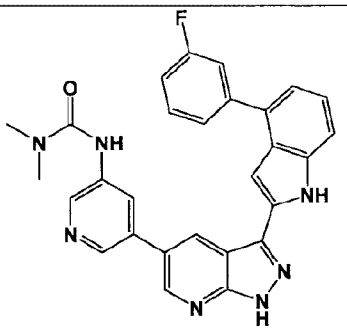
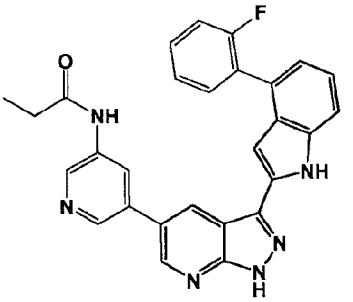
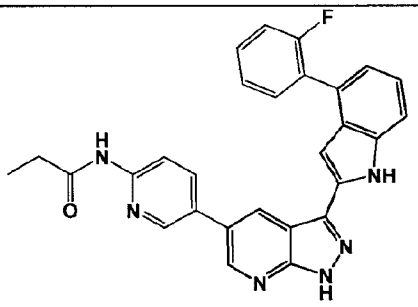
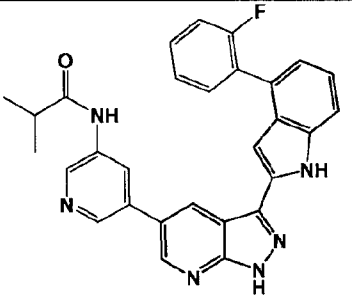
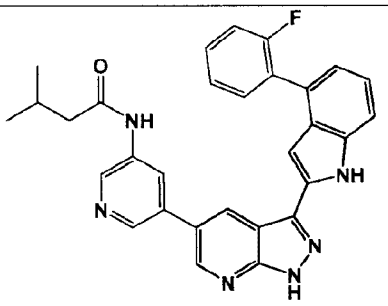
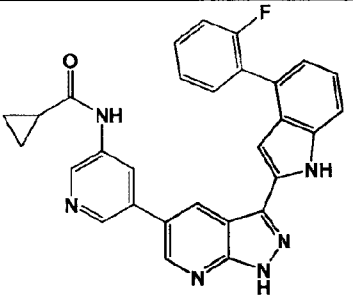
467		468	
469		470	
471		472	
473		474	

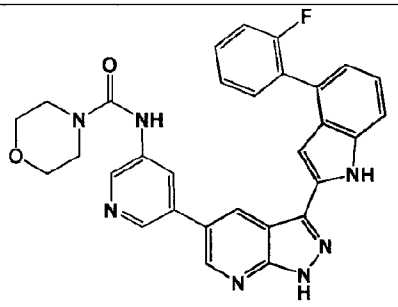
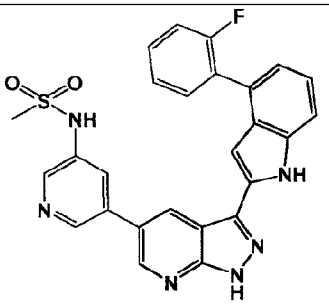
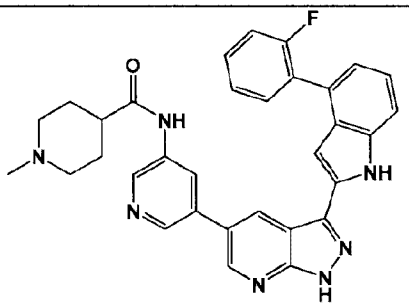
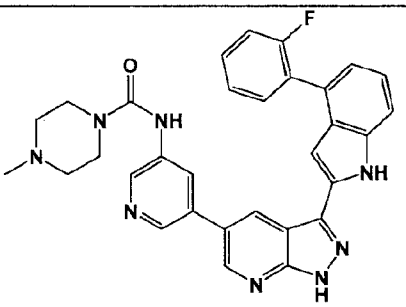
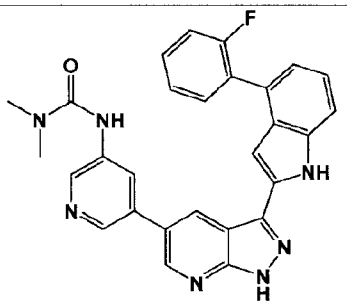
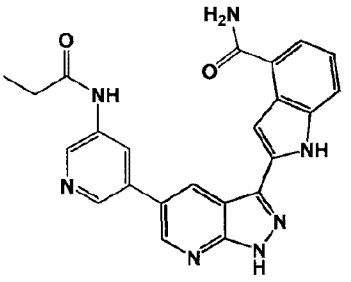
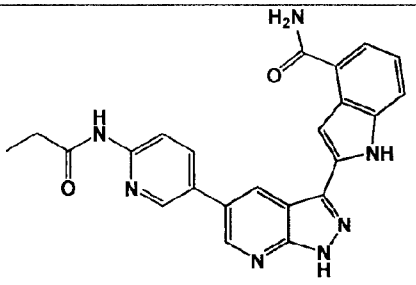
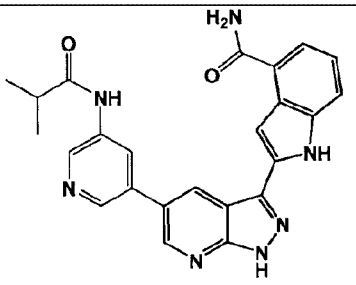
475		476	
477		478	
479		480	
481		482	

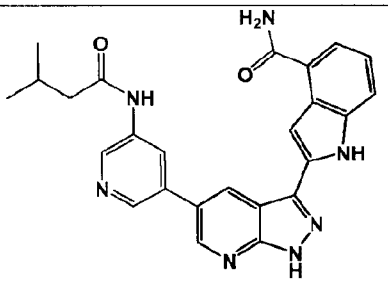
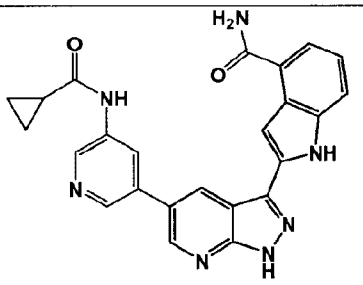
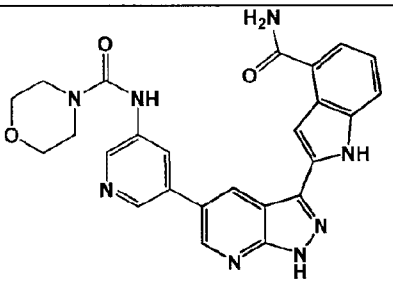
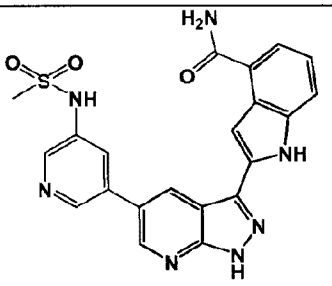
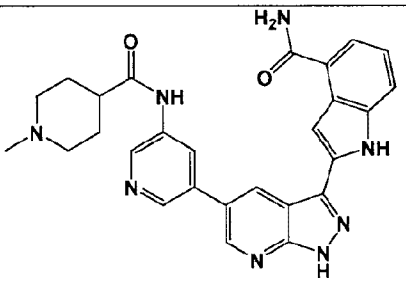
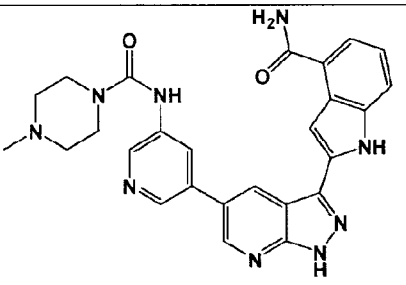
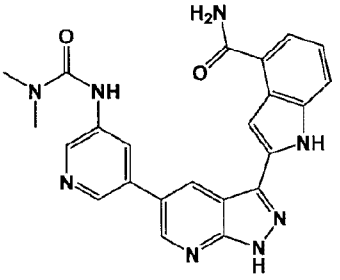
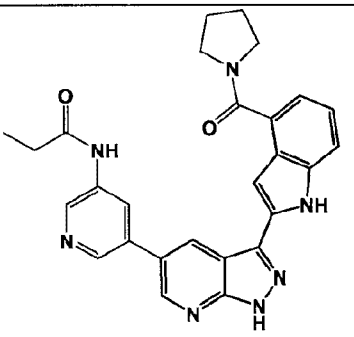
483		484	
485		486	
487		488	
489		490	

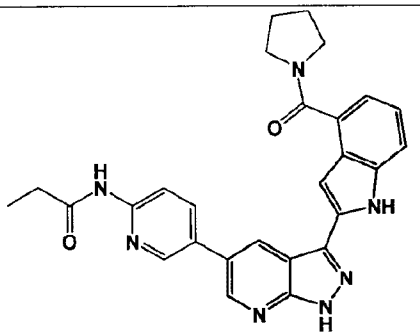
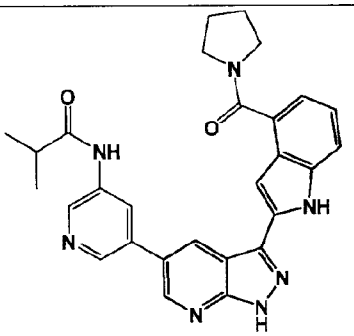
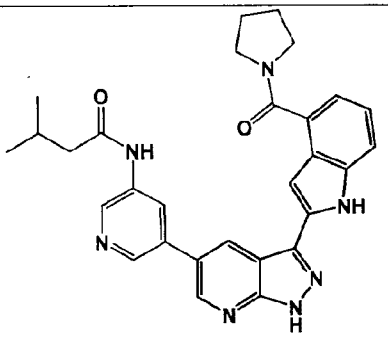
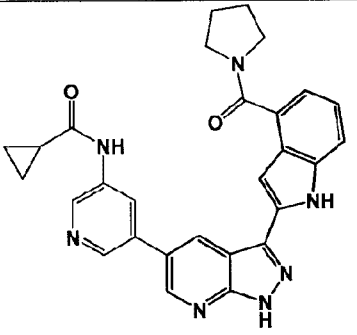
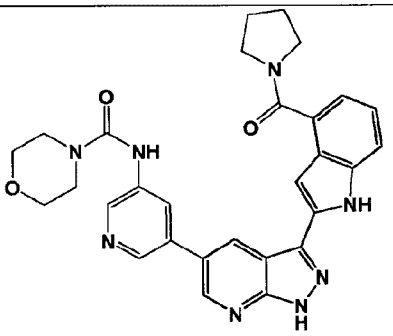
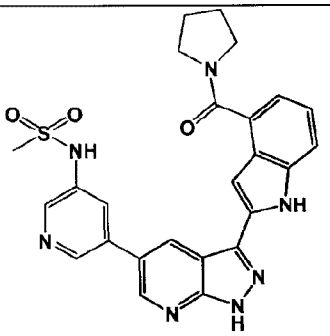
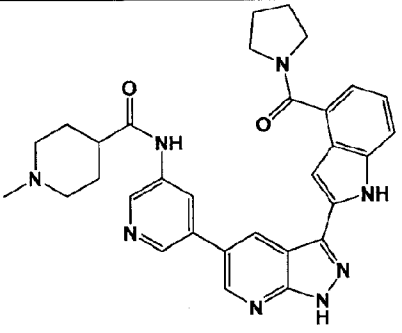
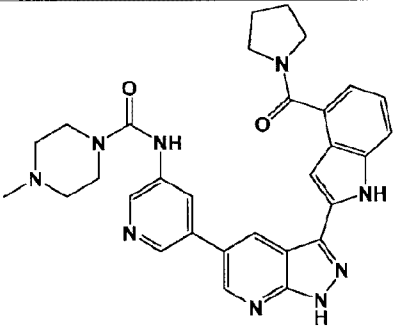
491		492	
493		494	
495		496	
497		498	

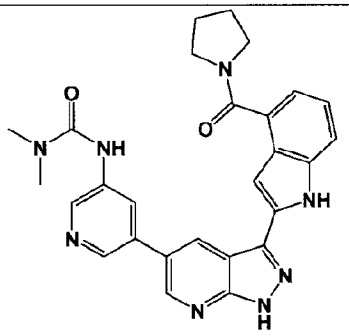
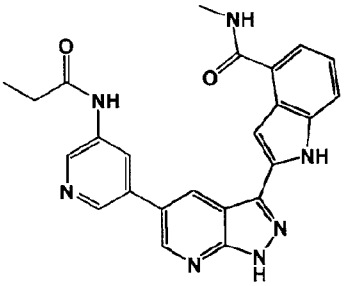
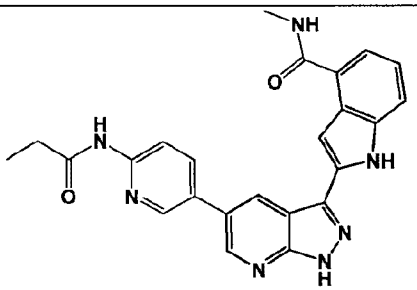
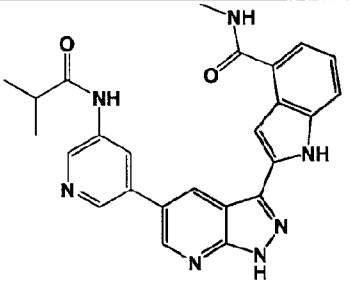
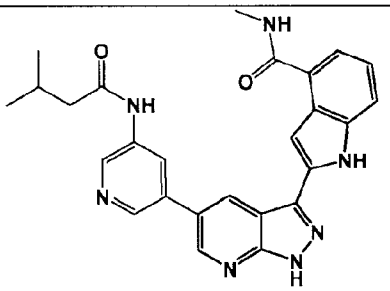
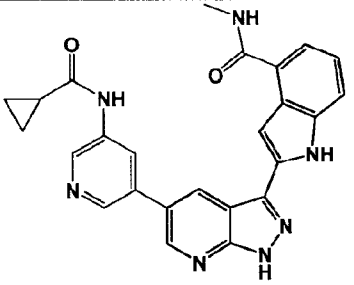
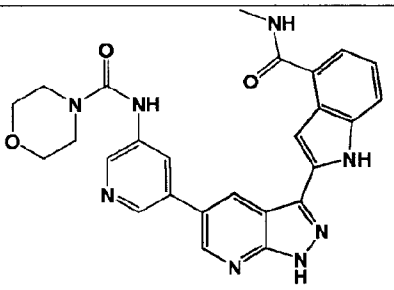
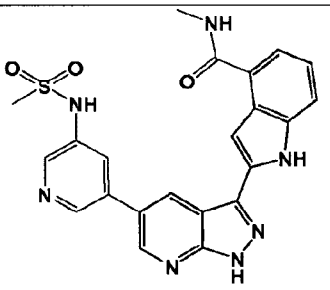
499		500	
501		502	
503		504	
505		506	

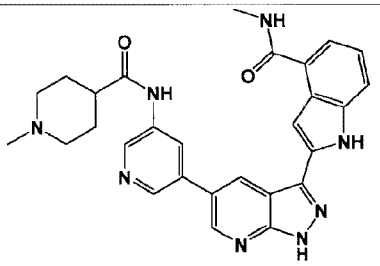
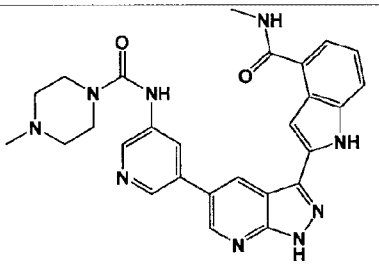
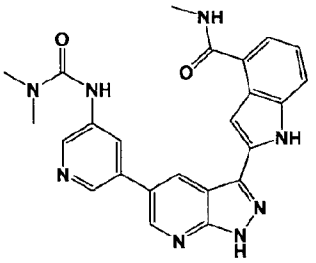
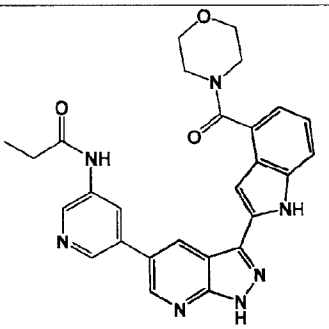
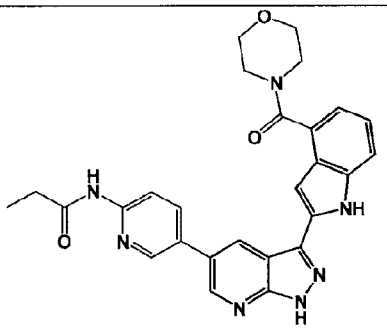
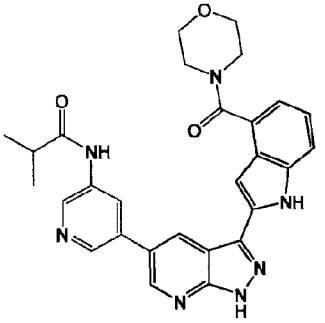
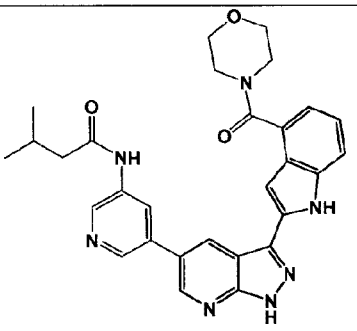
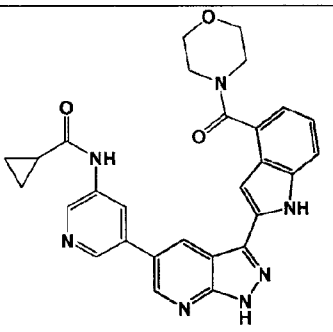
507		508	
509		510	
511		512	
513		514	

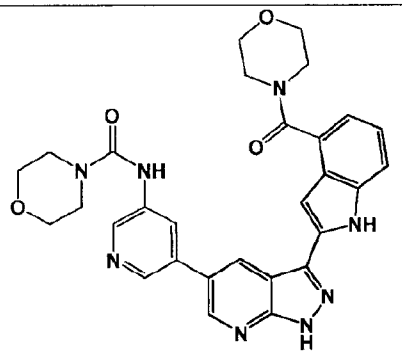
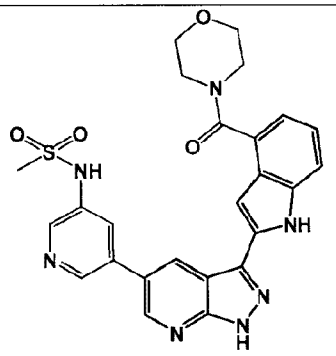
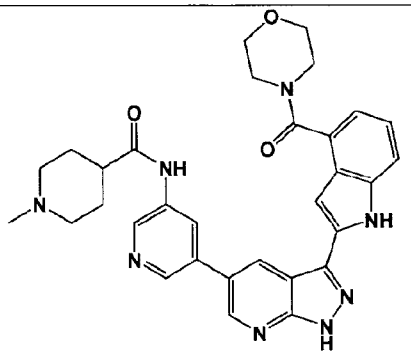
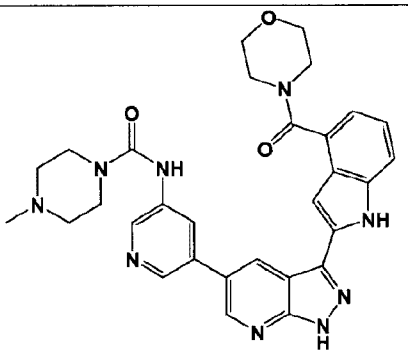
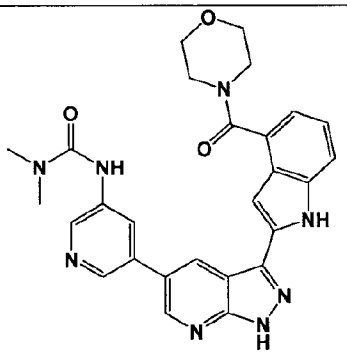
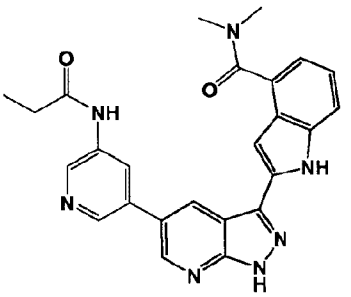
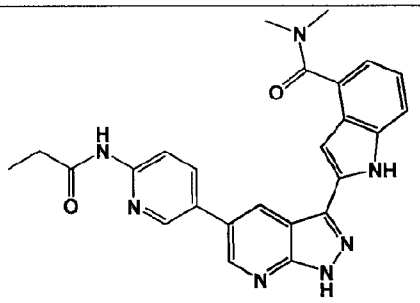
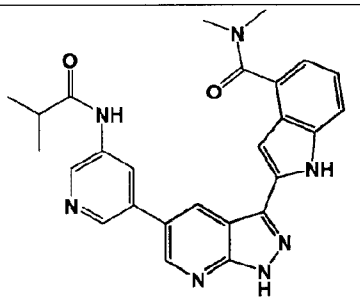
515		516	
517		518	
519		520	
521		522	

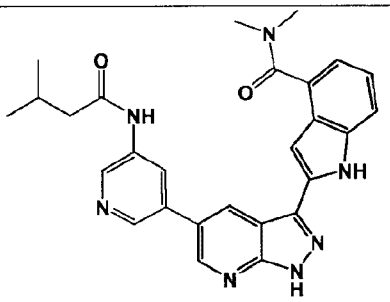
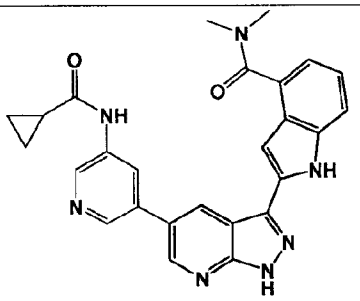
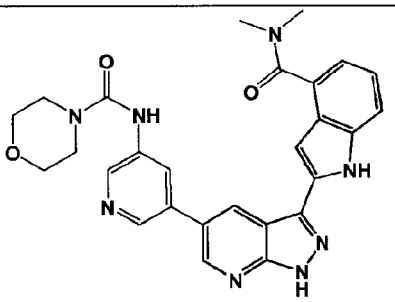
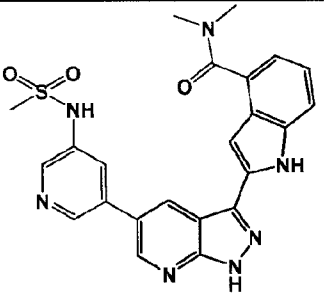
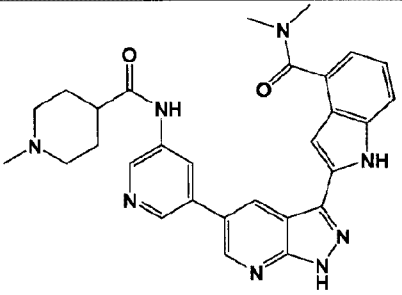
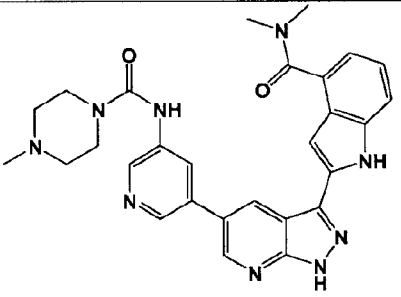
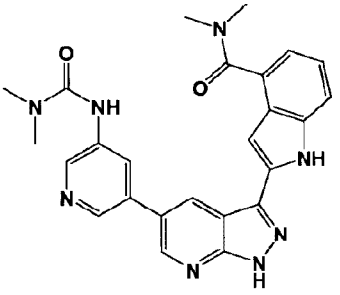
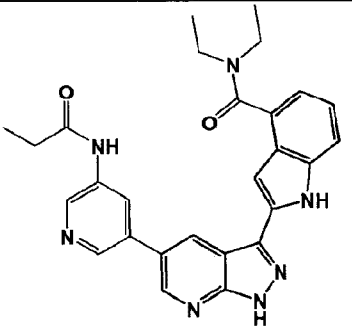
523		524	
525		526	
527		528	
529		530	

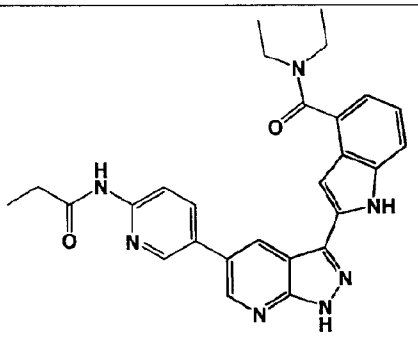
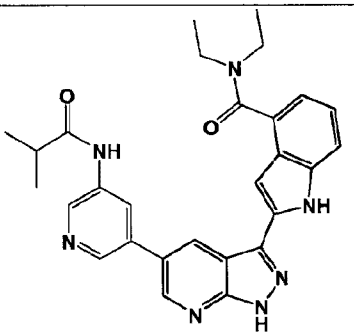
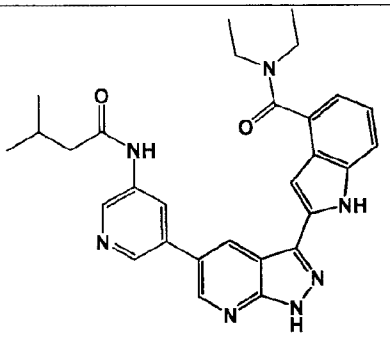
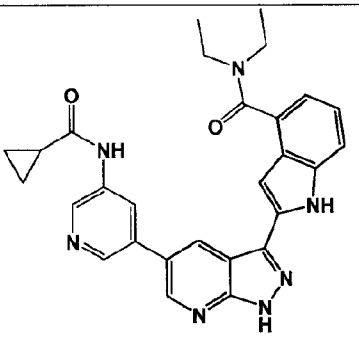
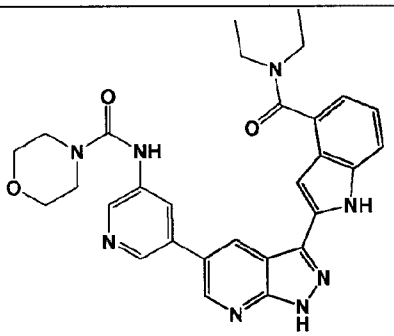
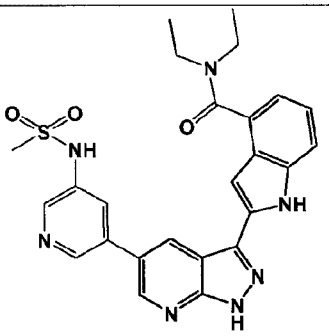
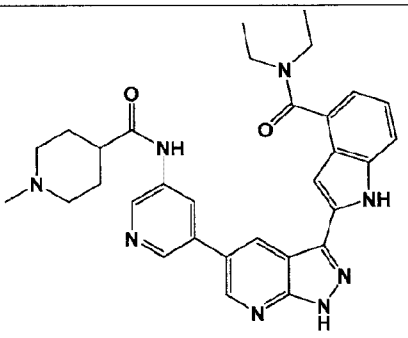
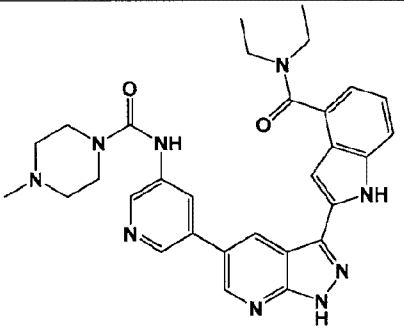
531		532	
533		534	
535		536	
537		538	

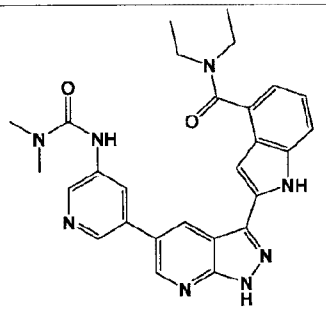
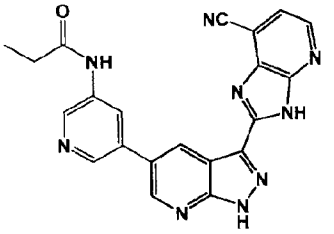
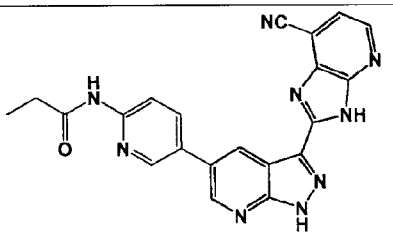
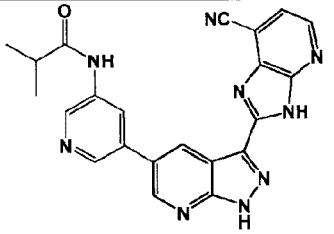
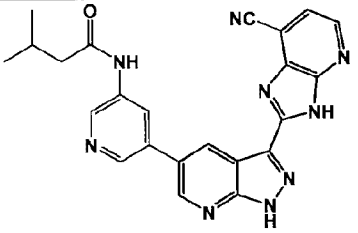
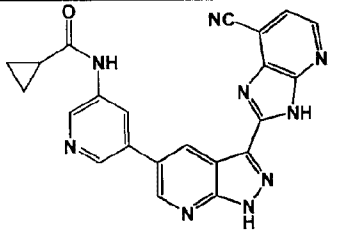
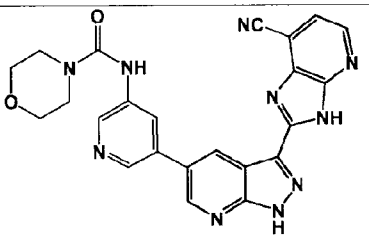
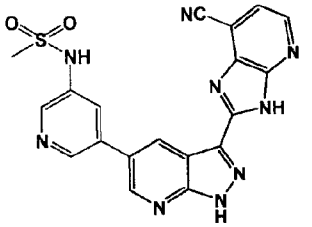
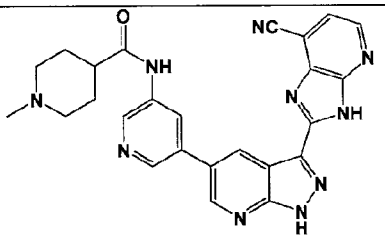
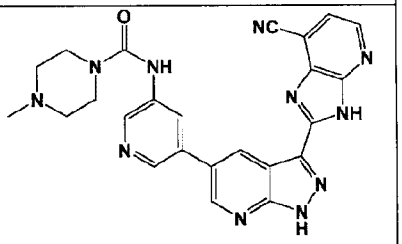
539		540	
541		542	
543		544	
545		546	

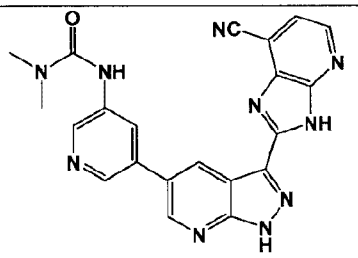
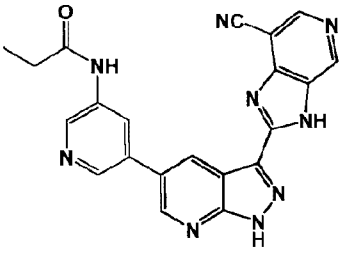
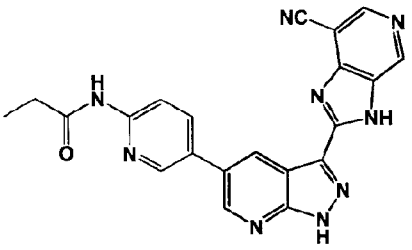
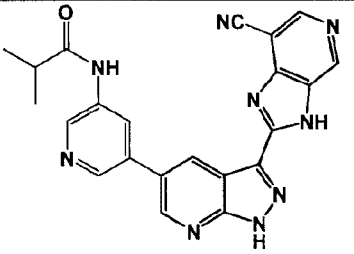
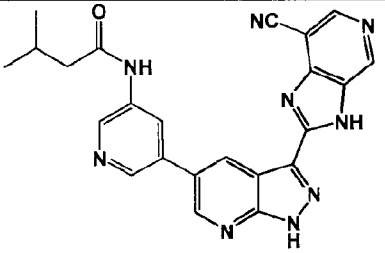
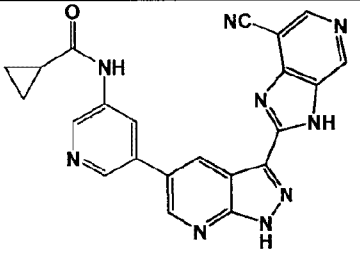
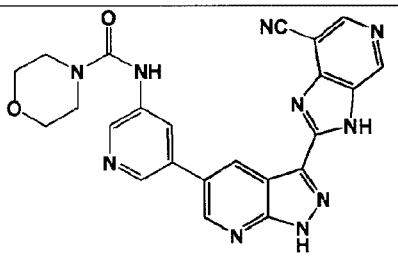
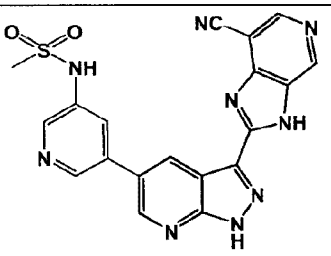
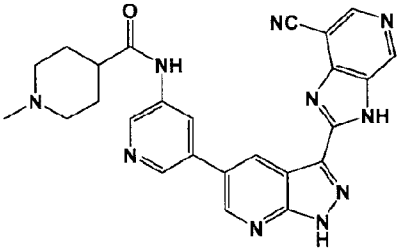
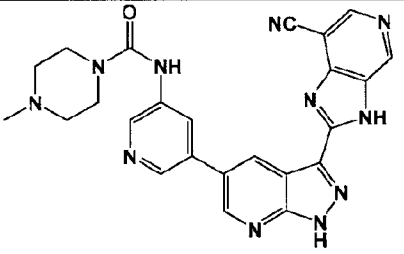
547		548	
549		550	
551		552	
553		554	

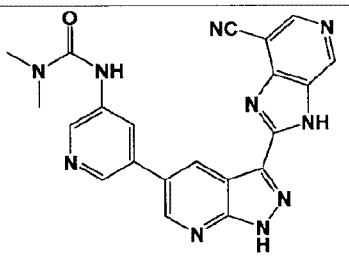
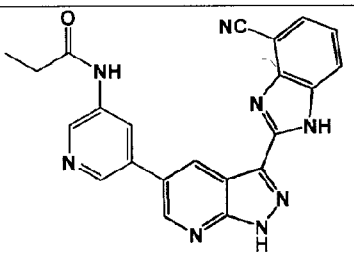
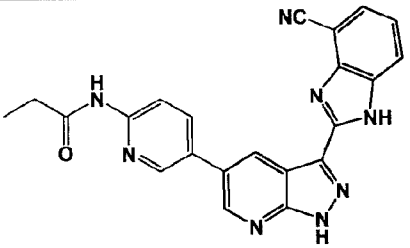
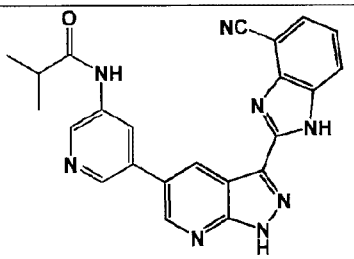
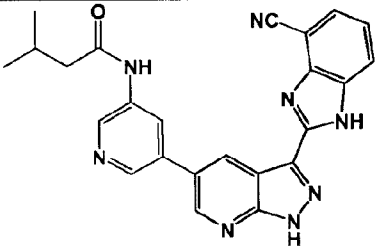
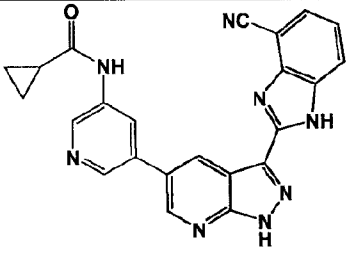
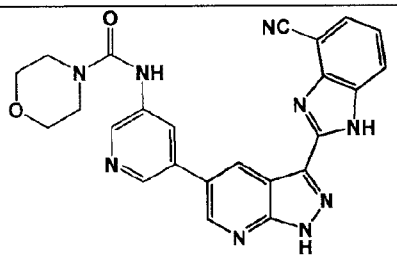
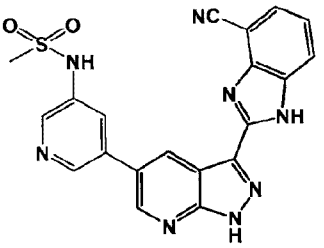
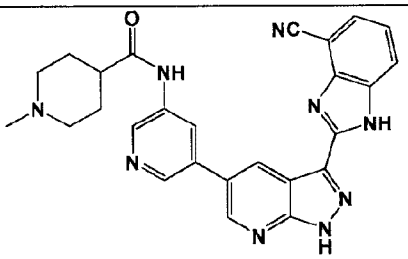
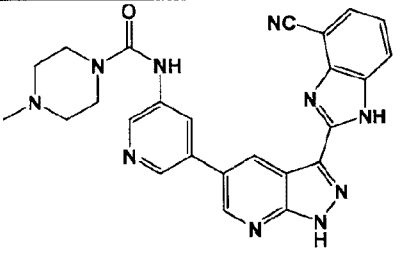
555		556	
557		558	
559		560	
561		562	

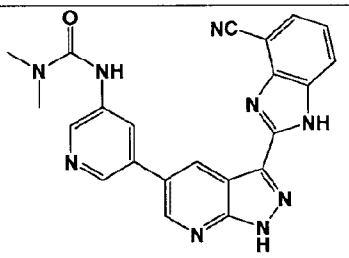
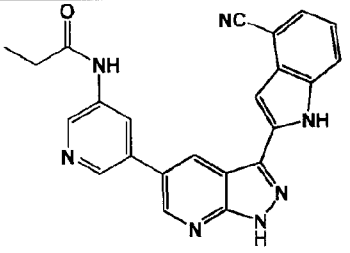
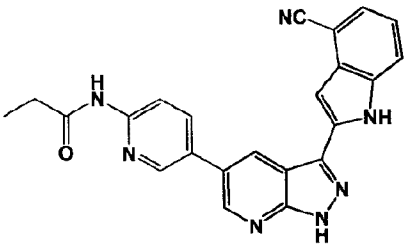
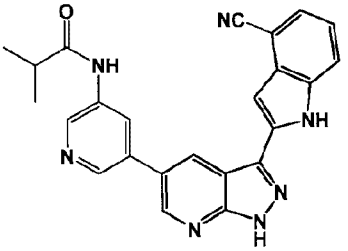
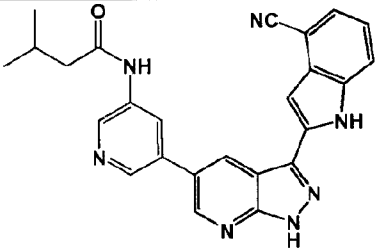
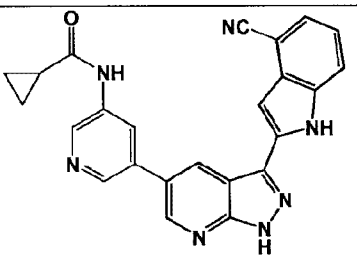
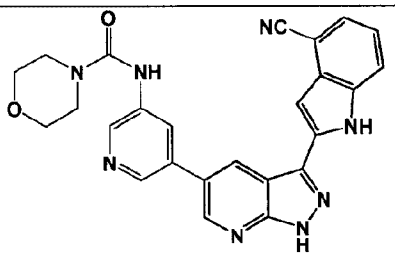
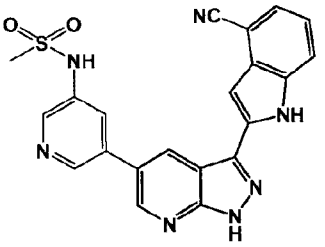
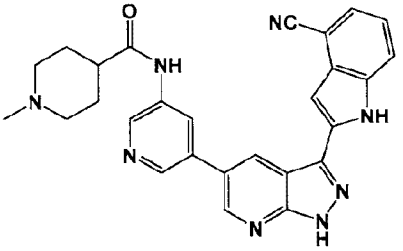
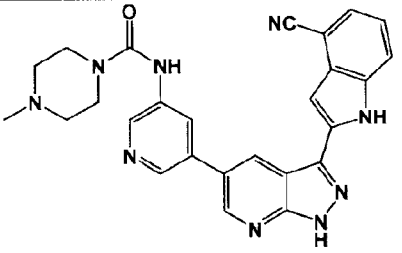
563		564	
565		566	
567		568	
569		570	

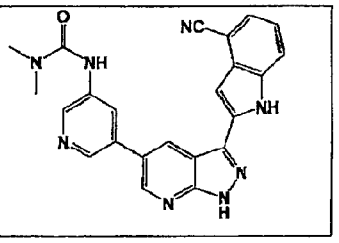
571		572	
573		574	
575		576	
577		578	

579		580	
581		582	
583		584	
585		586	
587		588	

589		590	
591		592	
593		594	
595		596	
597		598	

599		600	
601		602	
603		604	
605		606	
607		608	

609		610	
611		612	
613		614	
615		616	
617		618	

619	

Compound preparation

[00159] The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available. It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

[00160] It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* 6th Ed., John Wiley & Sons (2007), Carey and Sundberg, *Advanced Organic Chemistry* 5th Ed., Springer (2007), *Comprehensive Organic Transformations: A Guide to Functional Group Transformations*, 2nd Ed., John Wiley & Sons (1999) and the like.

[00161] The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be

found for example in T. Greene and P. Wuts *Protecting Groups in Organic Synthesis*, 4th Ed., John Wiley & Sons (2007).

[00162] The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application.

[00163] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the invention as described, and claimed herein. The reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the invention without exhaustive examples.

[00164] Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the invention.

[00165] (^{1}H) nuclear magnetic resonance spectra (NMR) were measured in the indicated solvents on a Bruker™ NMR spectrometer (Avance TM DRX300, 300 MHz for ^{1}H or Avance TM DRX500, 500 MHz for ^{1}H) or Varian™ NMR spectrometer (Mercury 400BB, 400 MHz for ^{1}H). Peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak multiplicities are denoted as follows, s, singlet; bs, broad singlet; d, doublet; bd, broad doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet.

[00166] The following abbreviations have the indicated meanings:

brine = saturated aqueous sodium chloride

$CDCl_3$ = deuterated chloroform

CDI = 1,1'-carbonyldiimidazole

DCM= dicloromethane

DIPEA = diisopropylethylamine

DMF= N,N-dimethylformamide

DMSO = dimethylsulfoxide

DMSO-d_6 = deuterated dimethylsulfoxide

ESIMS = electron spray mass spectrometry

EtOAc = ethyl acetate

EtOH = ethanol

HCl = hydrochloric acid

HOAc = acetic acid

H_2SO_4 = sulfuric acid

$KMnO_4$ = potassium permanganate

KOAc = potassium acetate

K_3PO_4 = potassium phosphate

LDA = lithium diisopropylamide

MeOH = methanol

$MgSO_4$ = magnesium sulfate

Na_2CO_3 = sodium carbonate

$NaHCO_3$ = sodium bicarbonate

$NaHSO_4$ = sodium bisulfate

NaOAc = sodium acetate

NaOH = sodium hydroxide

NH_4OH = ammonium hydroxide

NMR = nuclear magnetic resonance

Pd/C = palladium(0) on carbon

$Pd(dppf)_2Cl_2$ = 1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride

$Pd(PPh_3)_4$ = tetrakis(triphenylphosphine)palladium(0)

$Pd(PPh_3)_2Cl_2$ = bis(triphenylphosphine)palladium(II) chloride

PPTS = pyridinium p-toluenesulfonate

p-TsOH = *p*-toluenesulfonic acid

r.t. = room temperature

S(0) = elemental sulfur

TFA = trifluoroacetic acid

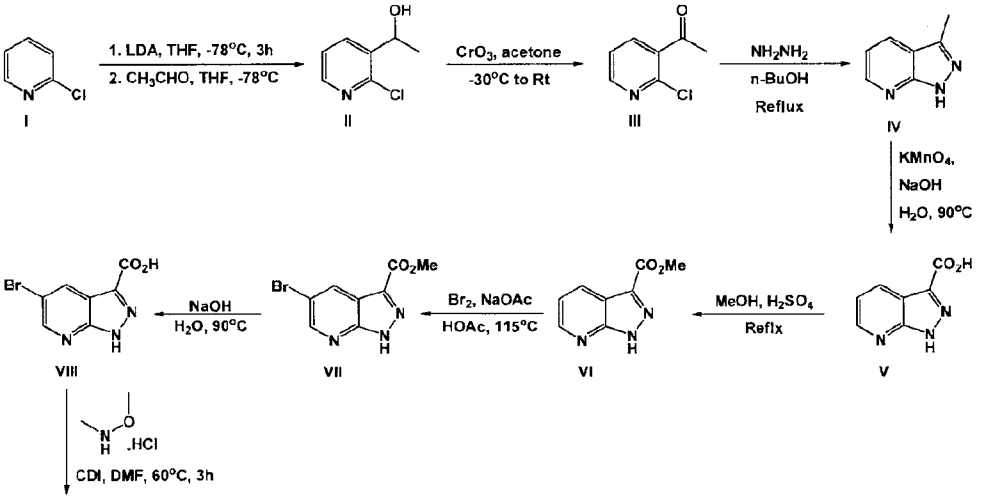
THF = tetrahydrofuran

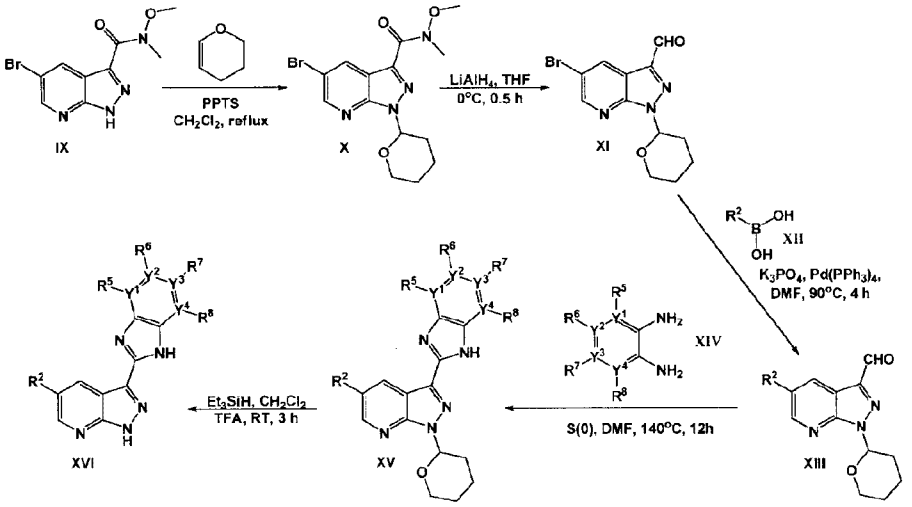
TLC = thin layer chromatography

[00167] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided herein. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

General procedures

[00168] Compounds of Formula **Ia** and **Ib** of the present invention can be prepared as depicted in Scheme **1**.

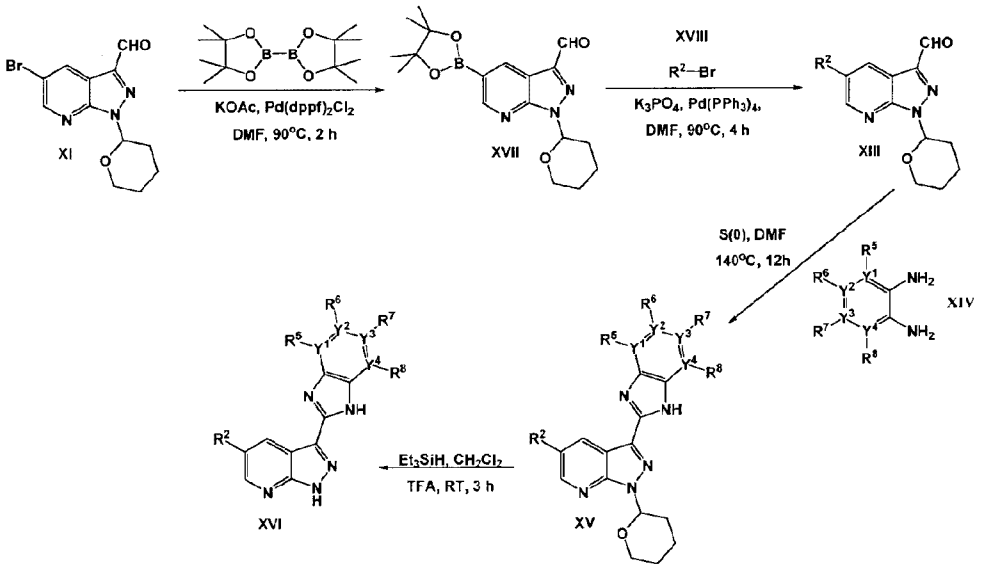




Scheme 1

[00169] Scheme **1** describes a method for preparation of 1H-pyrazolo[3,4-*b*]pyridine derivatives (**XVI**) by reacting the 3-anion of 2-chloropyridine (**I**) with acetaldehyde to form 1-(2-chloropyridin-3-yl)ethanol (**II**). The alcohol is then oxidized to (**III**) before cyclizing in the presence of hydrazine to 3-methyl-1H-pyrazolo[3,4-*b*]pyridine (**IV**). The methyl is oxidized and esterified to methyl 1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VI**). The ester (**VI**) is treated with bromine to form methyl 5-bromo-1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VII**) before hydrolyzing the ester to acid **VIII**. Acid **VIII** was reacted with N,O-dimethylhydroxylamine to form the Weinreb amide (**IX**). After protection of the 1H-pyrazolo[3,4-*b*]pyridine NH, the Weinreb amide is reduced to aldehyde **XI**. 5-substituted 1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde derivatives (**XIII**) are prepared by Suzuki Coupling of 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**XI**) with various boronic acid derivatives (**XII**). Aldehyde **XIII** is reacted with various substituted and unsubstituted aryl/heteroaryl-3,4-diamines (**XIV**) to form **XV**. Final deprotection of the pyrazolone nitrogen yields the desired 1H-pyrazolo[3,4-*b*]pyridine derivative (**XVI**).

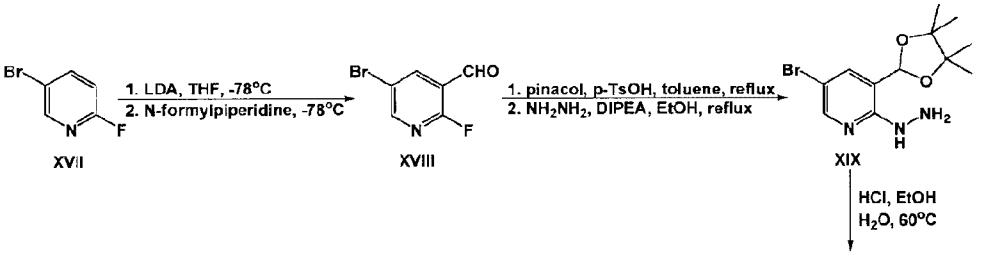
[00170] Compounds of Formula **Ia** and **Ib** of the present invention can also be prepared as depicted in Scheme **2**.

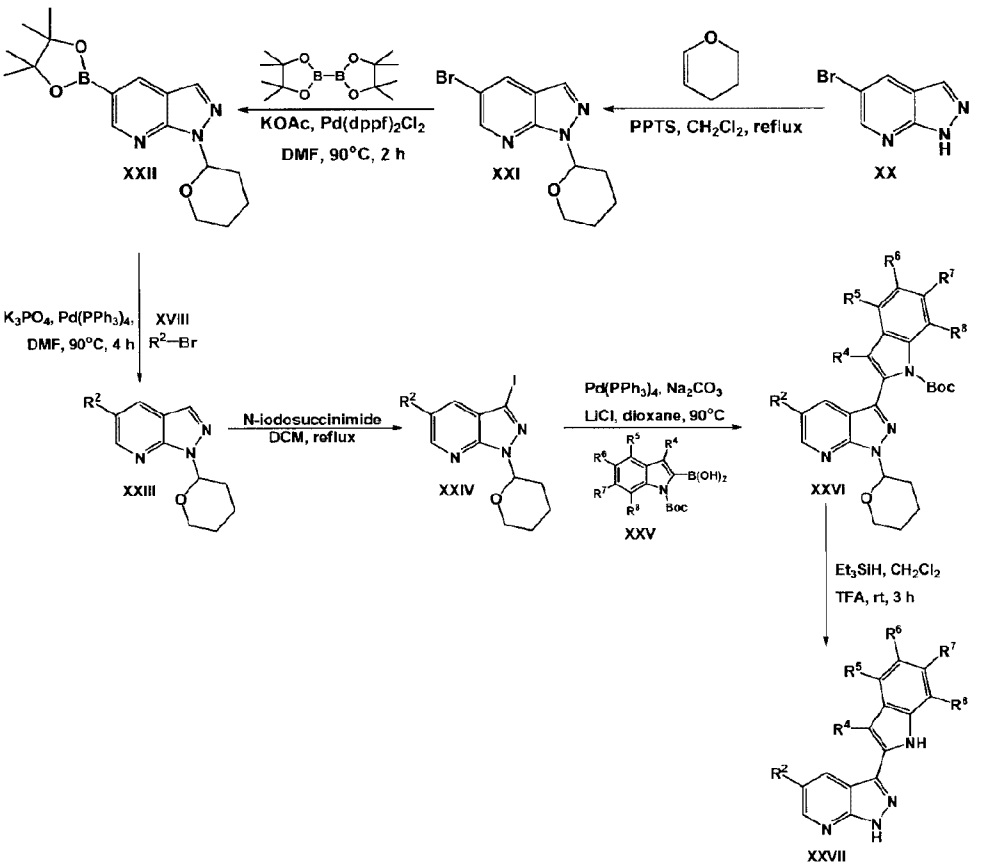


Scheme 2

[00171] Scheme **2** describes an alternative method for preparation of 1H-pyrazolo[3,4-*b*]pyridine derivatives (**XVI**) by reacting 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**XI**) with bis(pinacolato)diboron to form the borate ester (**XVII**). Suzuki coupling with various bromides (**XVIII**) or chlorides yields 1H-pyrazolo[3,4-*b*]pyridine derivatives (**XIII**). Aldehyde (**XIII**) is reacted with various 1,2-diamines (**XIV**) to produce (**XV**). Final deprotection of the pyrazole nitrogen yields the desired 1H-pyrazolo[3,4-*b*]pyridine derivatives (**XVI**).

[00172] Compounds of Formula **Ic** of the present invention can also be prepared as depicted in Scheme **3**.





Scheme 3

[00173] Scheme **3** describes a method for preparation of 3-(1H-indol-2-yl)-1H-pyrazolo[3,4-*b*]pyridine derivatives (**XXVII**) by first selective deprotonation at position-3 of 5-bromo-2-fluoropyridine (**XVII**) with LDA followed by N-formylpiperidine quench to produce 5-bromo-2-fluoronicotinaldehyde (**XVIII**). Aldehyde **XVIII** was condensed with pinacol followed by nucleophilic aromatic substitution by hydrazine to give 5-bromo-2-hydrazinyl-3-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)pyridine (**XIX**). XIX was then cyclized under acidic conditions to yield 5-bromo-1H-pyrazolo[3,4-*b*]pyridine (**XX**). The 1H-pyrazolo[3,4-*b*]pyridine NH was THP protection followed by reaction of the bromide (**XXI**) with bis(pinacolato)diboron to form the borate ester (**XXII**). Suzuki coupling with various bromides (**XVIII**) or chlorides yields 1H-pyrazolo[3,4-*b*]pyridine derivatives (**XXIII**). Iodization of position-3 of 1H-pyrazolo[3,4-*b*]pyridine (**XXIII**) with N-iodosuccinimide followed by Suzuki Coupling with various Boc-protected 1H-indol-2-

ylboronic acids (XXV) to produce (XXVI). Final deprotection of the pyrazole and indole nitrogens yields the desired 3-(1H-indol-2-yl)-1H-pyrazolo[3,4-*b*]pyridine derivatives (XXVII).

Illustrative Compound Examples

[00174] Synthesis of intermediate 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde **XI** is depicted above in scheme **1**.

Step 1

[00175] A solution of 2-chloropyridine (I) (9.39 mL, 0.1 mol) in anhydrous THF (50 mL) was added slowly to a solution of LDA (2.0 M solution in THF/hexane/ethylbenzene, 50 mL, 0.1 mol) in THF (200 mL) stirred at -78°C under nitrogen. The stirring was continued at -78°C for an additional 3 h before adding acetaldehyde (6.17 mL, 0.110 mol). The solution was stirred at -78°C for another 2 h before allowing the temperature to rise to -40°C. A solution of water (4 mL) in THF (40 mL) was added slowly to the solution. When the temperature reached -10°C, additional water (200 mL) was added to the solution. The solution was extracted with ethyl ether (3 x 100 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to get a brown viscous residue. The crude product was purified on a flash silica gel column (1:1 DCM:hexane→100% DCM) to produce 1-(2-chloropyridin-3-yl)ethanol (II) as a brown viscous oil (6 g, 38.1 mmol, 38% yield). ^1H NMR ($CDCl_3$) δ ppm 1.52 (d, *J*=6.41 Hz, 3 H), 2.51 (bs, 1 H), 5.24 (m, 1 H), 7.28 (m, 1 H), 7.97 (dd, *J*=7.72, 1.70, 1 H), 8.27 (dd, *J*=7.72, 1.79, 1 H).

Step 2

[00176] To a solution of 1-(2-chloropyridin-3-yl)ethanol (II) in dry acetone at -30°C under nitrogen was added in portions chromium (VI) oxide (1.80 g, 18 mmol). The solution was further stirred 15 min at -30°C and allowed to warm to room temperature. The solution was stirred for 3 h at room temperature before adding isopropanol (10 mL). The solution was made alkaline by slowly adding a saturated $NaHCO_3$ solution. The solution was filtered through a bed of Celite™. The solids were washed by DCM. The

organic phase of the filtrate was separated and the aqueous phase extracted with DCM (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 1-(2-chloropyridin-3-yl)ethanone (**III**) as a brown liquid (0.72 g, 4.63 mmol, 77% yield). ^{1}H NMR ($CDCl_3$) δ ppm 2.71 (s, 3 H), 7.35 (dd, *J*=7.63, 4.80 Hz, 1 H), 7.91 (dd, *J*=7.54, 1.88 Hz, 1 H), 8.55 (dd, *J*=4.71, 1.88 Hz, 1 H).

Step 3

[00177] To a solution of 1-(2-Chloropyridin-3-yl)ethanone (**III**) (0.311 g, 2 mmol) in n-butanol (10 mL) was added hydrazine hydrate (1.45 mL, 30 mmol). The reaction was refluxed overnight. The solution was cooled and the solvent was evaporated under vacuum. The residue was dissolved in DCM and washed successively by water and brine. The organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 3-methyl-1H-pyrazolo[3,4-*b*]pyridine (**IV**) as a white solid (192 mg, 1.44 mmol, 72% yield). ^{1}H NMR ($CDCl_3$) δ ppm 2.64 (s, 3 H), 7.14 (dd, *J*=8.01, 4.62 Hz, 1 H), 8.14 (dd, *J*=7.54, 1.88 HZ, 1 H), 8.59 (dd, *J*=4.52, 1.32 HZ, 1 H), 11.68 (brs, 1H).

Step 4

[00178] To a solution of NaOH (0.88 g, 22 mmol) in water (20 mL) was added 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (**IV**) (0.4 g, 3 mmol). The suspension was heated at 80°C until a clear solution was obtained. A solution of $KMnO_4$ (1.73 g, 11 mmol) in water (180 mL) was added slowly over 2 h while heating the solution at 80°C. The solution was heated at 90°C for an additional 2 h until the complete disappearance of starting material was observed by TLC. The solution was cooled to 70°C and filtered through a pad of Celite. The solids were washed by boiling water. The combined filtrate was cooled to 0°C, acidified with conc. H_2SO_4 to pH=2 and extracted with n-butanol (2 x 10 mL). The n-butanol layer was concentrated under reduced pressure to get a white residue which was dissolved in DCM by adding minimum amount of MeOH and then filtered. The filtrate was concentrated to give 1H-pyrazolo[3,4-*b*]pyridine-3-carboxylic acid (**V**) as a white solid (390 mg, 2.39 mmol, 81% yield). ^{1}H NMR ($CDCl_3$) δ ppm 7.37

(dd, *J*=8.10, 4.52 Hz, 1 H), 8.47 (dd, *J*=7.54, 1.88 Hz, 1 H), 8.62 (dd, *J*=4.52, 1.32 Hz, 1 H), 14.37 (brs, 1 H).

Step 5

[00179] To a solution of 1*H*-pyrazole[3,4-*b*]pyridine-3-carboxylic acid (**V**) (0.39 g, 2.4 mmol) in dry MeOH (10 mL) was added concentrated H_2SO_4 (4 drops) and refluxed for 6 h under nitrogen. The solution was cooled and the solvent was evaporated under vacuum. The residue was partitioned between DCM and saturated $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified on a flash silica gel column (100% DCM →100:3 DCM:MeOH) to produce methyl 1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VI**) as a white solid (382 mg, 2.16 mmol, 90% yield). ^{1}H NMR ($CDCl_3$) δ ppm 4.08 (s, 3 H), 7.38 (m, 1 H), 8.63 (dd, *J*=8.10, 1.51 Hz, 1 H), 8.72 (dd, *J*=4.62, 1.41 Hz, 1 H); ESIMS found for $C_8H_7N_3O_2$ *m/z* 178.2 (M+H).

Step 6

[00180] A mixture of methyl 1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VI**) (0.177 g, 1 mmol), sodium acetate (0.492 g, 6 mmol) and bromine (0.308 mL, 6 mmol) in glacial acetic acid (5 mL) was heated overnight at 120°C in a sealed tube. The solution was cooled and poured into water. The solids formed were filtered, washed with water and dried at room temperature under vacuum. The crude product was purified on a flash silica gel column (100% DCM →100:2 DCM:MeOH) to produce methyl 5-bromo-1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VII**) as a white solid (78 mg, 0.31 mmol, 30% yield). ^{1}H NMR ($CDCl_3$) δ ppm 3.95 (s, 3 H), 8.62 (d, *J*=3.01 Hz, 1 H), 8.73 (d, *J*=3.01 Hz, 1 H); ESIMS found for $C_8H_6BrN_3O_2$ *m/z* 256.3 (M+H).

Step 7

[00181] A suspension of methyl 5-bromo-1H-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**VII**) (70 mg, 0.27 mmol) in aqueous 1N NaOH solution (20 mL) was heated at 90°C for 3 h until the solution became clear. The solution was then cooled to 0°C and acidified with a 10% HCl solution. The solids formed were filtered, washed with cold

water and dried at room temperature under vacuum to give 5-bromo-1H-pyrazolo[3,4-*b*]pyridine-3-carboxylic acid (**VIII**) as a white solid (60 mg, 0.25 mmol, 92% yield). ^{1}H NMR ($CDCl_3$) δ ppm 8.58 (d, *J*=3.01 Hz, 1 H), 8.66 (d, *J*=3.01 Hz, 1 H); ESIMS found for $C_7H_4BrN_3O_2$ *m/z* 242.1 (M+H).

Step 8

[00182] To a solution of 5-bromo-1*H*-pyrazole[3,4-*b*]pyridine-3-carboxylic acid (**VIII**) (0.242 g, 1 mmol) in dry DMF (5 mL) was added CDI (0.178 g, 1.1 mmol) and heated for 3 h at 65°C under nitrogen. The solution was cooled to room temperature and N,O-dimethyl hydroxylamine hydrochloride (0.107 g, 1.1 mmol) was added to the solution. The solution was again heated for 3 h at 65°C under nitrogen. The solution was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM, washed successively with a 10% HCl solution, a saturated $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to produce 5-bromo-N-methoxy-N-methyl-1H-pyrazolo[3,4-*b*]pyridine-3-carboxamide (**IX**) as a white solid (260 mg, 0.91 mmol, 92% yield). ^{1}H NMR ($CDCl_3$) δ ppm 3.55 (s, 3H), 3.78 (s, 3H), 8.59 (d, *J*=3.01 Hz, 1 H), 8.67 (d, *J*=3.01 Hz, 1 H); ESIMS found for $C_9H_9BrN_4O_2$ *m/z* 285.4 (M+H).

Step 9

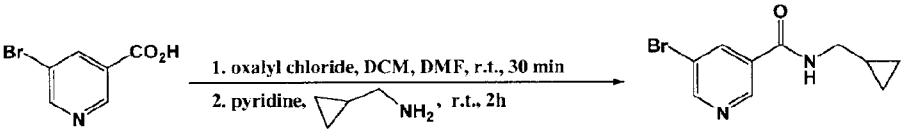
[00183] To a solution of 5-bromo-N-methoxy-N-methyl-1H-pyrazolo[3,4-*b*]pyridine-3-carboxamide (**IX**) (0.250 g, 0.88 mmol) in dry DCM (10 mL) was added 3,4-dihydro-2H-pyran (0.179 mL, 1.98 mmol) and PPTS (22 mg, 0.08 mmol) and refluxed 5 h under nitrogen. Another equivalent of 3,4-dihydro-2H-pyran (0.179 mL, 1.98 mmol) and PPTS (22 mg, 0.08 mmol) was added and the solution was further heated at refluxed overnight under nitrogen. The solution was cooled, diluted with DCM, washed subsequently with a saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 5-bromo-N-methoxy-N-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carboxamide (**X**) as a viscous liquid (302 mg, 0.82 mmol, 93% yield). ^{1}H NMR ($CDCl_3$) δ ppm 1.51-1.62 (m, 2 H), 1.91-2.13 (m, 2H), 2.33-2.44 (m, 2H), 3.40 (s, 3 H), 3.66 (m,

1H), 3.75 (s, 3H), 3.87-3.98 (m, 1 H), 6.07 (dd, *J*=10.07, 2.52 Hz, 1 H), 8.57 (d, *J*=3.01 Hz, 1 H), 8.73 (d, *J*=3.01 Hz, 1 H); ESIMS found for $C_{14}H_{17}BrN_4O_3$ *m/z* 369.4 (M+H).

Step **10**

[00184] To a solution of 5-bromo-N-methoxy-N-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carboxamide (**X**) (0.290 g, 0.78) in dry THF (5 mL) stirred at 0°C under nitrogen was added lithium aluminum hydride (36 mg, 0.94 mmol). The solution was further stirred at 0°C for 30 min. The reaction was quenched with a 0.4 N $NaHSO_4$ solution (10 mL). The solution was extracted with DCM (3 x 15 mL). The combined organic layer was washed subsequently with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to produce 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**XI**) as a viscous liquid (218 mg, 0.70 mmol, 91% yield). ^{1}H NMR ($CDCl_3$) δ ppm 1.52-1.74 (m, 2 H), 1.95-2.18 (m, 2H), 2.37-2.49 (m, 2H) 3.87-3.98 (m, 1 H), 3.99 (m, 1H), 6.18 (dd, *J*=10.20, 2.39 Hz, 1 H), 8.73 (d, *J*=3.01 Hz, 1 H), 8.85 (d, *J*=3.01 Hz, 1 H), 10.16 (s, 1 H); ESIMS found for $C_{12}H_{12}BrN_3O_2$ *m/z* 310.4 (M+H).

[00185] Preparation of intermediate 5-bromo-N-(cyclopropylmethyl) nicotinamide (**XXIX**) is depicted below in Scheme **4**.



XXVIII **XXIX**

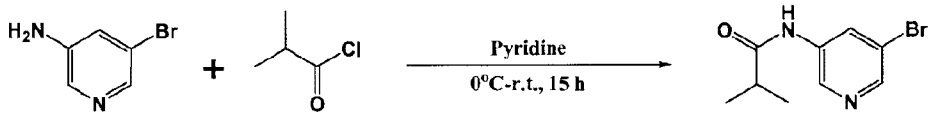
Scheme 4

Step **1-2**

[00186] To a solution of 5-bromonicotinic acid (**XXVIII**) (1.01 g, 5 mmol) in dry DCM (10 mL) under nitrogen was added oxalyl chloride (0.654 mL, 7.5 mmol) followed by dry DMF (0.1 mL). The solution was stirred at r.t. for 30 min. The solvent was evaporated under vacuum before adding dry pyridine (10 mL) followed by cyclopropylmethanamine (0.39 mL, 4.5 mmol). The solution was stirred at r.t. under

nitrogen for 2 h. The solution was poured into ice water, basified with sat. aq. $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over $MgSO_4$, concentrated and dried under vacuum to yield 5-bromo-N-(cyclopropylmethyl) nicotinamide (**XXIX**) as an off-white solid (0.82 g, 3.2 mmol, 71% yield). ^1H NMR (DMSO-d_6) δ ppm -0.07-0.07 (m, 2H), 0.15-0.29 (m, 2H), 0.68-0.88 (m, 1H), 2.93 (t, *J*=6.22 Hz, 2H), 8.20 (t, *J*=1.88 Hz, 1H), 8.62 (d, *J*=1.70 Hz, 2H), 8.75 (s, 1H); ESIMS found $C_{10}H_{11}BrN_2O$ *m/z* 254, 256 (M+, M+2).

[00187] Preparation of intermediate N-(5-bromopyridin-3-yl)isobutyramide (**XXXII**) is depicted below in Scheme **5**.



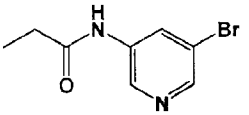
XXX **XXXI** **XXXII**

Scheme 5

Step **1**

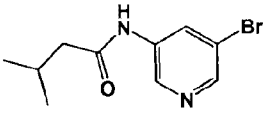
[00188] 3-Amino-5-bromo pyridine (**XXX**)(1eq) was dissolved in DCM and cooled to 0°C before adding pyridine (2.2 eq) and isobutyryl chloride (**XXXI**) (1.1 eq). The reaction mixture was stirred at r.t. for 15 h until TLC showed the reaction was complete. The reaction mixture was diluted with DCM and washed with water. The organic extract was dried, concentrated and purified by column chromatography using silica gel (100-200 mesh) to afford N-(5-bromopyridin-3-yl)isobutyramide (**XXXII**) as a off white solid, (71% yield). ^1H NMR ($CDCl_3$) δ ppm 8.55-8.35 (m, 3H), 7.32 (s, 1H), 2.59-2.48 (m, 1H), 1.28-1.27 (d, 6H); ESIMS found $C_9H_{11}BrN_2O$ *m/z* 243.05(M+H).

[00189] The following intermediates were prepared in accordance with the procedure described in the above Scheme **5**.



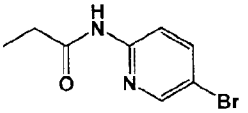
XXXIII

[00190] N-(5-bromopyridin-3-yl)propionamide (**XXXIII**): Off white solid (92% yield). ^{1}H NMR (DMSO-d_6) δ ppm 1.09 (t, *J*=7.54 Hz, 3H), 2.36 (q, *J*=7.54 Hz, 2H), 8.36 (m, 2H), 8.65 (d, *J*=2.07 Hz, 1H), 10.26 (s, 1H); ESIMS found $C_8H_9BrN_2O$ *m/z* 231 (M+H).



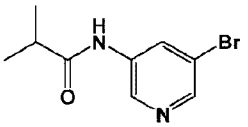
XXXIV

[00191] N-(5-bromopyridin-3-yl)-3-methylbutanamide **(XXXIV):** Off white solid, (67% yield), ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.55-8.42 (m, 3H), 7.62 (s, 1H), 2.31-2.18 (m, 3H), 1.02-1.01 (d, *J* = 6Hz, 6H); ESIMS found $C_{10}H_{13}BrN_2O$ *m/z* 258.80 (M+H).



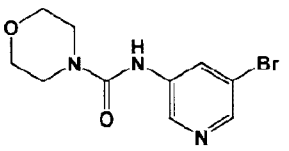
XXXV

[00192] N-(5-bromopyridin-2-yl)propionamide (**XXXV**): White solid (89% yield); ESIMS found $C_8H_9BrN_2O$ *m/z* 231 (M+H).



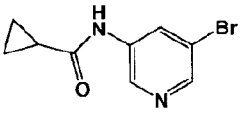
XXXVI

[00193] N-(5-bromopyridin-3-yl)isobutyramide (**XXXVI**): Off white solid (98% yield). ^{1}H NMR (DMSO-d_6) δ ppm 1.11 (d, *J*=5.6 Hz, 6H), 2.63 (m, 1H), 8.36 (d, *J*=4.0 Hz, 1H), 8.39 (m, 1H), 8.67 (d, *J*=4.0 Hz, 1H), 10.24 (s, 1H); ESIMS found $C_9H_{11}BrN_2O$ *m/z* 243 (M).



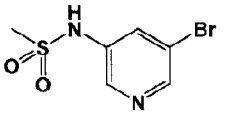
XXXVII

[00194] N-(5-bromopyridin-3-yl)morpholine-4-carboxamide (**XXXVII**): Tan solid (0.82 g, 48%). ^{1}H NMR (DMSO-d_6) 3.43-3.45 (m, 4H), 3.60-3.62 (m, 4H), 8.21 (t, J = 2.0 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.62 (d, J = 2.2 Hz, 1H), 8.91 (s, 1H); ESIMS found $C_{10}H_{12}BrN_3O_2$ m/z 286 (M+H).



XXXVIII

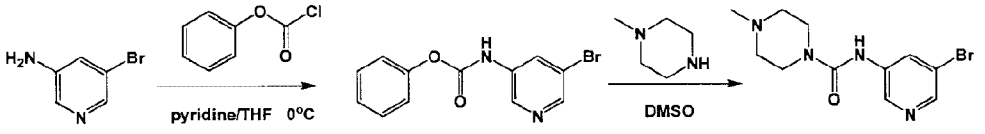
[00195] N-(5-bromopyridin-3-yl)cyclopropanecarboxamide (**XXXVIII**): Off white solid, (83% yield), ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.46-8.39 (m, 3H), 7.54 (bs, 1H), 1.56-1.50 (m, 1H), 1.13-1.07 (m, 2H), 0.96-0.90 (m, 2H); ESIMS found $C_9H_9BrN_2O$ m/z 240.85 (M+H).



XXXIX

[00196] N-(5-bromopyridin-3-yl)methanesulfonamide (**XXXIX**): Off white solid (87% yield). ^{1}H NMR (DMSO-d_6) δ ppm 3.13 (s, 3H), 7.79 (m, 1H), 8.40 (d, J=2.0 Hz, 1H), 8.44 (d, J=1.6 Hz, 1H), 10.28 (s, 1H); ESIMS found $C_6H_7BrN_2O_2$ m/z 252 (M+1).

[00197] Preparation of intermediate N-(5-bromopyridin-3-yl)-4-methyl piperazine-1-carboxamide (**XLII**) is depicted below in Scheme **6**.



XL **XLI** **XLII**

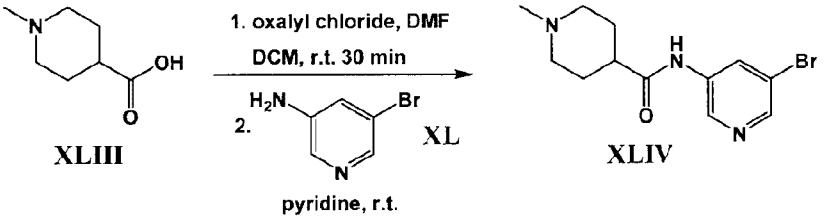
Scheme 6

Step 1-2

[00198] 3-Amino-5-bromopyridine (**XL**) (1.05 g, 6.0 mmol) was dissolved in THF (12.0 mL) and cooled to 0°C. Pyridine (0.61 mL, 7.6 mmol) was added, followed

by phenyl chloroformate (0.78 mL, 6.2 mmol). The ice bath was removed, and the suspension was warmed to ambient temperature and stirred overnight. The solvent was removed, and the residue partitioned between EtOAc and water. The organic phase was separated and washed sequentially with water and brine, dried over $MgSO_4$, and concentrated. The crude was then precipitated from DCM/hexane with the resulting solids triturated with hexane to remove some colored impurities resulting in 1.62 g of the intermediate phenyl 5-bromopyridin-3-ylcarbamate (**XLI**) which was used without further purification. Intermediate **XLI** was then dissolved in DMSO (10.5 mL). N-Methylpiperazine (0.60 mL, 5.4 mmol) was then added dropwise via syringe, and the reaction was stirred at ambient temperature for 3 hours. The reaction was poured into water, and the product extracted with 20% isopropanol/chloroform. The organic phase was separated, washed sequentially with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography using a 25 g Thomson normal phase silica gel cartridge eluting with a gradient of 0-10% MeOH/chloroform to afford N-(5-bromopyridin-3-yl)-4-methylpiperazine-1-carboxamide (**XLII**) (1.15 g, 64%) as a white crystalline solid. ^1H NMR (DMSO-d_6) 2.20 (s, 3H), 2.31-2.33 (m, 4H), 3.44-3.46 (m, 4H), 8.20-8.21 (m, 1H), 8.25 (d, J = 2.1 Hz, 1H), 8.62 (d, J = 2.1 Hz, 1H), 8.88 (s, 1H); ESIMS found $C_{11}H_{15}BrN_4O$ m/z 299 (M+H).

[00199] Preparation of intermediate N-(5-bromopyridin-3-yl)-1-methyl piperidine-4-carboxamide (**XLIV**) is depicted below in Scheme 7.



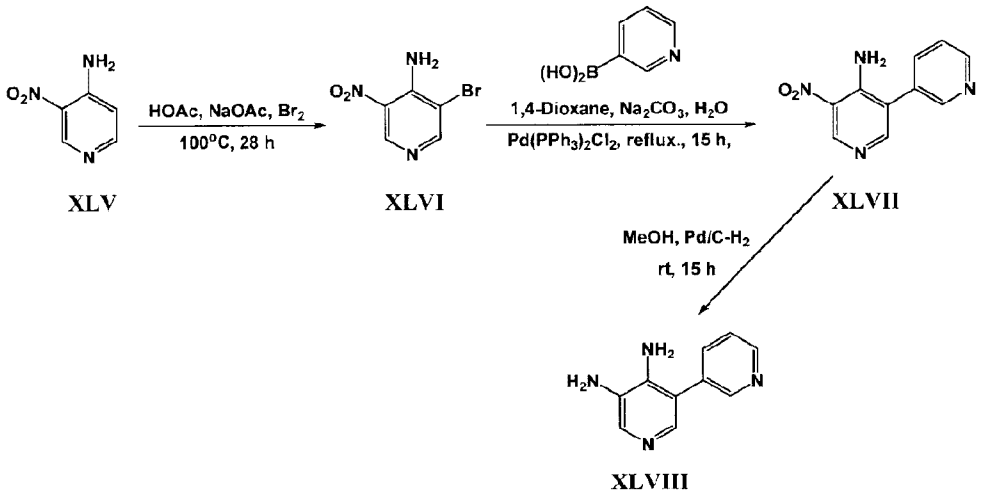
Scheme 7

Steps 1-2

[00200] Oxalyl chloride (8.67 mmol) followed by DMF (2drops) was added to a solution of 1-methyl piperidine-4-carboxylic acid (**XLIII**) (5.78 mmol) in DCM and stirred 30 min at room temperature under argon. The volatiles were evaporated under

vacuum by avoiding contact with air. Pyridine was added to the residue followed by addition of 3-amino-5-bromopyridine (**XL**) (5.20 mmol). The solution was further stirred at room temperature for 3 h under argon. The pyridine was evaporated under vacuum. The residue was treated with water, basified by saturated $NaHCO_3$ solution and washed with DCM. The aqueous layer was extracted with n-butanol. The combined organic layer was evaporated. The residue was dissolved in DCM with the addition of few drops of MeOH. The insoluble inorganic solids were filtered off. The filtrate was concentrated under vacuum to get N-(5-bromopyridin-3-yl)-1-methylpiperidine-4-carboxamide (**XLIV**) as a brown viscous liquid (0.74 g, 43% yield). ^{1}H NMR (DMSO-d_6) 1.61-1.69 (m, 2H), 1.77-1.79 (m, 2H), 1.93-1.97 (m, 2H), 2.20 (s, 3H), 2.29-2.35 (m, 1H), 2.84-2.87 (m, 2H), 8.36 (d, J = 1.6 Hz, 1H), 8.39 (m, 1H), 8.66 (d, J = 1.6 Hz, 1H), 10.33 (s, 1H); ESIMS found $C_{12}H_{16}BrN_3O$ *m/z* 299 (M+H).

[00201] Preparation of intermediate 3,3'-bipyridine-4,5-diamine (**XLVIII**) is depicted below in Scheme **8**.



Scheme 8

Step 1

[00202] A mixture of 3-nitropyridin-4-amine (**XLV**) (10 g, 71.94mmol) and acetic acid (120 ml) was added to a sealed tube followed by addition of NaOAc (29.50g, 93.52mmol) and dropwise addition of bromine (4.7ml 359.7 mmol) under stirring. The

sealed tube was heated at 100°C for 28 h until TLC showed consumption of starting material. The reaction mixture was concentrated to obtain a solid which was dissolved in water, basified with $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried and concentrated to produce 3-bromo-5-nitropyridin-4-amine (**XLVI**) as a yellow solid (12 g, 55 mmol, 77% yield). ^{1}H NMR (DMSO-d_6) δ ppm 9.19 (s, 1H), 8.58 (s, 1H); ESIMS found for $C_5H_4BrN_3O_2$ *m/z* 217, 219 (M+, M+2).

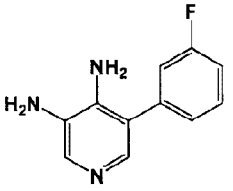
Step 2

[00203] A solution of 3-bromo-5-nitropyridin-4-amine (**XLVI**) (6 g, 26 mmol), pyridin-3-ylboronic acid (3.54g, 29 mmol), 1N Na_2CO_3 solution (78 ml) and 1,4-dioxane (150 mL) was degassed with argon thrice. $Pd(PPh_3)_2Cl_2$ (927 mg, 5 mmol%) was added to the reaction and the solution was refluxed for 15h until TLC showed the reaction was complete. The reaction was passed through a pad of Celite and then concentrated under reduced pressure. The reaction mixture was concentrated and the residue was taken up in ethyl acetate. The organic extract was washed with water, dried and concentrated under vacuum. The crude product was purified on a silica gel column (100% EtOAc → 2:98 MeOH:DCM) to give 5-nitro-3,3'-bipyridin-4-amine (**XLVII**) as a yellow solid (5 g, 23.1 mmol, 87% yield). ^{1}H NMR ($CDCl_3$, 400 MHz,) δ ppm9.31 (s, 1H), 8.80-8.79 (m, 1H), 8.70 (s, 1H), 8.23 (s, 1H), 7.80-7.73 (m, 1H),7.52-7.48 (m, 1H). ESIMS found $C_{10}H_8N_4O_2$ *m/z* 216.95 (M+H).

Step 3

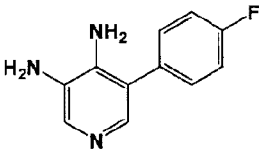
[00204] To a solution of 5-nitro-3,3'-bipyridin-4-amine (**XLVII**) (5g, 23 mmol) in MeOH (20 mL) was added 10% Pd/C. The solution was purged with hydrogen and stirred at room temperature under hydrogen for 15 h. The suspension was filtered through Celite and the concentrated under vacuum to produce 3,3'-bipyridine-4,5-diamine (**XLVIII**) as off white solid (3.3 g, 17.7 mmol, 76% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 8.63-8.53 (m, 1H), 7.90-7.83 (m, 1H), 7.75 (s, 1H), 7.58 (s, 1H), 7.48-7.43 (m, 2H), 6.13 (bs, 2H), 5.31 (bs, 2H). ESIMS found $C_{10}H_{10}N_4$ *m/z* 187.10 (M+H).

[00205] The following intermediates were prepared in accordance with the procedure described in the above Scheme **8**.



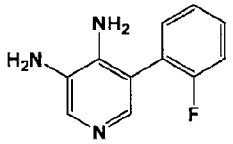
XLIX

[00206] 5-(3-fluorophenyl)pyridine-3,4-diamine (**XLIX**): Brown viscous oil (48% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 4.72 (s, 2H), 5.07 (s, 2H), 7.20 (m, 3H), 7.44 (s, 1H), 7.50 (m, 1H), 7.67 (s, 1H). ESIMS found $C_{11}H_{10}FN_3$ *m/z* 204 (M+H).



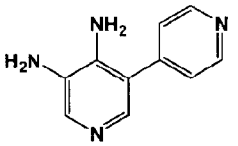
L

[00207] 5-(4-fluorophenyl)pyridine-3,4-diamine (**L**): White solid (36% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 4.69 (s, 2H), 4.97 (s, 2H), 7.29-7.26 (m, 2H), 7.42-7.39 (m, 3H), 7.67 (s, 1H). ESIMS found $C_{11}H_{10}FN_3$ *m/z* 204 (M+H).



LI

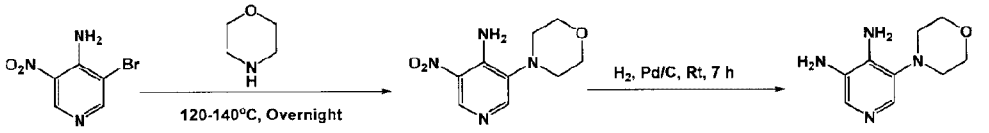
[00208] 5-(2-fluorophenyl)pyridine-3,4-diamine (**LI**): Off white solid (22% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 4.70 (s, 2H), 4.95 (s, 2H), 7.27-7.32 (m, 3H), 7.33 (s, 1H), 7.38-7.45 (m, 1H), 7.68 (s, 1H). ESIMS found $C_{11}H_{10}FN_3$ *m/z* 204 (M+H).



LII

[00209] 3,4'-bipyridine-4,5-diamine (**LII**): Off white solid (87% yield). ^{1}H NMR (DMSO-d6) 4.79 (s, 2H), 5.26 (s, 2H), 7.41 -7.44 (m, 2H), 7.47 (s, 1H), 7.69 (s, 1H), 8.60-8.64 (m, 2H). ESIMS found $C_{10}H_{10}N_4$ *m/z* 187.10 (M+H).

[00210] Preparation of intermediate 5-morpholinopyridine-3,4-diamine (**LIV**) is depicted below in Scheme **9**.



XLVI LIII LIV

Scheme 9

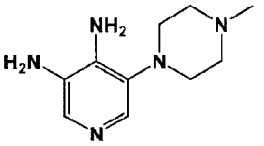
Step **1**

[00211] A solution of 3-bromo-5-nitropyridin-4-amine (**XLVI**) (1 eq.), in neat morpholine in a sealed tube was heated at 120-140°C overnight. The solution was poured into a mixture of EtOAc and water. The organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers was washed with brine, dried over $MgSO_4$ and concentrated to get a residue. The crude product was purified on a silica gel column eluting with chloroform:MeOH gradient. The fractions containing product were mixed and concentrated under vacuum. The residue was triturated with hexane to give 3-morpholino-5-nitropyridin-4-amine (**LIII**).

Step **2**

[00212] To a solution of 3-morpholino-5-nitropyridin-4-amine (**LIII**) (1 eq) in MeOH was added 10% Pd/C. The solution was purged with hydrogen and stirred overnight at r.t. under hydrogen. The suspension was filtered through Celite and concentrated under vacuum to produce 5-morpholinopyridine-3,4-diamine (**LIV**) as a purple solid (37% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 3.09-3.11 (m, 4H), 3.64-3.66 (m, 4H), 3.92 (s, 2H), 5.23 (s, 2H), 6.94 (s, 1H), 7.33 (s, 1H). ESIMS found $C_9H_{14}N_4O$ *m/z* 195 (M+H).

[00213] The following intermediate was prepared in accordance with the procedure described in the above Scheme **9**.

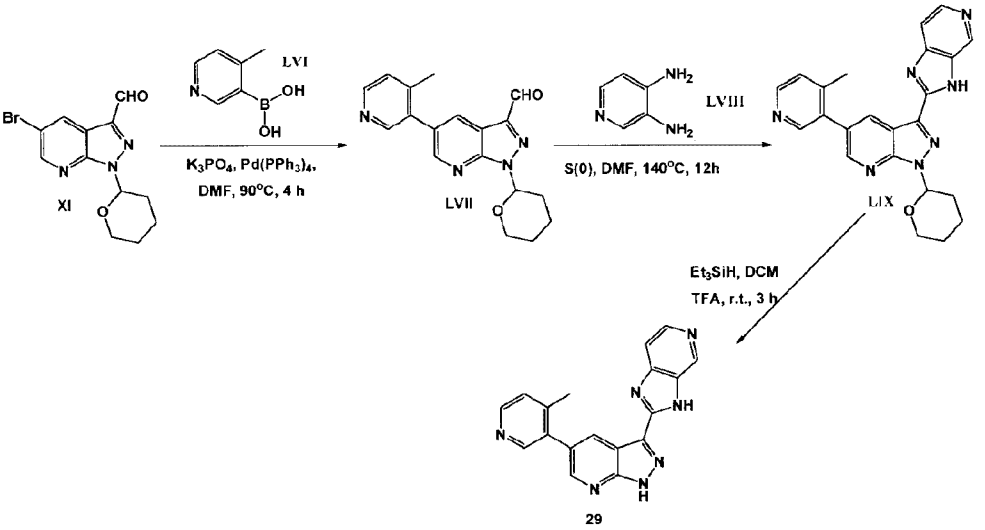


LV

[00214] 5-(4-methylpiperazin-1-yl)pyridine-3,4-diamine (**LV**): Purple solid (56% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 2.18 (s, 3H), 2.34-2.36 (m, 4H), 3.13-3.16 (m, 4H), 3.89 (s, 2H), 5.20 (s, 2H), 5.94 (s, 1H), 7.31 (s, 1H). ESIMS found $C_{10}H_{17}N_5$ *m/z* 208 (M+H).

Example 1.

[00215] Preparation of 3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-5-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-*b*]pyridine (**29**) is depicted below in Scheme **10**.



Scheme 10

Step 1

[00216] To a heterogeneous solution of 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**XI**) (0.21 g, 0.67 mmol) and K_3PO_4 (0.212 g, 1 mmol) in DMF (5 mL) and water (0.5 mL) was added 4-methyl-pyridine-3-boronic acid (**LVI**) (0.101 g, 0.74 mmol). The solution was purged with nitrogen by using nitrogen/vacuum cycle (3x). $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was added to the solution and again purged with nitrogen. The solution was heated at 90°C for 4 h under nitrogen. The solution was filtered through a pad of Celite while it was still hot. The Celite was washed with DCM (3x). The combined filtrate was concentrated under vacuum. The residue was dissolved in DCM, and washed subsequently with saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to produce 5-(4-methylpyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**LVII**). The crude product was used directly for step 2 without further purification. ESIMS found for $C_{18}H_{18}N_4O_2$ *m/z* 323.4 (M+H).

Step 2

[00217] A solution of 5-(4-methylpyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine-3-carbaldehyde (**LVII**) (0.120 g, 0.37 mmol), 3,4-diaminopyridine (**LVIII**) (42 mg, 0.39 mmol) and sulfur (13 mg, 0.39 mmol) in dry DMF (5 mL) was heated at 140°C under nitrogen for 12 h. The solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was dissolved in DCM and washed with water (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to yield 3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-5-(4-methylpyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine (**LIX**). The crude product was used directly for step 3 without further purification. ESIMS found for $C_{23}H_{21}N_7O$ *m/z* 412.7 (M+H).

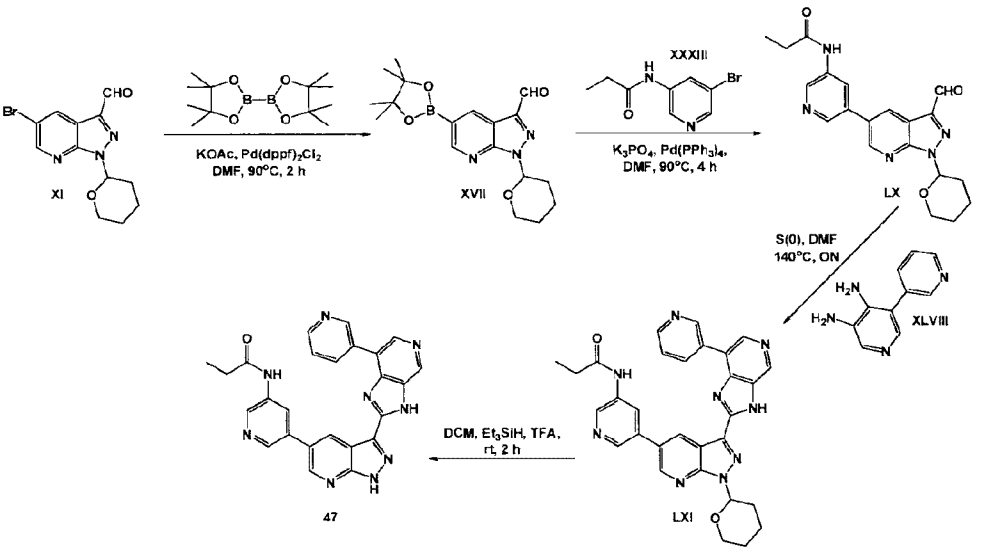
Step 3

[00218] To a solution of 3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-5-(4-methylpyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridine (**LIX**) (0.110 g, 0.26 mmol) in dry DCM (5 mL) was added triethylsilane (0.104 mL, 0.65 mmol) followed by TFA (2.5 mL) and stirred at room temperature for 3 h under nitrogen.

The solvent was evaporated under reduced pressure, the residue was taken up water (10 mL), and basified with concentrated NH_4OH. The precipitates were filtered, washed by cold water and dried under vacuum at room temperature. The crude product was suspended in DCM (10 mL), sonicated briefly and then heated to boiling for 5 min. The solution was cooled to room temperature and the solids were filtered, washed with DCM and dried under vacuum at room temperature to produce 3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-5-(4-methylpyridin-3-yl)-1H-pyrazolo[3,4-*b*]pyridine (**29**) as a white solid (37 mg, 0.11 mmol, 43% yield). ^{1}H NMR (DMSO-d_6) δ ppm 2.33 (s, 3H), 7.45 (d, *J*=4.78 Hz, 1 H), 7.75 (bd, 1 H), 8.43 (d, *J*=5.29 Hz, 1 H), 8.54 (bs, 2 H), 8.69-8.82 (m, 3 H), 14.64 (s, 1 H); ESIMS found for $C_{18}H_{13}N_7$ *m/z* 328.4 (M+H).

Example **2.**

[00219] Preparation of N-(5-(3-(7-(pyridin-3-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide (**47**) is depicted below in Scheme **11**.



Scheme 11

Steps **1-2**

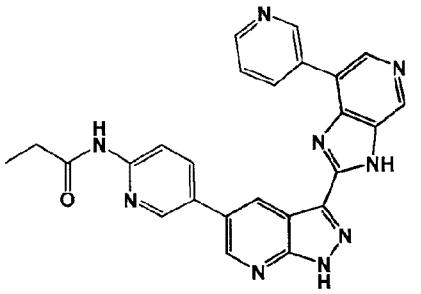
[00220] A solution of 5-bromo-1-(tetrahydro-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-3-yl]-carbaldehyde (**XI**) (0.218 g, 0.70 mmol), bis (pinacolato)diboron (0.213 g, 0.84 mmol), and KOAc (0.206 g, 2.1 mmol) in DMF (10 ml) was purged with argon. $PdCl_2(dppf)_2$. DCM was added to the solution and purged again with argon. The solution was heated at 90°C for 2 h under argon and cooled to the room temperature. N-(5-bromopyridin-3-yl)propionamide (**XXXIII**) (0.70 mmol), potassium phosphate (0.223 g, 1.05 mmol) and water (1 mL) was added to the solution and purged with argon. $Pd(PPh_3)_4$ was added to the solution and again purged with the argon. The solution was heated at 90°C for 4 h under argon. The solution was filtered through a bed of Celite and the solvent was distilled under vacuum. The residue was treated with water and extracted with DCM. The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (100% DCM → 5:95 MeOH:DCM) to get N-(5-(3-formyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo [3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide (**LX**) as a off white solid (45% yield). ^1H NMR (DMSO-d_6) δ ppm 1.13 (t, *J*=7.55 Hz, 3H), 1.51 - 1.74 (m, 2H), 1.96 – 2.18 (m, 2H), 2.41 (q, *J*=7.55 Hz, 2H), 3.68 (m, 1H), 3.92 (m, 1H), 6.26 (dd, *J*=10.20, 2.14, 1H), 8.48 (m, 1H), 8.70 (m, 2H), 8.77 (m, 1H), 9.07 (m, 1Hz), 10.17 (s, 1H), 10.24 (s, 1H); ESIMS found $C_{20}H_{21}N_5O_3$ *m/z* 380 (M+H).

Steps **3-4**

[00221] A solution of N-(5-(3-formyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide (**LX**) (1 eq), sulfur (1 eq) and 3,3'-bipyridine-4,5-diamine (**XLVIII**) (1 eq) in DMF was heated overnight at 140°C under argon. The solution was cooled and the DMF was distilled under vacuum. The residue was taken in DCM. Triethylsilane (2.5 eq) followed by TFA (30% by volume) was added to the solution and stirred for 2 h at room temperature until TLC showed disappearance of starting material. The solvent was removed under vacuum. Water was added to the residue, sonicated briefly and basified with 5 N NH_4OH solution. The solids formed were filtered, washed with cold water and dried at room temperature. The solids were triturated with DCM followed by MeOH to get N-(5-(3-(7-(pyridin-3-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo [3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide

(**47**) as a brown solid (49% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.67 (t, *J*=6 Hz, 3H), 2.45 (q, *J*=6 Hz, 2H), 7.62 (m, 1H), 8.50 (s, 1H), 8.62 (m, 1H), 8.72 (s, 1H), 8.77 (m, 3H), 8.91 (m, 1H), 8.99 (m, 2H), 9.41 (s, 1H), 10.31 (s, 1H), 13.95 (s, 1H), 14.62 (s, 1H). ESIMS found $C_{25}H_{19}N_9O$ *m/z* 462.50 (M+H).

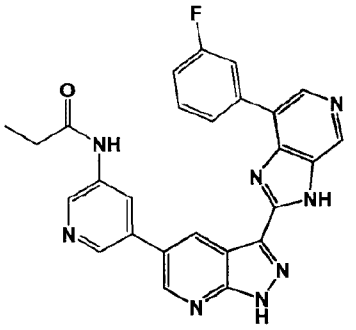
[00222] The following compounds was prepared in accordance with the procedure described in the above Example **2**.



48

[00223] N-(5-(3-(7-(pyridin-3-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo [3,4-*b*]pyridin-5-yl)pyridin-2-yl)propionamide **48**.

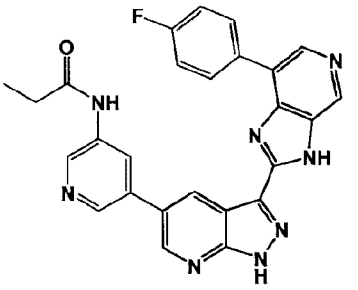
[00224] Brown solid (55% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.11 (t, *J*=6 Hz, 3H), 2.43 (q, *J*=6 Hz, 2H), 7.10 (m, 1H), 7.59 (m, 1H), 8.27 (m, 2H), 8.68 (m, 2H), 8.76 (s, 1H), 8.96 (m, 3H), 9.49 (bs, 1H), 10.66 (s, 1H), 13.90 (bs, 1H), 14.56 (s, 1H). ESIMS found $C_{25}H_{19}N_9O$ *m/z* 462 (M+H).



49

[00225] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide **49**.

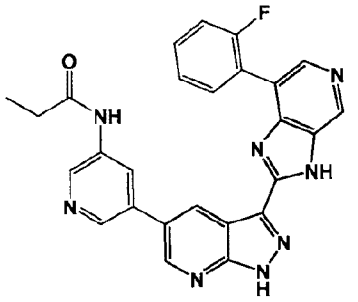
[00226] Brown solid (48% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.14 (t, *J*=5.6 Hz, 3H), 2.43 (q, *J*=5.6 Hz, 2H), 7.24 (m, 1H), 7.61 (m, 1H), 8.23 (m, 1H), 8.32 (m, 1H), 8.55 (s, 1H), 8.71 (m, 3H), 8.88 (s, 1H), 9.01 (m, 2H), 10.28 (s, 1H) 13.90 (s, 1H), 14.61 (s, 1H). ESIMS found $C_{26}H_{19}FN_8O$ *m/z* 479 (M+H).



50

[00227] N-(5-(3-(7-(4-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide **50**.

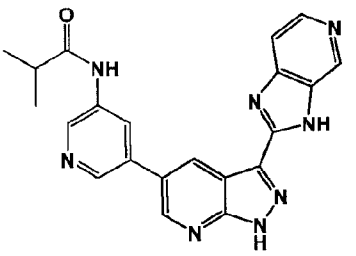
[00228] Brown solid (38% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.19 (t, *J*=6.0 Hz, 3H), 2.46 (q, *J*=6.0 Hz, 2H), 7.44 (m, 2H), 8.43 (m, 2H), 8.74 (s, 1H), 8.85 (s, 1H), 9.04 (m, 2H), 10.35 (s, 1H), 13.85 (s, 1H), 14.60 (s, 1H). ESIMS found $C_{26}H_{19}FN_8O$ *m/z* 479 (M+H).



51

[00229] N-(5-(3-(7-(2-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide **51**.

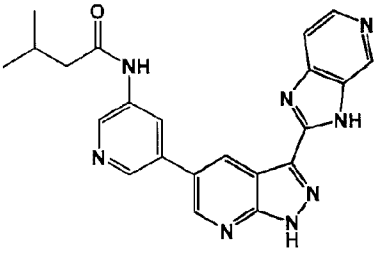
[00230] Brown solid (35% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.15 (t, *J*=5.2 Hz, 3H), 2.44 (m, 2H), 7.42 (m, 2H), 7.55 (m, 1H), 7.63 (m, 1H), 8.32 (m, 1H), 8.51 (m, 1H), 8.71 (m, 1H), 8.90 (m, 2H), 8.98 (m, 2H), 10.30 (s, 1H) 13.85 (s, 1H), 14.55 (s, 1H). ESIMS found $C_{26}H_{19}FN_8O$ *m/z* 479 (M+H).



52

[00231] N-(5-(3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)isobutyramide **52**.

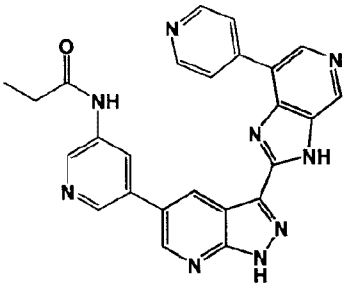
[00232] Brown solid (46% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.15 (d, *J*=5.6 Hz, 6H), 2.67 (m, 1H), 7.54 (m, 1H), 8.35 (d, J=4 Hz, 1H), 8.43 (s, 1H), 8.71 (d, *J*=1.2 Hz, 1H), 8.90 (m, 1H), 8.96 (m, 2H), 9.07 (s, 1H), 10.26 (s, 1H), 13.61 (s, 1H), 14.54 (s, 1H). ESIMS found $C_{21}H_{18}N_8O$ *m/z* 399 (M+H).



53

[00233] N-(5-(3-(3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)-3-methylbutanamide **53**.

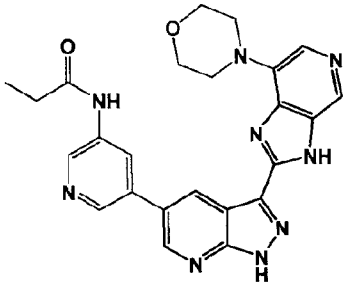
[00234] Brown solid (36% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 0.98 (d, *J*=5.2 Hz, 6H), 2.12 (m, 1H), 2.29 (d, *J*=5.6 Hz, 2H), 7.55 (m, 1H), 8.35 (d, J=4.4 Hz, 1H), 8.42 (s, 1H), 8.71 (m, 1H), 8.88 (m, 1H), 8.96 (m, 2H), 9.07 (s, 1H), 10.29 (s, 1H), 13.62 (s, 1H), 14.53 (s, 1H). ESIMS found $C_{22}H_{20}N_8O$ *m/z* 413 (M+H).



54

[00235] N-(5-(3-(7-(pyridin-4-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide **54**.

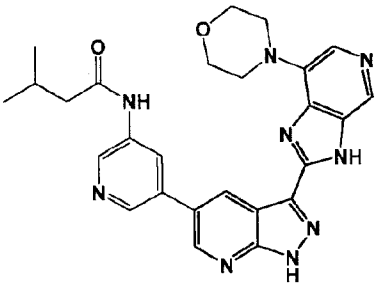
[00236] Brown solid (31% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.18 (t, *J*=6 Hz, 3H), 2.46 (m, 2H), 8.42 (m, 2H), 8.70 (s, 2H), 8.75 (m, 3H), 8.85 (s, 1H), 8.94 (s, 1H), 9.07 (m, 2H), 10.35 (s, 1H), 13.98 (s, 1H), 14.64 (s, 1H). ESIMS found $C_{25}H_{19}N_9O$ *m/z* 462 (M+H).



55

[00237] N-(5-(3-(7-morpholino-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)propionamide **55**.

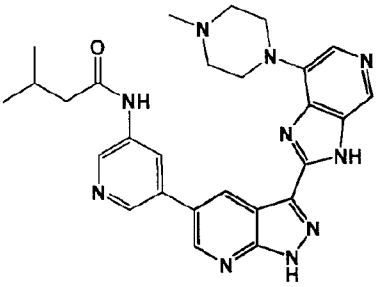
[00238] Brown solid (22% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.19 (t, *J*=6 Hz, 3H), 2.41 (q, *J*=6 Hz, 2H), 3.42 (m, 4H), 3.75 (m, 4H) 6.71 (s, 1H), 8.40 (s, 1H), 8.70 (m, 2H), 8.85 (m, 1H), 8.91 (m, 1H), 8.97 (m, 1H), 10.29 (s, 1H), 13.13 (s, 1H), 14.41 (s, 1H). ESIMS found $C_{24}H_{23}N_9O_2$ *m/z* 470 (M+H).



56

[00239] 3-methyl-N-(5-(3-(7-morpholino-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)butanamide **56**.

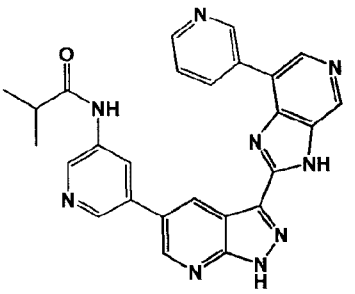
[00240] Brown solid (43% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 0.96 (d, *J*=5.2 Hz, 6H), 2.13 (m, 1H), 2.28 (d, *J*=5.6 Hz, 2H), 3.42 (m, 4H), 3.75 (m, 4H) 6.71 (s, 1H), 8.40 (s, 1H), 8.70 (m, 2H), 8.89 (m, 1H), 8.92 (m, 1H), 8.97 (m, 1H), 10.29 (s, 1H), 13.13 (s, 1H), 14.41 (s, 1H). ESIMS found $C_{26}H_{27}N_9O_2$ *m/z* 498 (M+H).



57

[00241] 3-methyl-N-(5-(3-(7-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-*c*] pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)butanamide **57**.

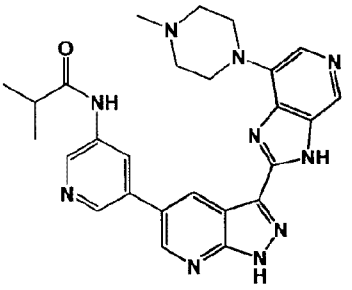
[00242] Light brown solid (38% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 0.96 (d, *J*=5.2 Hz, 6H), 2.11 (m, 1H), 2.22(s, 3H), 2.27 (d, *J*=5.6 Hz, 2H), 2.45 (m, 4H), 3.45 (m, 4H) 6.69 (s, 1H), 8.39 (s, 1H), 8.66 (m, 1H), 8.70 (m, 1H), 8.89 (d, *J*=1.6 Hz, 1H), 8.91 (d, *J*=1.6 Hz, 1H), 8.97 (d, *J*=1.6 Hz, 1H), 10.29 (s, 1H), 13.08 (s, 1H), 14.40 (s, 1H). ESIMS found $C_{27}H_{30}N_{10}O$ *m/z* 511 (M+H).



58

[00243] N-(5-(3-(7-(pyridin-3-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)isobutyramide **58**.

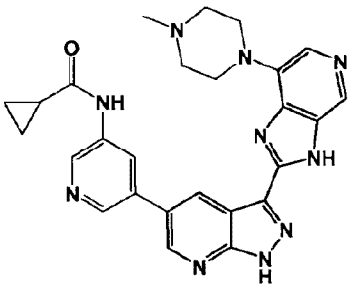
[00244] Brown solid (46% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.19 (d, *J*=5.6 Hz, 6H), 2.70 (m, 1H), 7.63 (m, 1H), 8.57 (s, 1H), 8.60 (m, 1H), 8.71 (m, 1H), 8.75 (m, 1H), 8.79 (m, 1H), 8.83 (m, 1H), 8.91 (s, 1H), 9.01 (m, 2H), 9.41 (s, 1H), 10.27 (s, 1H), 13.92 (s, 1H), 14.63 (s, 1H). ESIMS found $C_{26}H_{21}N_9O$ *m/z* 476 (M+H).



59

[00245] N-(5-(3-(7-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)isobutyramide **59**.

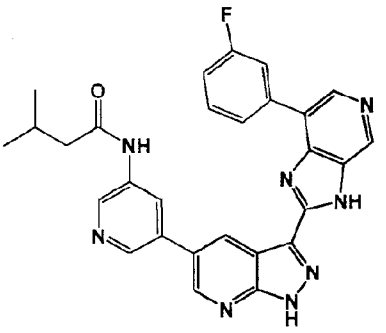
[00246] Orange solid (17% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 1.15 (d, *J*=5.6 Hz, 6H), 2.26(s, 3H), 2.66 (m, 1H), 3.46 (m, 4H) 6.70 (s, 1H), 8.41 (m, 1H), 8.67 (m, 1H), 8.71 (d, *J*=1.6 Hz, 1H), 8.92 (dd, *J*=4.8 & 1.6 Hz, 2H), 8.97 (d, *J*=1.6 Hz, 1H), 10.25 (s, 1H), 13.09 (s, 1H), 14.40 (s, 1H). ESIMS found $C_{26}H_{28}N_{10}O$ *m/z* 497 (M+H).



60

[**00247**] N-(5-(3-(7-(4-methylpiperazin-1-yl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)cyclopropanecarboxamide **60**.

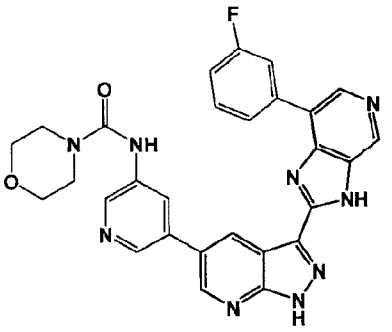
[**00248**] Yellow solid (25% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 0.88 (m, 4H), 1.85(m, 1H), 2.24 (s, 3H), 2.47 (m, 4H), 3.45 (m, 4H), 6.69 (s, 1H), 8.39 (s, 1H), 8.66 (m, 1H), 8.70 (m, 1H), 8.87 (m, 1H), 8.91 (m, 1H), 8.97 (m, 1H), 10.62 (s, 1H), 13.09 (s, 1H), 14.40 (s, 1H). ESIMS found $C_{26}H_{26}N_{10}O$ *m/z* 495 (M+H).



61

[**00249**] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)-3-methylbutanamide **61**.

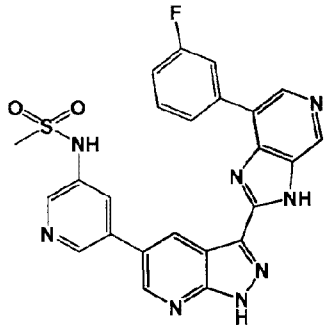
[**00250**] Brown solid (63% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 0.98 (d, *J*=5.2 Hz, 6H), 2.12 (m, 1H), 2.28 (d, *J*=5.6 Hz, 2H), 7.22 (m, 1H), 7.61 (m, 1H), 8.23 (m, 1H), 8.33 (m, 1H), 8.54 (s, 1H), 8.71 (m, 1H), 8.76 (m, 2H), 8.89 (s, 1H), 9.00 (m, 1H), 9.05 (m, 1H), 10.28 (s, 1H) 13.91 (s, 1H), 14.62 (s, 1H). ESIMS found $C_{28}H_{23}FN_8O$ *m/z* 507 (M+H).



62

[00251] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)morpholine-4-carboxamide **62**.

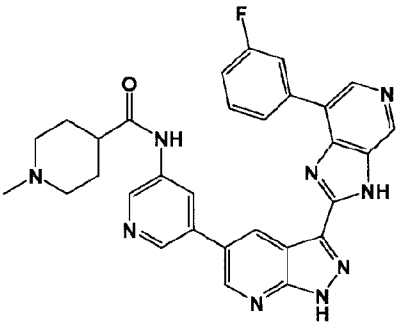
[00252] Brown solid (20% yield). ESIMS found $C_{28}H_{22}FN_9O_2$ *m/z* 536 (M+H).



63

[00253] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)methanesulfonamide **63**.

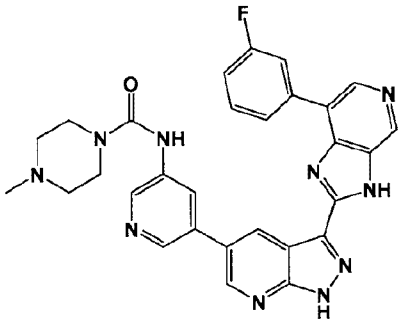
[00254] Brown solid (26% yield). ^{1}H NMR (DMSO-d6, 400 MHz,): δ 3.16 (s, 3H), 7.97 (m, 1H), 8.10-8.30 (br m, 2H), 8.54 (d, *J*=2.0 Hz, 1H), 8.78 (m, 2H), 9.03 (m, 1H), 9.15 (s, 1H), 10.22 (s, 1H) 14.80 (s, 1H). ESIMS found $C_{24}H_{17}FN_8O_2S$ *m/z* 501 (M+H).



64

[00255] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)-1-methylpiperidine-4-carboxamide **64**.

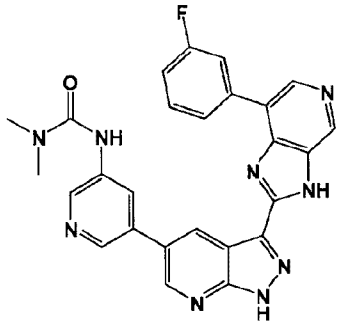
[00256] Brown solid (22% yield). ^{1}H NMR (DMSO-d_6) δ ppm, 1.72 - 1.76 (m, 2H), 1.85-1.87 (m, 2H), 2.02– 2.07 (m, 2H), 2.25 (s, 3H), 2.36-2.40 (m, 1H), 2.92 (m, 2H), 7.23 (m, 1H), 7.62 (m, 1H), 8.26-8.32 (m, 2H), 8.57 (m, 1H), 8.72 (d, *J*=1.6 Hz, 1H), 8.79 (m, 2H), 8.89 (m, 1H), 9.01 (m, 1H), 9.05 (m, 1H), 10.31 (s, 1H), 13.95 (bs, 1H); 14.60 (bs, 1H); ESIMS found $C_{30}H_{26}FN_9O$ *m/z* 548 (M+H).



65

[00257] N-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)-4-methylpiperazine-1-carboxamide **65**.

[00258] Brown solid (2% yield). ESIMS found $C_{29}H_{25}FN_{10}O$ *m/z* 549 (M+H).



66

[00259] 3-(5-(3-(7-(3-fluorophenyl)-3H-imidazo[4,5-*c*]pyridin-2-yl)-1H-pyrazolo[3,4-*b*]pyridin-5-yl)pyridin-3-yl)-1,1-dimethylurea **66**.

[00260] Brown solid (13% yield). ^{1}H NMR (DMSO-d_6) δ ppm, 3.00 (s, 6H), 7.25-7.30 (m, 1H), 7.62-7.64 (m, 1H), 8.16-8.37 (m, 2H), 8.62 (m, 1H), 8.69 (m, 1H), 8.78 (m, 2H), 8.89 (m, 1H), 9.01 (m, 2H), 9.07 (m, 1H), 13.90 (bs, 1H); 14.58 (bs, 1H); ESIMS found $C_{26}H_{20}FN_9O$ *m/z* 494 (M+H).

Administration and Pharmaceutical Compositions

[00261] Some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound as described herein, or its corresponding enantiomer, diastereoisomer or tautomer, or pharmaceutically acceptable salt; and (b) a pharmaceutically acceptable carrier.

[00262] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications.

[00263] Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. Pharmaceutically acceptable compositions include solid, semi-solid, liquid and aerosol dosage forms, such as, *e.g.*, tablets, capsules, powders, liquids, suspensions, suppositories, aerosols or the like. They may be obtained, for example, as films by methods such as precipitation, crystallization,

freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate. Preferably, the compositions are provided in unit dosage forms suitable for single administration of a precise dose.

[00264] The compounds can be administered either alone or more typically in combination with a conventional pharmaceutical carrier, excipient or the like. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens™ or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-b-cyclodextrins, or other solubilized derivatives can also be advantageously used to enhance delivery of compounds of the formulae described herein. Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. The contemplated compositions may contain 0.001%-100% active ingredient, in one embodiment 0.1-95%, in another embodiment 75-85%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins. 2005).

[00265] In one preferred embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils or triglycerides) is encapsulated in a gelatin capsule. Unit dosage forms in which the two active ingredients are physically separated are also contemplated; *e.g.*, capsules with granules of each drug; two-layer tablets; two-compartment gel caps, etc.

[00266] Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound as defined above and optional pharmaceutical adjuvants in a carrier (*e.g.*, water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) to form a solution or suspension. If desired, the pharmaceutical composition can also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, solubilizing agents, pH buffering agents and the like (*e.g.*, sodium acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, and the like). Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, as emulsions, or in solid forms suitable for dissolution or suspension in liquid prior to injection. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject. However, percentages of active ingredient of 0.01% to 10% in solution are employable, and will be higher if the composition is a solid, which will be subsequently diluted to the above percentages. In some embodiments, the composition will comprise 0.2-2% of the active agent in solution.

[00267] It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set

forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00268] Solid compositions can be provided in various different types of dosage forms, depending on the physicochemical properties of the drug, the desired dissolution rate, cost considerations, and other criteria. In one of the embodiments, the solid composition is a single unit. This implies that one unit dose of the drug is comprised in a single, physically shaped solid form or article. In other words, the solid composition is coherent, which is in contrast to a multiple unit dosage form, in which the units are incoherent.

[00269] Examples of single units which may be used as dosage forms for the solid composition include tablets, such as compressed tablets, film-like units, foil-like units, wafers, lyophilized matrix units, and the like. In a preferred embodiment, the solid composition is a highly porous lyophilized form. Such lyophilizates, sometimes also called wafers or lyophilized tablets, are particularly useful for their rapid disintegration, which also enables the rapid dissolution of the active compound.

[00270] On the other hand, for some applications the solid composition may also be formed as a multiple unit dosage form as defined above. Examples of multiple units are powders, granules, microparticles, pellets, beads, lyophilized powders, and the like. In one embodiment, the solid composition is a lyophilized powder. Such a dispersed lyophilized system comprises a multitude of powder particles, and due to the lyophilization process used in the formation of the powder, each particle has an irregular, porous microstructure through which the powder is capable of absorbing water very rapidly, resulting in quick dissolution.

[00271] Another type of multiparticulate system which is also capable of achieving rapid drug dissolution is that of powders, granules, or pellets from water-soluble excipients which are coated with the drug, so that the drug is located at the outer surface of the individual particles. In this type of system, the water-soluble low molecular weight excipient is useful for preparing the cores of such coated particles, which can be subsequently coated with a coating composition comprising the drug and, preferably, one or more additional excipients, such as a binder, a pore former, a saccharide, a sugar

alcohol, a film-forming polymer, a plasticizer, or other excipients used in pharmaceutical coating compositions.

[00272] Also provided herein are kits. Typically, a kit includes one or more compounds or compositions as described herein. In certain embodiments, a kit can include one or more delivery systems, e.g., for delivering or administering a compound as provided above, and directions for use of the kit (e.g., instructions for treating a patient). In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with cancer. In another embodiment, the kit can include a compound or composition as described herein and a label that indicates that the contents are to be administered to a patient with one or more of hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma, ovarian cancer, diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, osteoarthritis, polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome

[00273] The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

Methods of Treatment

[00274] The compounds and compositions provided herein can be used as inhibitors of one or more members of the Wnt pathway, including one or more Wnt proteins, and thus can be used to treat a variety of disorders and diseases in which

aberrant Wnt signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, and cell cycling. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct an genetic disorder due to mutations in Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, psoriasis, mycotic and viral infections, bone and cartilage diseases, Alzheimer's disease, osteoarthritis, polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

[00275] With respect to cancer, the Wnt pathway is known to be constitutively activated in a variety of cancers including, for example, colon cancer, hepatocellular carcinoma, lung cancer, ovarian cancer, prostate cancer , pancreatic cancer and leukemias such as CML, CLL and T-ALL. The constitutive activation is due to constitutively active β-catenin, perhaps due to its stabilization by interacting factors or inhibition of the degradation pathway. Accordingly, the compounds and compositions described herein may be used to treat these cancers in which the Wnt pathway is constitutively activated. In certain embodiments, the cancer is chosen from hepatocellular carcinoma, colon cancer, leukemia, lymphoma, sarcoma and ovarian cancer.

[00276] Other cancers can also be treated with the compounds and compositions described herein.

[00277] More particularly, cancers that may be treated by the compound, compositions and methods described herein include, but are not limited to, the following:

[00278] 1) Breast cancers, including, for example ER^+ breast cancer, ER^- breast cancer, $her2^-$ breast cancer, $her2^+$ breast cancer, stromal tumors such as fibroadenomas, phyllodes tumors, and sarcomas, and epithelial tumors such as large duct papillomas; carcinomas of the breast including *in situ* (noninvasive) carcinoma that includes ductal carcinoma *in situ* (including Paget's disease) and lobular carcinoma *in situ*, and invasive (infiltrating) carcinoma including, but not limited to, invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, colloid (mucinous) carcinoma, tubular carcinoma, and invasive papillary carcinoma; and miscellaneous malignant neoplasms. Further examples of breast cancers can include luminal A, luminal B, basal A, basal B, and triple negative breast cancer, which is estrogen receptor negative (ER^-), progesterone receptor negative, and her2 negative ($her2^-$). In some embodiments, the breast cancer may have a high risk Oncotype score.

[00279] 2) Cardiac cancers, including, for example sarcoma, e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma; myxoma; rhabdomyoma; fibroma; lipoma and teratoma.

[00280] 3) Lung cancers, including, for example, bronchogenic carcinoma, e.g., squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma; alveolar and bronchiolar carcinoma; bronchial adenoma; sarcoma; lymphoma; chondromatous hamartoma; and mesothelioma.

[00281] 4) Gastrointestinal cancer, including, for example, cancers of the esophagus, e.g., squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma; cancers of the stomach, e.g., carcinoma, lymphoma, and leiomyosarcoma; cancers of the pancreas, e.g., ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, and vipoma; cancers of the small bowel, e.g., adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma; cancers of the large bowel, e.g., adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma.

[00282]) Genitourinary tract cancers, including, for example, cancers of the kidney, e.g., adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, and leukemia; cancers of the bladder and urethra, e.g., squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma; cancers of the prostate, e.g., adenocarcinoma, and

sarcoma; cancer of the testis, e.g., seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma.

[00283] 6) Liver cancers, including, for example, hepatoma, e.g., hepatocellular carcinoma; cholangiocarcinoma; hepatoblastoma; angiosarcoma; hepatocellular adenoma; and hemangioma.

[00284] 7) Bone cancers, including, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochrondroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors.

[00285] 8) Nervous system cancers, including, for example, cancers of the skull, e.g., osteoma, hemangioma, granuloma, xanthoma, and osteitis deformans; cancers of the meninges, e.g., meningioma, meningiosarcoma, and gliomatosis; cancers of the brain, e.g., astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, and congenital tumors; and cancers of the spinal cord, e.g., neurofibroma, meningioma, glioma, and sarcoma.

[00286] 9) Gynecological cancers, including, for example, cancers of the uterus, e.g., endometrial carcinoma; cancers of the cervix, e.g., cervical carcinoma, and pre tumor cervical dysplasia; cancers of the ovaries, e.g., ovarian carcinoma, including serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa theca cell tumors, Sertoli Leydig cell tumors, dysgerminoma, and malignant teratoma; cancers of the vulva, e.g., squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma; cancers of the vagina, e.g., clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma, and embryonal rhabdomyosarcoma; and cancers of the fallopian tubes, e.g., carcinoma.

[00287] 10) Hematologic cancers, including, for example, cancers of the blood, e.g., acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, and

myclodysplastic syndrome, Hodgkin's lymphoma, non Hodgkin's lymphoma (malignant lymphoma) and Waldenström's macroglobulinemia.

[00288] 11) Skin cancers and skin disorders, including, for example, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, and psoriasis.

[00289] 12) Adrenal gland cancers, including, for example, neuroblastoma.

[00290] Cancers may be solid tumors that may or may not be metastatic. Cancers may also occur, as in leukemia, as a diffuse tissue. Thus, the term "tumor cell," as provided herein, includes a cell afflicted by any one of the above identified disorders.

[00291] A method of treating cancer using a compound or composition as described herein may be combined with existing methods of treating cancers, for example by chemotherapy, irradiation, or surgery (e.g., oophorectomy). In some embodiments, a compound or composition can be administered before, during, or after another anticancer agent or treatment.

[00292] The compounds and compositions described herein can be used as anti-angiogenesis agents and as agents for modulating and/or inhibiting the activity of protein kinases, thus providing treatments for cancer and other diseases associated with cellular proliferation mediated by protein kinases. For example, the compounds described herein can inhibit the activity of one or more kinases, such as CDKs, VEGF, CLK, HIPK, Abl, JAK and CHK-1, or cyclin complexes thereof. Accordingly, provided herein is a method of treating cancer or preventing or reducing angiogenesis through kinase inhibition, such as through inhibition of VEGF, CHK-1, CLK, HIPK, Abl, JAK, CDK4 or CDK4/D-type cyclin complexes and/or CDK2 or CDK2/E-type cyclin complexes.

[00293] In addition, and including treatment of cancer, the compounds and compositions described herein can function as cell-cycle control agents for treating proliferative disorders in a patient. Disorders associated with excessive proliferation include, for example, cancers, psoriasis, immunological disorders involving undesired proliferation of leukocytes, and restenosis and other smooth muscle disorders. Furthermore, such compounds may be used to prevent de-differentiation of post-mitotic tissue and/or cells.

[00294] Diseases or disorders associated with uncontrolled or abnormal cellular proliferation include, but are not limited to, the following:

- a variety of cancers, including, but not limited to, carcinoma, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system and other tumors including melanoma, seminoma and Kaposi's sarcoma.
- a disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.
- defective apoptosis-associated conditions, such as cancers (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus erythematosus, rheumatoid arthritis, psoriasis, autoimmune mediated glomerulonephritis, inflammatory bowel disease and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, Parkinson's disease, AIDS-related dementia, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteroporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

- genetic diseases due to mutations in Wnt signaling components, such as polyposis coli, bone density and vascular defects in the eye (Osteoporosis-pseudoglioma Syndrome, OPPG), familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia, Müllerian-duct regression and virilization, SERKAL syndrome, type II diabetes, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman's syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

[00295] The compounds and compositions may also be useful in the inhibition of the development of invasive cancer, tumor angiogenesis and metastasis.

[00296] Moreover, the compounds and compositions, for example, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis and therefore are expected to be useful in the treatment of viral infections such as HIV, human papilloma virus, herpes virus, Epstein-Barr virus, adenovirus, Sindbis virus, pox virus and the like.

[00297] Compounds and compositions described herein can inhibit the kinase activity of, for example, CDK/cyclin complexes, such as those active in the G_0 or G_1 stage of the cell cycle, e.g., CDK2, CDK4, and/or CDK6 complexes.

Evaluation of Biological Activity

[00298] The biological activity of the compounds described herein can be tested using any suitable assay known to those of skill in the art, e.g., WO 2001/053268 or WO 2005/009997. For example, the activity of a compound may be tested using one or more of the test methods outlined below.

[00299] In one example, tumor cells may be screened for Wnt independent growth. In such a method, tumor cells of interest are contacted with a compound (i.e. inhibitor) of interest, and the proliferation of the cells, e.g. by uptake of tritiated

thymidine, is monitored. In some embodiments, tumor cells may be isolated from a candidate patient who has been screened for the presence of a cancer that is associated with a mutation in the Wnt signaling pathway. Candidate cancers include, without limitation, those listed above.

[00300] In another example, one may utilize *in vitro* assays for Wnt biological activity, e.g. stabilization of β-catenin and promoting growth of stem cells. Assays for biological activity of Wnt include stabilization of β-catenin, which can be measured, for example, by serial dilutions of a candidate inhibitor composition. An exemplary assay for Wnt biological activity contacts a Wnt composition in the presence of a candidate inhibitor with cells, e.g. mouse L cells. The cells are stimulated by Wnt-conditioned medium for a period of time sufficient to stabilize β-catenin, usually at least 16-20 hours, and lysed. The cell lysate is resolved by SDS PAGE, then transferred to nitrocellulose and probed with antibodies specific for β-catenin.

[00301] In a further example, the activity of a candidate compound can be measured in a Xenopus secondary axis bioassay (Leyns, L. *et al. Cell* (**1997**), *88(6)*, 747-756).

Example **3.**

[00302] Another screening assay for Wnt activity is described as follows. Reporter cell lines can be generated by stably transducing cells of cancer cell lines (e.g., colon cancer) with a lentiviral construct that include a wnt-responsive promoter driving expression of the firefly luciferase gene.

[00303] Lentiviral constructs can be made in which the SP5 promoter, a promoter having eight TCF/LEF binding sites derived from the SP5 promoter, is linked upstream of the firefly luciferase gene. The lentiviral constructs can also include a hygromycin resistance gene as a selectable marker. The SP5 promoter construct can be used to transduce SW480 cells, a colon cancer cell line having a mutated APC gene that generates a truncated APC protein, leading to de-regulated accumulation of β-catenin. A control cell line can be generated using another lentiviral construct containing the luciferase gene under the control of the SV40 promoter which does not require β-catenin for activation.

[00304] Cultured SW480 cells bearing a reporter construct can be distributed at approximately 10,000 cells per well into 96 well or 384 well plates. Compounds from a small molecule compound library can then be added to the wells in half-log dilutions using a ten micromolar top concentration. A series of control wells for each cell type receive only buffer and compound solvent. Twenty-four to forty hours after the addition of compound, reporter activity for luciferase can be assayed, for example, by addition of the BrightGlo luminescence reagent (Promega) and the Victor3 plate reader (Perkin Elmer). Readings can be normalized to DMSO only treated cells, and normalized activities can then be used in the IC_{50} calculations. Table 2 shows the activity of selected compounds of the invention.

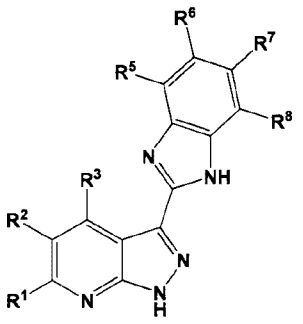
Table 2.

Compound	Wnt inhibition, IC_{50}	Compound	Wnt inhibition, IC_{50}
29	3-5 μM	**55**	>10 μM
45	0.2-1.2 μM	**56**	10 μM
46	1-2 μM	**57**	1-4 μM
47	7-10 μM	**58**	10 μM
48	10 μM	**59**	2-3 μM
49	<0.005 μM	**60**	10 μM
50	<0.0015 μM	**62**	<0.02 μM
51	<0.045 μM	**63**	10 μM
52	>10 μM	**64**	10 μM
53	>10 μM	**66**	<0.015 μM
54	10 μM		

[00305] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

CLAIMS:

1. A compound or pharmaceutically acceptable salt thereof having the structure of Formula **Ia**:



Ia

wherein:

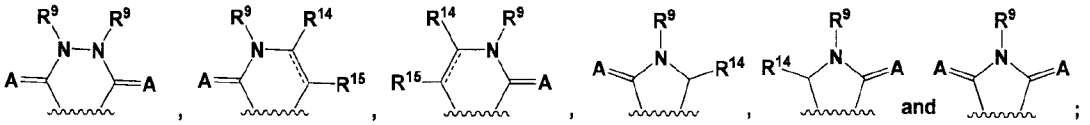
R^1, R^3, R^5, R^6, R^7 and R^8 are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

if R^1 and R^3 are H then R^2 is independently selected from the group consisting of $-C(=O)NH(C_{1-9}\text{ alkyl}R^9)$, $-C(=S)NH(C_{1-9}\text{ alkyl}R^9)$, $-C(=O)N(R^{10})_2$, $-C(=S)N(R^{10})_2$, $-C(=NR^{11})N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{13}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{13}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{13}$ and $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{13}$;

if R^1 and R^3 are not both H then R^2 is independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}$

alkyl)$_n$SO$_2$N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$C(=A)N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)R^9, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)CH(R^9)$_2$, -NO$_2$, -CN, -(C$_{1-9}$ alkyl)$_n$CO$_2$R^9 and -(C$_{1-9}$ alkyl)$_n$C(=A)R^9;

alternatively, one of each R^1 and R^2, R^2 and R^3, R^5 and R^6, R^6 and R^7 or R^7 and R^8 are taken together to form a ring which is selected from the group consisting of aryl, heteroaryl,



wherein each bond represented by a dashed and solid line represents a bond selected from the group consisting of a single bond and a double bond;

each R^9 is independently selected from the group consisting of H, C$_{1-9}$ alkyl, -CF$_3$, -(C$_{1-9}$ alkyl)$_n$carbocyclyl, -(C$_{1-9}$ alkyl)$_n$heterocyclyl, -(C$_{1-9}$ alkyl)$_n$aryl and -(C$_{1-9}$ alkyl)$_n$heteroaryl;

alternatively, two adjacent R^9, may be taken together with the atoms to which they are attached to form a carbocyclyl or heterocyclyl;

each R^{10} is independently selected from the group consisting of C$_{1-9}$ alkyl, -CF$_3$, -(C$_{1-9}$ alkyl)$_n$carbocyclyl, -(C$_{1-9}$ alkyl)$_n$heterocyclyl, -(C$_{1-9}$ alkyl)$_n$aryl and -(C$_{1-9}$ alkyl)$_n$heteroaryl;

each R^{11} is independently selected from the group consisting of –OR^9 and R^9;

each R^{12} is 1-5 substituents each selected from the group consisting of H, C$_{1-9}$ alkyl, halide, -CF$_3$, carbocyclyl, heterocyclyl, aryl, heteroaryl, -(C$_{1-9}$ alkyl)$_n$OR^9, -(C$_{1-9}$ alkyl)$_n$SR^9, -(C$_{1-9}$ alkyl)$_n$S(=O)R^{10}, -(C$_{1-9}$ alkyl)$_n$SO$_2$R^9, -(C$_{1-9}$ alkyl)$_n$N(R^9)SO$_2$R^9, -(C$_{1-9}$ alkyl)$_n$SO$_2$N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$C(=A)N(R^9)$_2$, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)R^9, -(C$_{1-9}$ alkyl)$_n$N(R^9)C(=A)CH(R^9)$_2$, -NO$_2$, -CN, -(C$_{1-9}$ alkyl)$_n$CO$_2$R^9 and -(C$_{1-9}$ alkyl)$_n$C(=A)R^9;

R^{13} is 1-5 substituents each selected from the group consisting of $-N(R^9)C(=A)N(R^9)_2$, $-C(=A)N(R^9)_2$, $-N(R^9)C(=A)R^9$, $-N(R^9)C(=A)CH(R^9)_2$, $-N(R^9)SO_2R^9$ and $-SO_2(C_{1-9}\text{ alkyl})$;

R^{14} and R^{15} are independently selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-(C_{1-9}\text{ alkyl})_n\text{carbocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heterocyclyl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{aryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_n\text{heteroaryl}R^{12}$, $-(C_{1-9}\text{ alkyl})_nOR^9$, $-(C_{1-9}\text{ alkyl})_nSR^9$, $-(C_{1-9}\text{ alkyl})_nS(=O)R^{10}$, $-(C_{1-9}\text{ alkyl})_nSO_2R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)SO_2R^9$, $-(C_{1-9}\text{ alkyl})_nSO_2N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nC(=A)N(R^9)_2$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)R^9$, $-(C_{1-9}\text{ alkyl})_nN(R^9)C(=A)CH(R^9)_2$, $-NO_2$, $-CN$, $-(C_{1-9}\text{ alkyl})_nCO_2R^9$ and $-(C_{1-9}\text{ alkyl})_nC(=A)R^9$;

alternatively, R^{14} and R^{15} are taken together to form a ring which is selected from the group consisting of benzene and pyridine;

each A is independently selected from the group consisting of O, S and NR^{11};

each n is 0 or 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 0.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein n is 1.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein A is O.

5. The compound of claim 1 or 4, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^3 are H and R^2 is selected from the group consisting of $-\text{carbocyclyl}R^{13}$, $-\text{heterocyclyl}R^{13}$, $-\text{aryl}R^{13}$ and $-\text{heteroaryl}R^{13}$.

6. The compound of claim 1, 4 or 5, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-\text{heteroaryl}R^{13}$.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl in -heteroarylR^{13} is pyridine.

8. The compound of claim 1, 4, 5, 6 or 7, or a pharmaceutically acceptable salt thereof, wherein R^{13} is selected from the group consisting of -NHC(=O)N(R^9)$_2$, -C(=O)N(R^9)$_2$, -NHC(=O)R^9, -NHC(=O)CH(R^9)$_2$ and -NHSO$_2R^9$.

9. The compound of claim 1, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from the group consisting of H, -C_{1-4} alkyl, carbocyclyl and -heterocyclyl.

10. The compound of claim 1, 4, 5, 6 or 7, or a pharmaceutically acceptable salt thereof, wherein R^6, R^7 and R^8 are H and R^5 is selected from the group consisting of H, -heterocyclylR^{12}, -arylR^{12}, -heteroarylR^{12}, -N(R^9)C(=O)N(R^9)$_2$, -C(=O)N(R^9)$_2$, -N(R^9)C(=O)R^9, -N(R^9)C(=O)CH(R^9)$_2$, -CN, -CO$_2R^9$ and -C(=O)R^9.

11. The compound of claim 1, 4, 5, 6, 7 or 10, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of -heterocyclylR^{12}, -arylR^{12} and -heteroarylR^{12}.

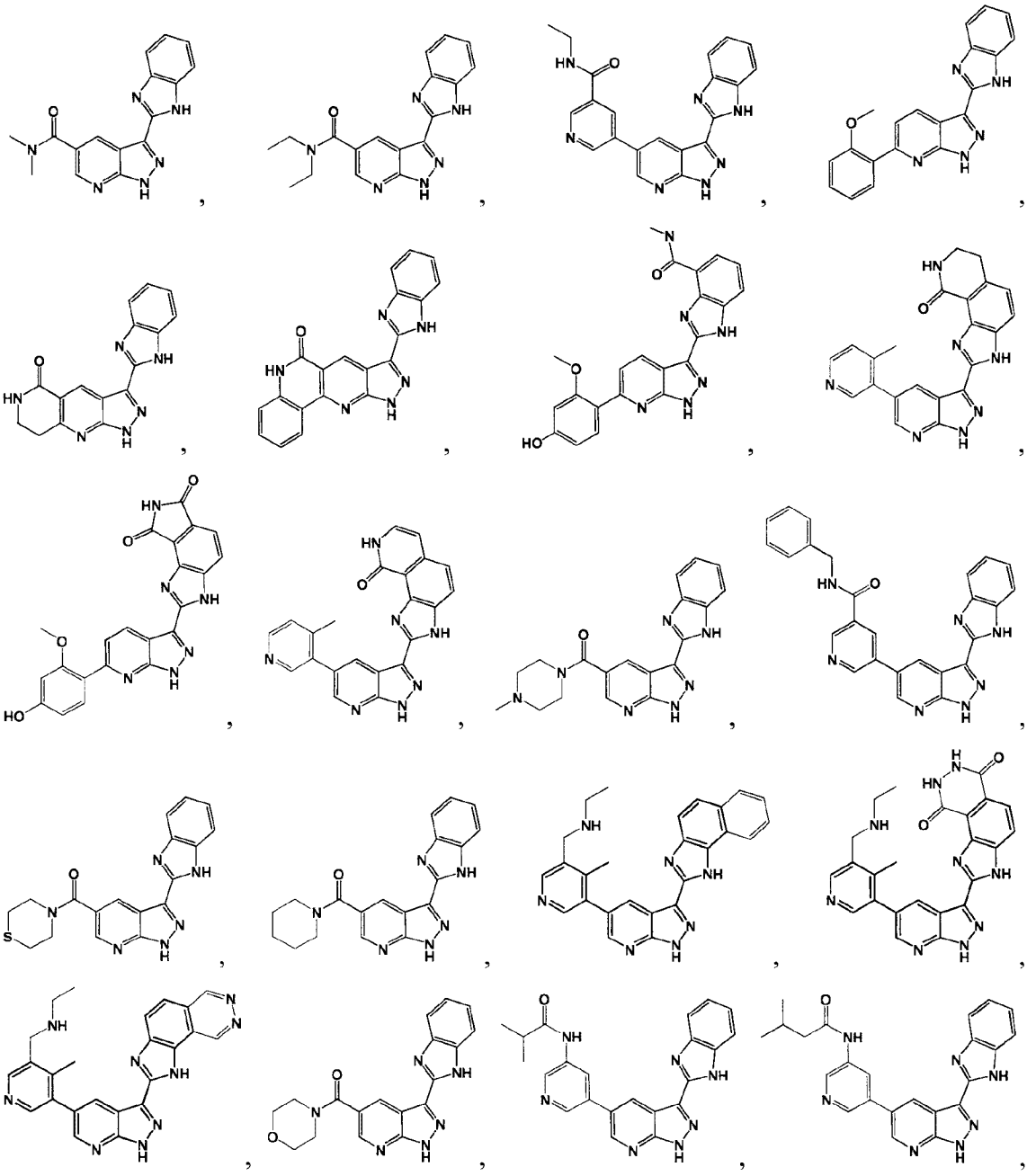
12. The compound claim 10 or 11, or a pharmaceutically acceptable salt thereof, wherein the heteroaryl in -heteroarylR^{12} is pyridine.

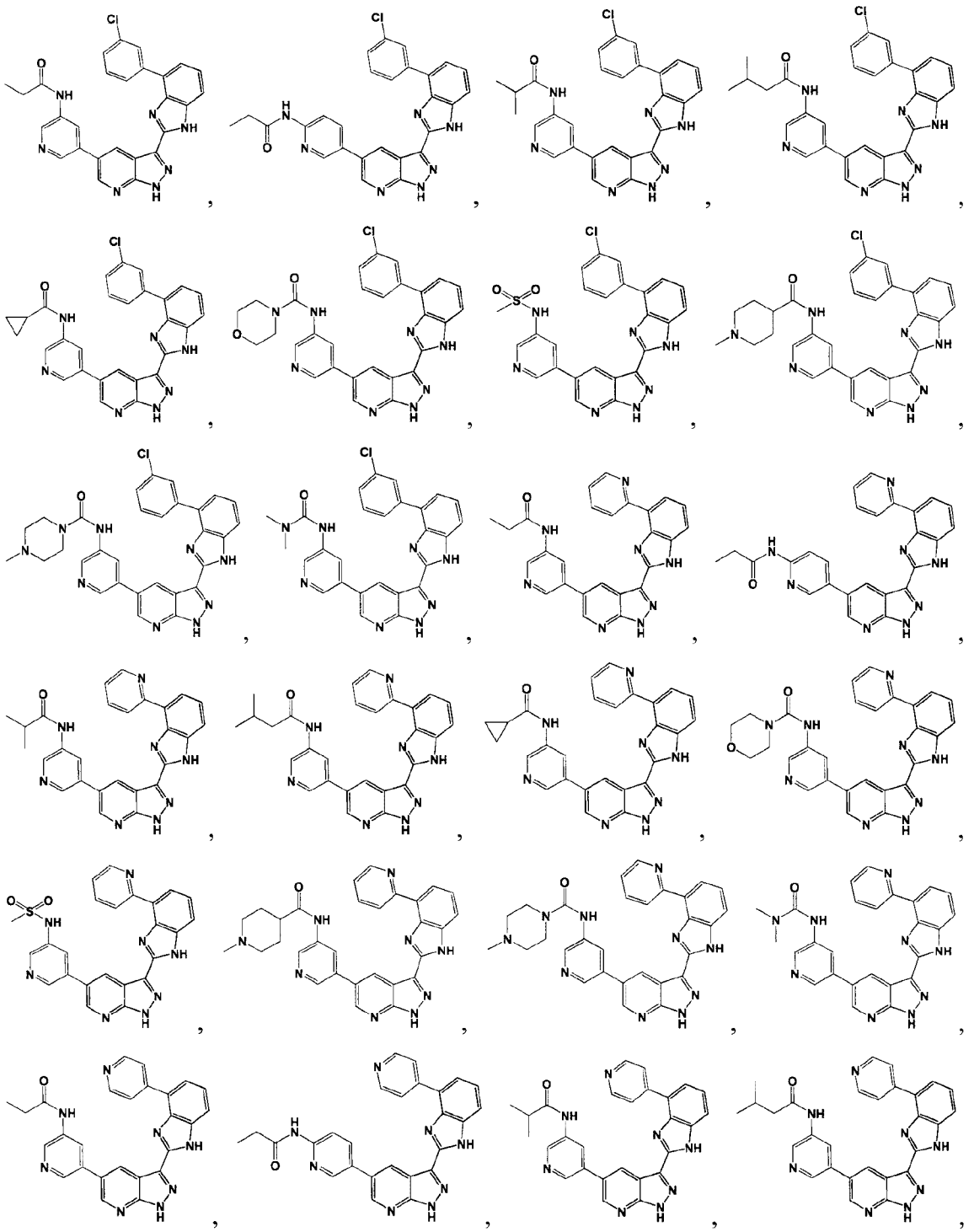
13. The compound of claim 1, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof, wherein R^5 is selected from the group consisting of H, -C(=O)N(R^9)$_2$ and -CN.

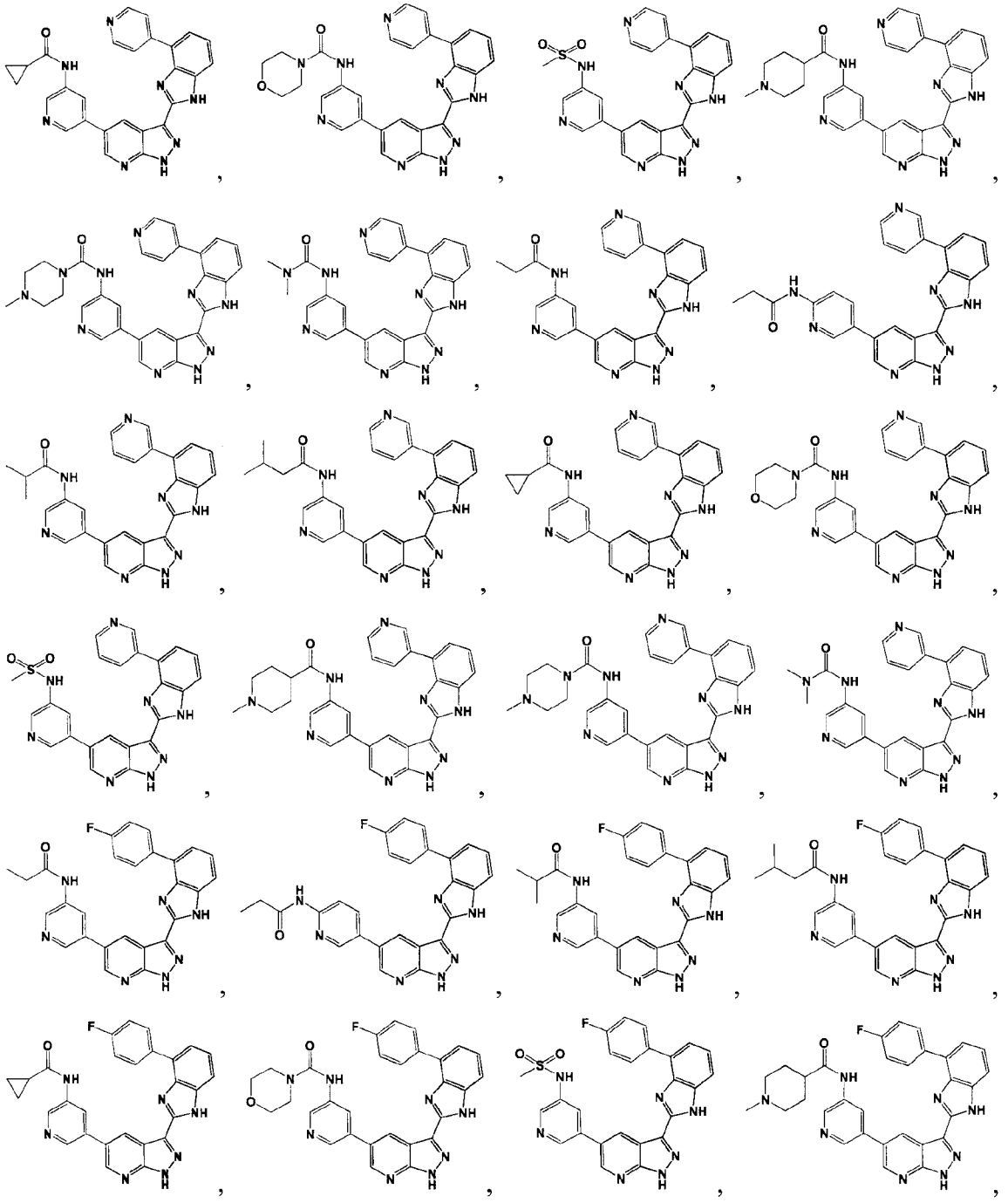
14. The compound of claim 1, 4, 5, 6, 7, 10, 11, 12 or 13, or a pharmaceutically acceptable salt thereof, wherein R^{12} is selected from the group consisting of H and halide.

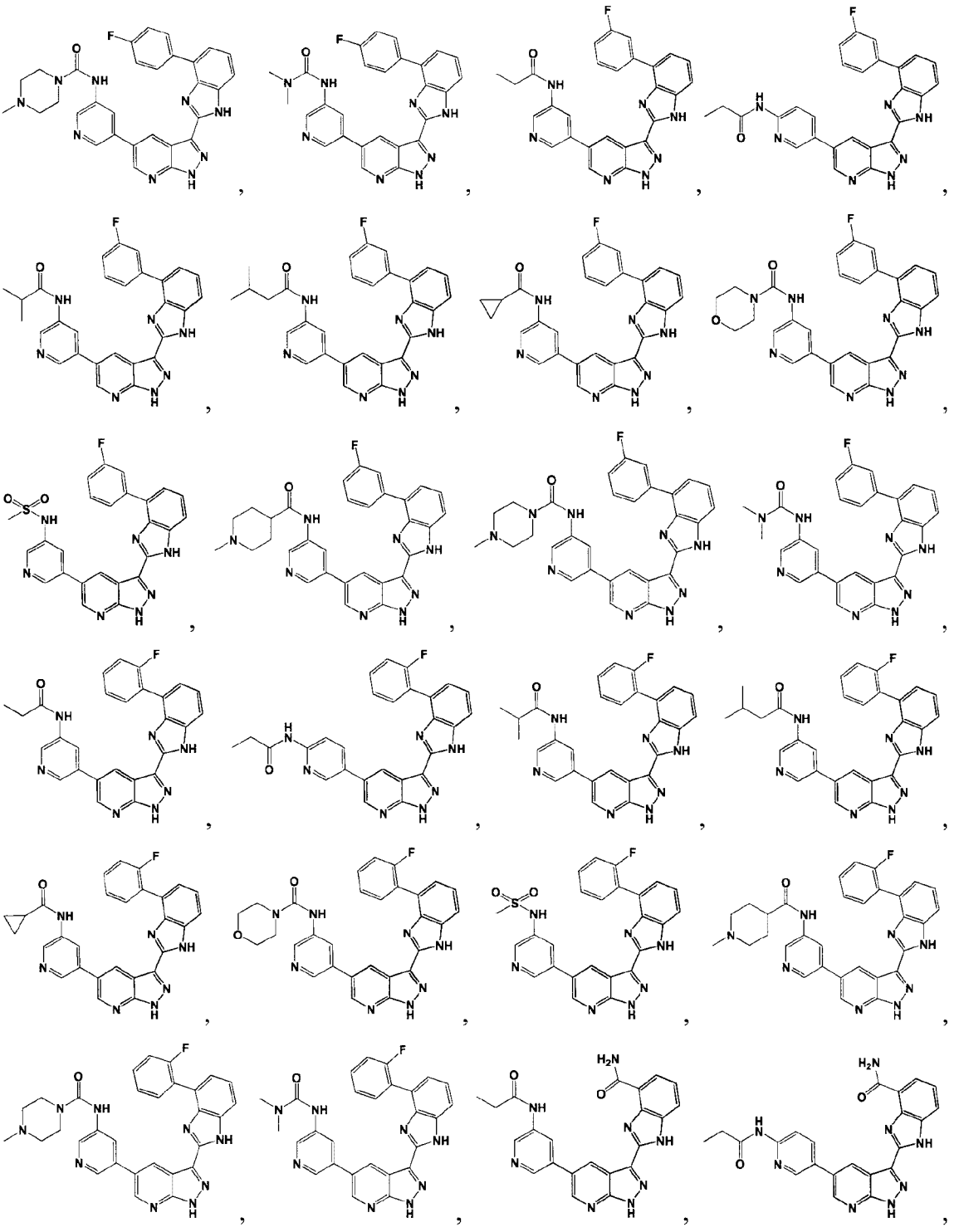
15. The compound of claim 1, 4, 5, 6, 7, 8, 10, 11, 12, 13 or 14, or a pharmaceutically acceptable salt thereof, wherein R^9 is selected from the group consisting of H and -C_{1-4} alkyl, alternatively, R^9 is taken together to form a fused ring with the nitrogen.

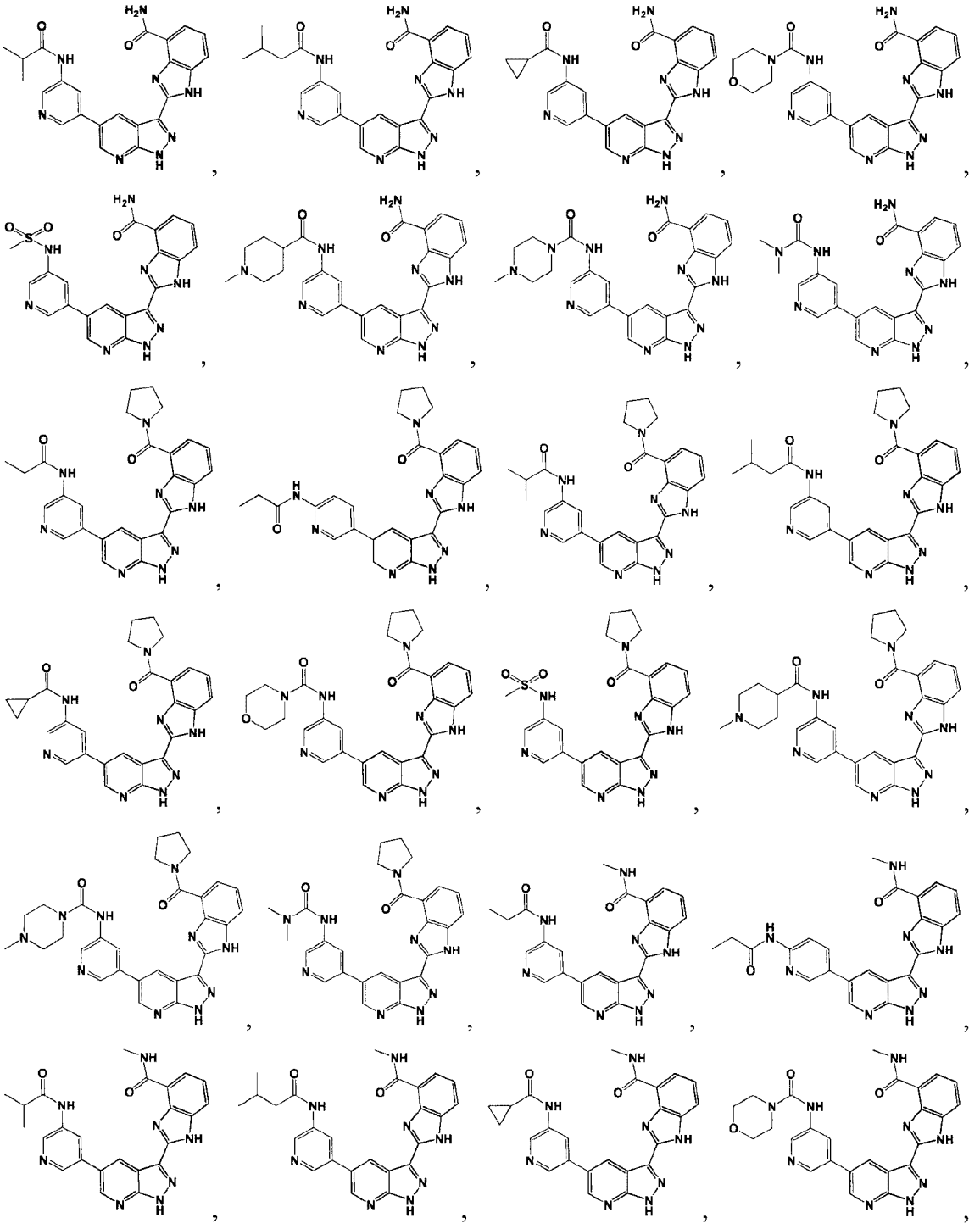
16. A compound having a structure selected from the group consisting of:

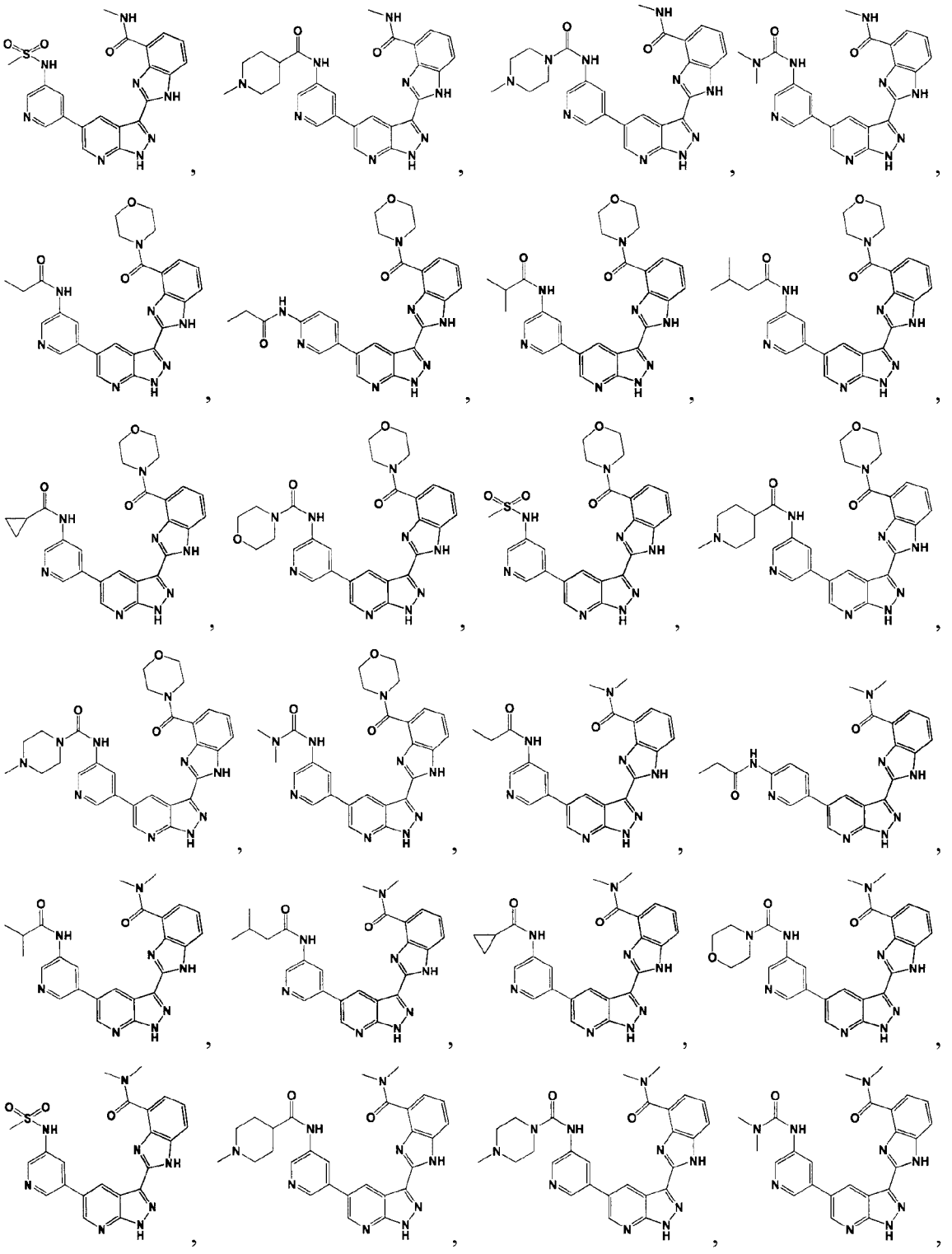


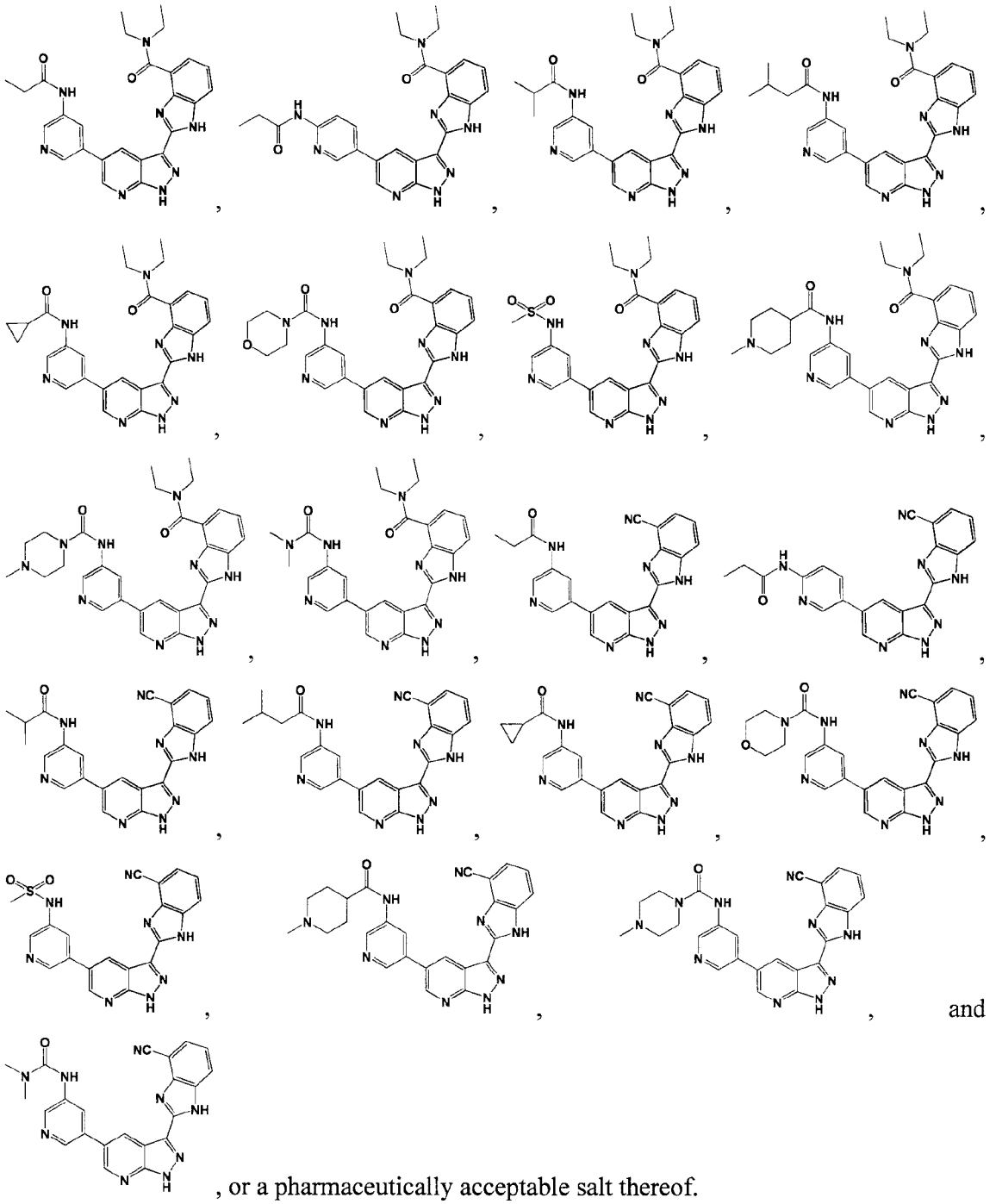






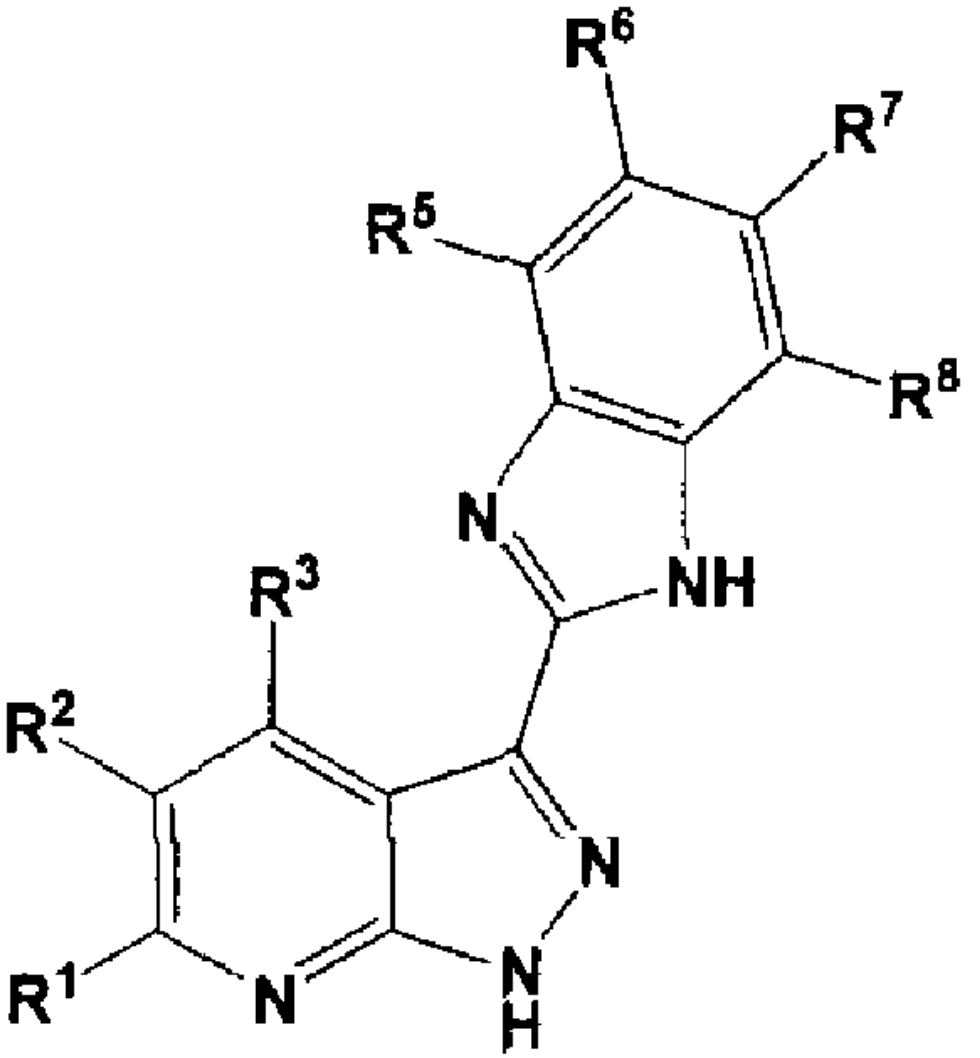






, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound as defined in any one of claims 1-16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.



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