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(54) Title: AMINO SUBSTITUTED PYRIMIDINE, PYROLLOPYRIDINE AND PYRAZOLOPYRIMIDINE DERIVATIVES USEFUL AS KINASE INHIBITORS AND IN TREATING PROLIFERATIVE DISORDERS AND DISEASES ASSOCIATED WITH ANGIOGENESIS

(57) Abstract: This invention relates to novel amino subsituted pyrimidine compounds, pharmaceutical compositions containing such compounds and the use of those compounds or compositions for treating hyper-proliferative and/or angiogenesis disorders, as a sole agent or in combination with other active ingredients.

AMINO SUBSTITUTED PYRIMIDINE, PYROLLOPYRIDINE AND PYRAZOLOPYRIMIDINE DERIVATIVES USEFUL AS KINASE INHIBITORS AND IN TREATING PROLIFERATIVE DISORDERS AND DISEASES ASSOCIATED WITH ANGIOGENESIS

INCORPORATION BY REFERENCE

Each of the applications and patents cited in this text, as well as each document or reference cited in each of the applications and patents (including during the prosecution of each issued patent; "application cited documents"), and each of the PCT and foreign applications or patents corresponding to and/or claiming priority from any of these applications and patents, and each of the documents cited or referenced in each of the application cited documents, are hereby expressly incorporated herein by reference. More generally, documents or references are cited in this text, either in a Reference List before the claims, or in the text itself; and, each of these documents or references ("herein-cited references"), as well as each document or reference cited in each of the herein-cited references (including any manufacturer's specifications, instructions, etc.), is hereby expressly incorporated herein by reference.

BACKGROUND OF THE INVENTION

Cancer is a disease resulting from an abnormal growth of tissue. Certain cancers have the potential to invade into local tissues and also metastasize to distant organs. This disease can develop in a wide variety of different organs, tissues and cell types. Therefore, the term "cancer" refers to a collection of over a thousand different diseases. Despite advancements in the art, there remains a need for cancer treatments and anti-cancer compounds.

The present invention is based on the discovery that certain pyrimidine derivatives possess valuable, pharmacologically useful properties. In particular the pyrimidine derivatives used according to the present invention exhibit specific inhibitory activities that are of pharmacological interest. They are effective especially as protein tyrosine kinase inhibitors;

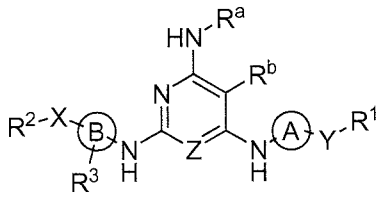
they exhibit, for example, powerful inhibition of the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) and the fusion protein of NPM-ALK .This protein tyrosine kinase results from a gene fusion of nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK), rendering the protein tyrosine kinase activity of ALK ligand-independent. NPM-ALK plays a key role in signal transmission in a number of hematopoetic and other human cells leading to hematological and neoplastic diseases, for example in anaplastic large-cell lymphoma (ALCL) and non-Hodgkin's lymphomas (NHL), specifically in ALK+NHL or Alkomas, in inflammatory myofibroblastic tumors (IMT) and neuroblastomas. In addition to NPM-ALK other gene fusions have been identified in human hematological and neoplastic diseases; mainly TPM3-ALK (a fusion of nonmuscle tropomyosin with ALK). ALK has been shown to become translocated to the echinoderm microtubule-associate protein-like 4 (EML4) in a subset of patients afflicted with Non small cell lung cancer (NSCLC). The EML4-ALK fusion tyrosine kinase generated transformed foci in culture and subcutaneous tumors in mice. Therefore EML4-ALK, which is inhibited by the compounds described in this application, maybe a relevant target for NSCLC patients or other patients with this or related ALK-containing fusion proteins (Nature. 2007 Aug 2;448(7153):561-6) The pyrimidine derivatives are useful for the inhibition of all such ALK-containing gene fusions.

The pyrimidine derivatives used according to the present invention also exhibit inhibition of the mitotic assembly checkpoint kinase MPS1 (also known as TTK). The enzymatic activity of this kinase is required for cells to undergo a mitotic checkpoint arrest in response to agents that disrupt mitosis such as compounds that interfere with tubulin polymerization/depolymerization. Normal cells have multiple redundant mechanisms for arresting in mitosis whereas cancer cells have a heightened dependence on TTK activity. Hence agents that can inhibit TTK kinase maybe able to preferentially kill tumor cells.

Compounds and compositions described herein, including salts, metabolites, solvates, solvates of salts, hydrates, prodrugs such as esters, polymorphs, and stereoisomeric forms thereof, exhibit anti-proliferative activity and are thus useful to prevent or treat the disorders associated with hyper-proliferation.

SUMMARY OF THE INVENTION

One embodiment of this invention encompasses a compound having the formula (I):



(I)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

Z is N or CH;

A is aryl or heteroaryl optionally substituted with one or more R^4 groups;

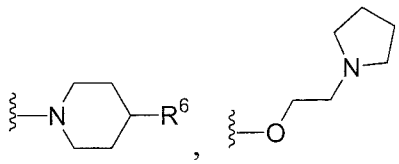
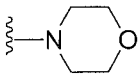
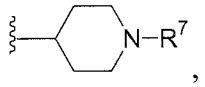
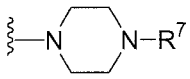
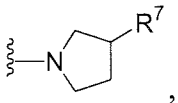
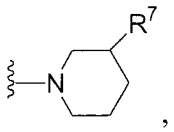
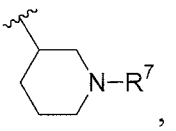
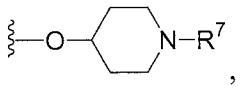
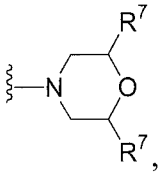
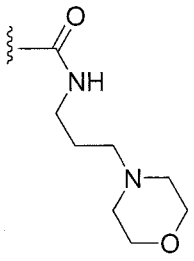
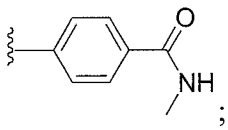
B is phenyl when Z is N; or B is phenyl, pyrazolyl or thiazolyl when Z is CH; wherein B is optionally substituted with one or more R^4 groups;

Y is $-SO_2-$, $-SO_2NH-$, $-NH-SO_2-$, -NH-C(O)-, –C(O)-NH-, -O-, or $-NR_2-$;

each occurrence of X is independently NH, O or S;

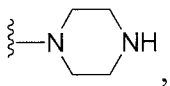
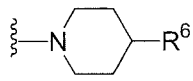
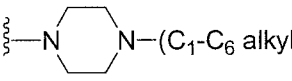
R^1 is H, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl;

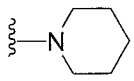
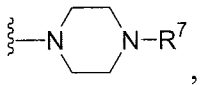
R^2 is H, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl;

R^3 is R^4, $-CO-R^5$,  , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ;

R^a is hydrogen and R^b is halogen, or R^a and R^b, taken together with the atoms to which they are bound form i) a pyrazolo ring fused to the pyrimidine ring when Z is N or ii) a pyrrolo ring fused to the the pyrimidine ring when Z is CH, said pyrazolo or pyrrolo ring optionally bearing one or two R^4 groups;

Each occurrence of R^4 is independently halogen, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxyl, nitro, azido, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide, ureido, amidino, guanidine, sulfonyl, sulphonylamino, aminosulphonyl;

Each occurrence of R^5 is independently is C_1-C_6 alkoxy,  , hydroxy,  ,  , dialkylamino, or $-N-R^7$;

Each occurrence of R^6 is independently is hydroxy,  ,  , or -$CONH_2$; and

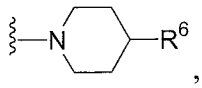
Each occurrence of R^7 is independently is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, or C_1-C_6 hydroxyalkyl;

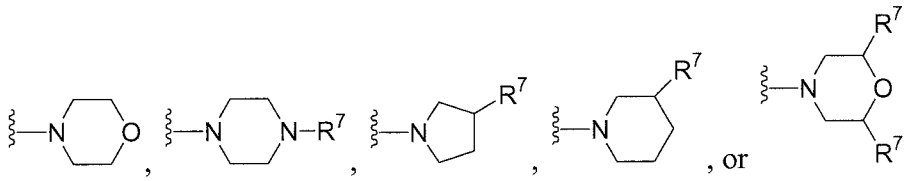
With the provisos that

(i) when Z is N, B is phenyl, and –X-R^2 is –NH-R^2,

then –X-R^2 is bound in the meta or para position on the phenyl group and R^3 and R^4, if present on B, are not bound to the meta or para position and are not -COR^5, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide or amidino ;

(ii) when Z is N, B is phenyl, and –X-R^2 is not –NH-R^2,

then R^3 is bound to the meta or para position and is  ,



or R^3 and R^4, if present on B, are each bound to the meta or para position and are independently nitro, azido, ureido, guanidine, sulphonylamino;

and

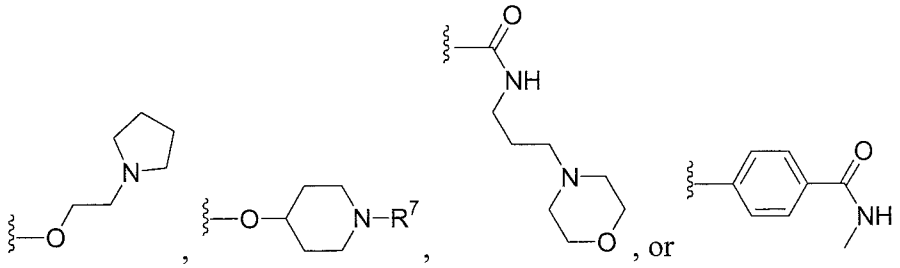
(iii) when Z is CH, and R^a and R^b are taken together with the atoms to which they are bound to form a pyrrolo ring fused to the pyridine ring,

then

(a) –X-R^2 is not isopropoxy bound to the othro postion and R^3 or R^4, if present on B, is methyl, ethyl, methoxy, ethoxy, chloro or bromo any of which is bound to the ortho postion

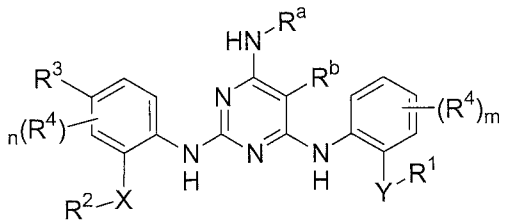
or

(b) R^3 is bound to the meta or para position and is



or R^3 and R^4, if present on B, are each bound to the meta or para position and are independently is $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkylthio, hydroxyl, nitro, azido, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide, ureido, amidino, guanidine, sulfonyl, sulphonylamino, aminosulphonyl; –CO-R^5, or phenyl substituted with aminosulphonyl, amino, alkynyl or carboxamide..

In another embodiment, the invention encompasses a compound having the formula (IA):



(IA)

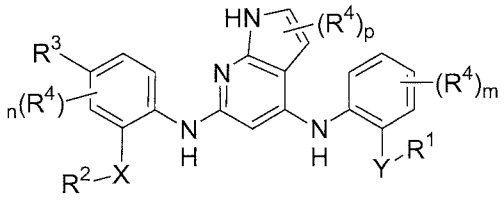
wherein :

n is an integer from 0-3;

m is an integer from 0-4;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^a and R^b are as defined in Formula (I).

In yet another embodiment, the invention encompasses a compound having the formula (II):



(II)

wherein:

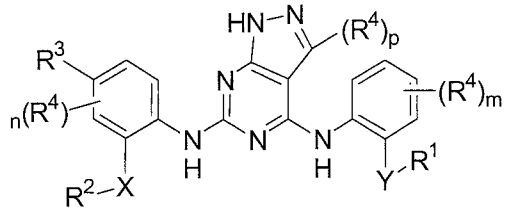
N is an integer from 0-3;

M is an integer from 0-4;

P is an integer from 0-2;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Formula (I).

In still another embodiment, the invention encompasses a compound having the formula (III):



(III)

wherein:

N is an integer from 0-3;

M is an integer from 0-4;

P is an integer from 0-1;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Formula (I).

In some embodiments, the invention encompasses a compound of formula I, IA, II or III, wherein X is O.

In still other embodiments, the invention encompasses a compound of formula I, IA, II or III, wherein R^2 is methyl, ethyl, propyl, isopropyl, cyclopropyl or cyclobutyl.

In yet other embodiments, the invention encompasses a compound of formula I, IA, II or III, wherein R^2 is methyl.

In another embodiment , the invention encompasses a compound of formula I, IA, II or III, wherein Y is SO_2.

In still another embodiment, the invention encompasses a compound of formula I, IA, II or III, wherein R^1 is methyl, ethyl, propyl, isopropyl, cyclopropyl or cyclobutyl.

In still yet another embodiments, the invention encompasses a compound of formula I, IA, II or III, wherein R^1 is isopropyl.

In yet another embodiment, the invention encompasses a compound of formula I, IA, II or III, wherein X is O, R^2 is methyl, Y is SO_2 and R^1 is isopropyl.

Another aspect of the invention encompasses a compound having the IUPAC name:

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-morpholinophenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

1-(4-(6-amino-5-chloro-2-(2-(isopropylsulfonyl)phenylamino)pyrimidin-4-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

5-chloro-N2-(2-ethoxy-4-morpholinophenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

N2-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-5-chloro-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N2-(2-ethoxy-4-morpholinophenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-ethoxyphenyl)piperidin-4-ol;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)pyrimidine-2,4,6-triamine;

2-(4-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazin-1-yl)ethanol;

(R)-1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)pyrrolidin-3-ol;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-3-ol;

N2-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidine-4-carboxamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

Still Another aspect of the invention encompasses a compound having the IUPAC name:

1-(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-3-methoxyphenyl)piperidin-4-ol;

1-(3-ethoxy-4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N4-(2-(isopropylsulfonyl)phenyl)-N6-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

N4-(2-(isopropylsulfonyl)phenyl)-N6-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-3-methoxyphenyl)piperidine-4-carboxamide;

N6-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

N6-(2-ethoxy-4-morpholinophenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(3-methoxy-4-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N6-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(3-isopropoxy-4-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N6-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

Yet another aspect of the invention encompasses a compound having the IUPAC name:

methyl 6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinate;

6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-N-methylnicotinamide;

(6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)(4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone;

1,4'-bipiperidin-1'-yl(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-3-methoxyphenyl)methanone;

(2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-4-yl)(4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone;

(2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-4-yl)(4-methylpiperazin-1-yl)methanone;

2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-N-(3-morpholinopropyl)isonicotinamide;

(4-(4-methylpiperazin-1-yl)piperidin-1-yl)(6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)methanone;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

Another aspect of the invention encompasses a pharmaceutical composition comprising a compound according to Formula I, IA, II or III or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof and a pharmaceutically acceptable diluent or carrier. In some embodiments,the pharmaceutical composition the invention encompasses a composition wherein the compound is present in a therapeutically effective amount.

In still another embodiment, the pharmaceutical composition the invention further encompasses at least one further active compound. In one embodiment, the further active compound is an anti-hyperproliferative agent.

Another aspect of the invention encompasses a packaged pharmaceutical composition comprising a container, the pharmaceutical composition of the invention and instructions for using the pharmaceutical composition to treat a disease or condition in a mammal.

Yet another aspect of the invention encompasses a method of inhibiting kinase activity in a cell comprising contacting a cell with one or more compounds of the invention. In one embodiment, the kinase activity inhibited is Anaplastic Lymphoma Kinase activity. In another embodiment, the kinase activity inhibited is hepatocyte growth factor receptor tyrosine kinase (c-Met) activity. In another embodiment, the kinase activity inhibited is monopolar spindle (Mps1) kinase activity.

Still another aspect of the invention encompasses a method of treating a hyperproliferative disorder in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of the invention. In some embodiments, the hyperproliferative disorder is cancer, including but not limited to, cancer of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid or a distant metastasis of a solid tumor, a lymphoma, sarcoma, melanoma or leukemia.

Still yet another aspect of the invention encompasses a method of treating an angiogenesis disorder in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of the invention.

It is noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as "comprises", "comprised", "comprising" and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean "includes", "included", "including", and the like; and that terms such as "consisting essentially of" and "consists essentially of" have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

These and other embodiments are disclosed or are obvious from and encompassed by, the following Detailed Description.

DETAILED DESCRIPTION

Definitions.

The following definitions can be referenced to assist in understanding the subject matter of the present application. Additional terms may be found defined throughout the detailed description.

The term "halogen" refers to radicals of fluorine, chlorine, bromine and iodine.

The term "alkyl" refers to a straight or branched hydrocarbon chain radical, containing solely carbon and hydrogen atoms, having in the range from one up to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, such as illustratively, methyl, ethyl, n-propyl 1-methylethyl (iso-propyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (tert-butyl).

The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system having in the range of 3 up to 14 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Examples of multicyclic cycloalkyl groups include decahydronaphthyl. Examples of bridged cycloalkyl groups or sprirobicycloalkyl groups include adamantyl norbornyl, and sprio[4.4]nonyl groups.

The term "alkoxy" denotes an alkyl group as defined herein attached via an oxygen linkage to the rest of the molecule. Representative examples of those groups are methoxy, ethoxy, iso-propoxy, n-butoxy, and tert-butoxy.

The term "cycloalkoxy" denotes a cycloalkyl group as defined herein attached via an oxygen linkage to the rest of the molecule. Representative examples of those groups are cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy, and cycloheptoxy.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, indanyl, and biphenyl.

The term "heteroaryl" refers to a stable 5- to 13-membered aromatic heterocycle having in the range of from 1 up to 4 heteroatoms from the group consisting of nitrogen, phosphorus, oxygen and sulfur, which ring or ring system can be linked via a carbon atom or a nitrogen atom, if such an atom is present. For purposes of this invention, the heteroaryl ring radical may be a monocyclic, bicyclic or tricyclic ring system. Examples of such heteroaryl

radicals are: pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, indolicenyl, indolyl, benzo[b]thienyl, benzo[b]furyl, benzothiazolyl, benzothiadiazolyl, indazolyl, quinolyl, isoquinolyl, isoquinolyl, naphthyridinyl, quinazolinyl, oxadiazolyl, benzoxazolyl, tetrazoyl, triazolyl, thiadiazolyl, and benzimidazolyl.

The term "heterocycloalkyl" refers to a stable 3 to 13 membered saturated or partially unsaturated heterocycle having in the range from 1 up to 4 heteroatoms from the group consisting of nitrogen, phosphorus, oxygen and sulfur, which ring or ring system can be linked via a carbon atom or a nitrogen atom, if such an atom is present. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems. Examples of such heterocyclyl radicals are: tetrahydropyranyl, aziridyl, azepanyl, tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, piperidinyl, 1,2 dihydropyridinyl, 1,4 dihydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, azepinyl, oxazolinyl, thiazolinyl and 1,4 diazepinyl.

The term "alkylamino" refers to an alkyl group as defined herein attached via amino linkage to the rest of the molecule. Ther term alkylamino further includes dialkyl amino moieties in which two alkyl groups as define herein are attached via amino linkage to the rest of the molecule. Representative examples of those groups are methylamino and dimethylamino.

Where the plural form of the word compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single compound, salt, polymorph, isomer, hydrate, solvate or the like.

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (R) or (S) configuration, resulting in racemic mixtures in the case of a single asymmetric center, and diastereomeric mixtures in the case of multiple asymmetric centers. In certain instances, asymmetry may also be present due to restricted rotation about a given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and

diastereomers), are included within the scope of the present invention. Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallization. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivitization, optimally chosen to maximize the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivitization, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, et al. "Pharmaceutical Salts," J. Pharm. Sci. 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound

functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and chorine salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, tartrate, thiocyanate, tosylate, and undecanoate.

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, and dibutyl sulfate; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and strearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Method of treating hyper-proliferative disorders

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof; etc. which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term "treating" or "treatment" as stated throughout this document is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder, such as a carcinoma.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

Compounds of the invention are selectively toxic or more toxic to rapidly propiferating cells than to normal cells, particularly in human cancer cells, e.g., cancerous tumors, the compound has significant antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis.

Methods of treating Anaplastic Lymphoma Kinase, Hepatocyte growth factor receptor tyrosine kinase (c-Met), and Nucleophosmin-ALK disorders

The present invention also provides methods for the treatment of disorders associated with aberrant expression of Anaplastic Lymphoma Kinase, Hepatocyte growth factor receptor tyrosine kinase (c-Met), and/or Nucleophosmin-ALK.

The compounds described in this application are ATP-competitive kinase inhibitors. As such they competitively block ATP from binding to the kinase active site and thereby prevent phosphorylation of downstream substrates. This effectively blocks signal transduction from the targeted kinases. Compounds in this application have the potential to interact with any kinase in the human kinome and have been tested for their ability to bind to a panel of 320 distinct protein kinases. This panel includes the following kinases: AAK1, ABL1, ABL1(E255K), ABL1(H396P), ABL1(M351T), ABL1(Q252H), ABL1(T315I), ABL1(Y253F), ABL2, ACVR1, ACVR1B, ACVR2A, ACVR2B, ACVRL1, ADCK3,ADCK4,AKT1,AKT2, AKT3,ALK,AMPK-alpha1,AMPK-alpha2, ANKK1, ARK5, AURKA, AURKB, AURKC, AXL, BIKE, BLK, BMPR1A, BMPR2, BMX, BRAF, BRAF(V600E), BRSK1, BRSK2, BTK, CAMK1, CAMK1D, CAMK1G, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CAMK4, CAMKK1, CAMKK2, CDC2L1, CDC2L2, CDK11, CDK2, CDK3, CDK5, CDK7, CDK8, CDK9, CHEK1, CIT, CLK1, CLK2, CLK3, CLK4, CSF1R, CSK, CSNK1A1L, CSNK1D, CSNK1E, CSNK1G1, CSNK1G2, CSNK1G3, CSNK2A1, CSNK2A2, DAPK1, DAPK2D, APK3, DCAMKL1, DCAMKL2, DCAMKL3, DDR1, DDR2, DLK, DMPK, DMPK2, DRAK1, DRAK2, DYRK1B, EGFR, EGFR(E746-A750del), EGFR(G719C), EGFR(G719S), EGFR(L747-E749del, A750P), EGFR(L747-S752del, P753S), EGFR(L747, T751del, Sins), EGFR(L858R), EGFR(L861Q), EGFR(S752-I759del), EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHB1, EPHB2, EPHB3, EPHB4, ERBB2, ERBB4, ERK1, ERK2, ERK3, ERK4, ERK5, ERK8, FER, FES, FGFR1, FGFR2, FGFR3, FGFR3(G697C), FGFR4, FGR, FLT1, FLT3, FLT3(D835H), FLT3(D835Y), FLT3(ITD), FLT3(N841I), FLT4, FRK, FYN, GAK, GCN2(Kin.Dom.2, S808G), GSK3A, GSK3B, HCK, IGF1R, IKKepsilon, INSR, INSRR,

IRAK3, ITK, JAK1(Kin.Dom.1), JAK2(Kin.Dom.2), JAK3(Kin.Dom.2), JNK1, JNK2, JNK3, KIT, KIT(D816V), KIT(V559D), KIT(V559D, T670I), KIT(V559D, V654A), LATS1, LATS2, LCK, LIMK1, LIMK2, LKB1, LOK, LTK, LYN, MAP3K4, MAP3K5, MAP4K1, MAP4K3, MAP4K4, MAP4K5, MAPKAPK2, MAPKAPK5, MARK1, MARK2, MARK3, MARK4, MEK1, MEK2, MEK3, MEK4, MEK6, MELK, MERTK, MET, MKNK1, MKNK2, MLCK, MLK1, MLK2, MLK3, MRCKA, MRCKB, MST1, MST2, MST3, MST4, MUSK, MYLK, MYLK2, MYO3A, MYO3B, NDR2, NEK1, NEK2, NEK5, NEK6, NEK7, NEK9, NLK, p38-alpha, p38-beta, p38-gamma, PAK1, PAK2, PAK3, PAK4, PAK6, PAK7/PAK5, PCTK1, PCTK2, PCTK3, PDGFRA, PDGFRB, PDPK1, PFTK1, PHKG1, PHKG2, PIK3CA, PIK3CA(E545K), PIM1, PIM2, PIM3, PIP5K1A, PIP5K2B, PKACalpha, PKACbeta, PKMYT1, PKN1, PKN2, PLK1, PLK3, PLK4, PRKCD, PRKCE, PRKCH, PRKCQ, PRKD1, PRKD2, PRKD3, PRKG1, PRKG2, PRKR, PRKX, PTK2, PTK2B, PTK6, RAF1, RET, RET(M918T), RIOK1, RIOK3, RIPK1, RIPK2, ROS1, RPS6KA1(Kin.Dom.1), RPS6KA1(Kin.Dom.2), RPS6KA2(Kin.Dom.1), RPS6KA2(Kin.Dom.2), RPS6KA3(Kin.Dom.1), RPS6KA4(Kin.Dom.1), RPS6KA4(Kin.Dom.2), RPS6KA5(Kin.Dom.1), RPS6KA5(Kin.Dom.2), RPS6KA6(Kin.Dom.1), RPS6KA6(Kin.Dom.2), SgK085, SLK, SNARK, SNF1LK, SNF1LK2, SRC, SRMS, SRPK1, SRPK2, STK16, STK33, STK36, SYK, TEC, TESK1, TGFBR1, TGFBR2, TIE1, TIE2, TLK1, TLK2, TNIK, TNK1, TNK2, TNNI3K, TRKA, TRKB, TRKC, TSSK1, TTK, TXK, TYK2(Kin.Dom.2), TYRO3, VEGFR2, WEE1, YANK2, YANK3, YES, YSK1, ZAK. This panel includes both the wild-type kinase and mutants that have been discovered to occur naturally or are predicted to appear based upon clinical experience with other kinases.

In particular, the compounds of the invention demonstrate inhibitory activity against: ADCK3, ADCK4, ALK, CLK1, CLK4, EGFR, EGFR(E746-A750del), EGFR(L747-E749del, A750P), EGFR(L747-S752del, P753S), EGFR(L747-T751del,Sins), EGFR(L858R), EGFR(L861Q), EGFR(S752-I759del), ERBB4, FER, FES, GAK, IGF1R, INSR, INSRR, LTK, PTK2, PTK2B, ROS1, RPS6KA1(Kin.Dom.2), TNK1, TNK2, TTK.

The ALK inhibitory activity and inhibitory activity against ALK-containing gene fusions of the compounds described herein make them useful pharmaceutical agents for the treatment of proliferative diseases. The inventive compounds are particularly useful for

treating a tumor which is a breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; in particular (i) a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, for example a small cell or non-small cell lung tumor; a gastrointestinal tumor, for example, a colorectal tumor; or a genitourinary tumor, for example, a prostate tumor (especially a hormone-refractory prostate tumor); or (ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or (iii) a tumor that is refractory to treatment with other chemotherapeutics due to multidrug resistance.

In a broader sense of the invention, a proliferative disease may furthermore be a hyperproliferative condition such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. Proliferative diseases treated according to the present method include tumors of blood and lymphatic system (e.g. Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and malignant plasma cell neoplasms, lymphoid leukemia, acute or chronic myeloid leukemia, acute or chronic lymphocytic leukemia, monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoletic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma). Myeloid cancer includes e.g. acute or chronic myeloid leukaemia.

Methods of Treating Monopolar Spindle Kinase Disorders

The present invention also provides methods of treating disorders and diseases associated with aberrant expression of the monopolar spindle kinase (Mps1, also known as TTK)

Monopolar spindle (Mps1 also known as TTK) kinase is a kinase for mitotic checkpoint and also controls correction of improper chromosome attachments. Both of these processes are important in maintaining chromosomal stability during cell division. Agents that block of Mps1 kinase activity may find application in cancer therapy due to their ability to induce apoptosis of cells that contain an improper number of chromosomes. In addition, Agents that block of Mps1 kinase activity may further enhance cytotoxicity of other chemotherapeutic agents.

Methods of Treating Neurotrophic Growth Factor Receptor Tyrosine Kinase A, B and C Disorders

The present invention also provides methods of treating disorders and diseases associated with aberrant expression of the neurotrophic growth factor receptor tyrosine kinase A, B and C (Trk A, B, C also known as NTRK1, 2, and 3).

The compounds in the present invention exhibit inhibition of the neurotrophic growth factor receptor tyrosine kinase A, B and C (Trk A, B, C also known as NTRK1, 2, and 3). Several lines of evidence have implicated NTRKs in the development and progression of cancer through deregulation of tyrosine kinase activity by mutations, chromosomal rearrangements, upregulation of either the receptor, their ligand (Nerve Growth Factor, Brain Derived Neurotropic Factor, Neurotrophins) or both. Chromosomal translocations involving both NTRK1 & 3 have been found in several different types of tumors. Gene rearrangements involving NTRK1 and a set of different fusion partners (TPR, TPM3, TFG) are a hallmark of a subset of papillary thyroid cancers (PTC) (Neuro Endocrinol Lett. 2007 Jun 12;28(3):221-229; Cancer Treat Res. 2004;122:207-19). Rare cancers such as secretory breast cancer,

infant fibrosarcoma and congenital mesoblastic nephroma have been shown to be associated with a chromosomal rearrangement t(12;15) generating a ETV6-NTRK3 fusion gene that has been shown to have constitutive kinase activity and transforming potential in several different cell lines including fibroblasts, hematopoietic cells and breast epithelial cells (Nat Genet. 1998 Feb;18(2):184-7; Oncogene. 2000 Feb 17;19(7):906-15). TrkB is of central importance in preventing anoikis (detachment-induced apoptosis) which is believed to an important requirement in the metastatic process. Genetic abnormalities such as point mutations and chromosomal rearrangements of NTRK2 and NTRK3 have been found in a variety of cancer types (Nature, vol 446, p. 153, 8 March 2007). Hence agents that block TrkB kinase activity may serve as antimetastatic agents (Cell Mol Life Sci. 2006 Apr;63(7-8):755-9).

Methods of treating angiogenic disorders

The present invention also provides methods of treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, e.g., diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity (Aiello et al. *New Engl. J. Med.* **1994**, *331*, 1480; Peer et al. *Lab. Invest.* **1995**, *72*, 638), age-related macular degeneration (AMD; see, Lopez et al. *Invest. Opththalmol. Vis. Sci.* **1996**, *37*, 855), neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, compounds of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, e.g., by inhibiting and/or reducing blood vessel formation; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or

other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredient to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. In certain applications, the average daily oral dosing will be from about 200 mg/day to about 600 mg/day which corresponds to 2.8-8.6 mg/kg for a person with an average weight of 70 kgs. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The

transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the specific compound employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a compound of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Combination therapies

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compounds of this invention can be combined with known anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof.

The additional pharmaceutical agent can be aldesleukin, alendronic acid, alfaferone, alitretinoin, allopurinol, aloprim, aloxi, altretamine, aminoglutethimide, amifostine, amrubicin, amsacrine, anastrozole, anzmet, aranesp, arglabin, arsenic trioxide, aromasin, 5-azacytidine, azathioprine, BCG or tice BCG, bestatin, betamethasone acetate, betamethasone sodium phosphate, bexarotene, bleomycin sulfate, broxuridine , bortezomib, busulfan, calcitonin, campath, capecitabine, carboplatin, casodex, cefesone, celmoleukin, cerubidine, chlorambucil, cisplatin, cladribine, cladribine, clodronic acid, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, DaunoXome, decadron, decadron phosphate, delestrogen, denileukin diftitox, depo-medrol, deslorelin, dexrazoxane, diethylstilbestrol, diflucan, docetaxel, doxifluridine, doxorubicin, dronabinol, DW-166HC, eligard, elitek, ellence, emend, epirubicin, epoetin alfa, epogen, eptaplatin, ergamisol, estrace, estradiol, estramustine

phosphate sodium, ethinyl estradiol, ethyol, etidronic acid, etopophos, etoposide, fadrozole, farston, filgrastim, finasteride, fligrastim, floxuridine, fluconazole, fludarabine, 5-fluorodeoxyuridine monophosphate, 5-fluorouracil (5-FU), fluoxymesterone, flutamide, formestane, fosteabine, fotemustine, fulvestrant, gammagard, gemcitabine, gemtuzumab, gleevec, gliadel, goserelin, granisetron HCl, histrelin, hycamtin, hydrocortone, eyrthro-hydroxynonyladenine, hydroxyurea, ibritumomab tiuxetan, idarubicin, ifosfamide, interferon alpha, interferon-alpha 2, interferon alfa-2A, interferon alfa-2B, interferon alfa-n1, interferon alfa-n3, interferon beta, interferon gamma-1a, interleukin-2, intron A, iressa, irinotecan, kytril, lentinan sulphate, letrozole, leucovorin, leuprolide, leuprolide acetate, levamisole, levofolinic acid calcium salt, levothroid, levoxyl, lomustine, lonidamine, marinol, mechlorethamine, mecobalamin, medroxyprogesterone acetate, megestrol acetate, melphalan, menest, 6-mercaptopurine, Mesna, methotrexate, metvix, miltefosine, minocycline, mitomycin C, mitotane, mitoxantrone, Modrenal, Myocet, nedaplatin, neulasta, neumega, neupogen, nilutamide, nolvadex, NSC-631570, OCT-43, octreotide, ondansetron HCl, orapred, oxaliplatin, paclitaxel, pediapred, pegaspargase, Pegasys, pentostatin, picibanil, pilocarpine HCl, pirarubicin, plicamycin, porfimer sodium, prednimustine, prednisolone, prednisone, premarin, procarbazine, procrit, raltitrexed, rebif, rhenium-186 etidronate, rituximab, roferon-A, romurtide, salagen, sandostatin, sargramostim, semustine, sizofiran, sobuzoxane, solu-medrol, sparfosic acid, stem-cell therapy, streptozocin, strontium-89 chloride, synthroid, tamoxifen, tamsulosin, tasonermin, tastolactone, taxotere, teceleukin, temozolomide, teniposide, testosterone propionate, testred, thioguanine, thiotepa, thyrotropin, tiludronic acid, topotecan, toremifene, tositumomab, trastuzumab, treosulfan, tretinoin, trexall, trimethylmelamine, trimetrexate, triptorelin acetate, triptorelin pamoate, UFT, uridine, valrubicin, vesnarinone, vinblastine, vincristine, vindesine, vinorelbine, virulizin, zinecard, zinostatin stimalamer, zofran, ABI-007, acolbifene, actimmune, affinitak, aminopterin, arzoxifene, asoprisnil, atamestane, atrasentan, BAY 43-9006 (sorafenib), avastin, CCI-779, CDC-501, celebrex, cetuximab, crisnatol, cyproterone acetate, decitabine, DN-101, doxorubicin-MTC, dSLIM, dutasteride, edotecarin, eflornithine, exatecan, fenretinide, histamine dihydrochloride, histrelin hydrogel implant, holmium-166 DOTMP, ibandronic acid, interferon gamma, intron-PEG, ixabepilone, keyhole limpet hemocyanin, L-651582,

lanreotide, lasofoxifene, libra, lonafarnib, miproxifene, minodronate, MS-209, liposomal MTP-PE, MX-6, nafarelin, nemorubicin, neovastat, nolatrexed, oblimersen, onco-TCS, osidem, paclitaxel polyglutamate, pamidronate disodium, PN-401, QS-21, quazepam, R-1549, raloxifene, ranpirnase, 13-cis -retinoic acid, satraplatin, seocalcitol, T-138067, tarceva, taxoprexin, thymosin alpha 1, tiazofurine, tipifarnib, tirapazamine, TLK-286, toremifene, TransMID-107R, valspodar, vapreotide, vatalanib, verteporfin, vinflunine, Z-100, zoledronic acid or combinations thereof.

Optional anti-hyper-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Dosage Forms and Modes of Administration

Preferred modes of administration include oral administration and parenteral administration.

Oral Dosage Forms

Compounds of the invention and compositions comprising them that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, *Remington's Pharmaceutical Sciences, 18th ed.*, Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent very advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can

be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. An specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103.TM and Starch 1500 LM.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W. R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection and constant

infusion), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products (including, but not limited to lyophilized powders, pellets, and tablets) ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

Transdermal, Topical, And Mucosal Dosage Forms

Transdermal, topical, and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, sprays, aerosols, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal, topical, and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form lotions, tinctures, creams, emulsions, gels or ointments, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990).

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea;

and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Kits

This invention encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises one or more unit dosage forms of a compound of the invention or one or more compositions comprising a compound of the invention, or physiologically acceptable salts thereof, and instructions for use.

Kits of the invention can further comprise devices that are used to administer a compound of the invention to a patient. Examples of such devices include, but are not limited to, intravenous cannulation devices, syringes, drip bags, patches, topical gels, pumps, tubing, containers that provide protection from photodegredation, and inhalers.

Kits of the invention can further comprise pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride

Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

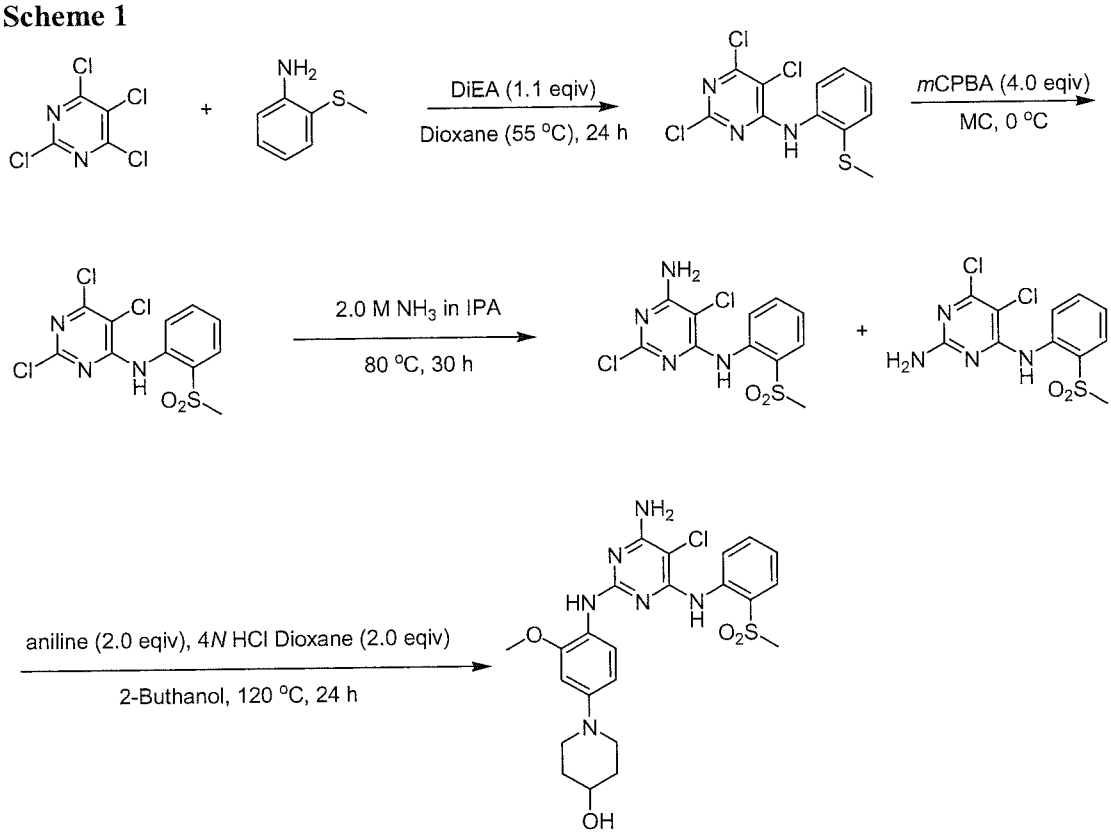
* * *

The invention will now be further described by way of the following non-limiting examples.

EXAMPLES

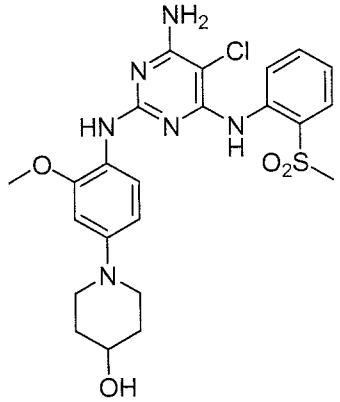
In general, the compounds of Formula I, particularly Formula IA can be prepared through the preparation shown in the Reaction Scheme 1 below.

Scheme 1

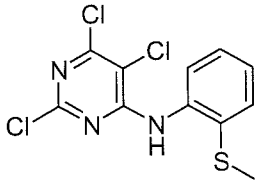


Example 1-0

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol

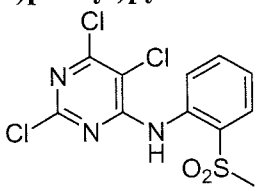


2,5,6-trichloro-*N*-(2-(methylthio)phenyl)pyrimidin-4-amine



To a solution of 2,3,5,6-tetrachloropyrimidine (5.0 g, 22.94 mmol) in dioxane (100 mL) was added 2-(methylthio)benzenamine (2.9 mL, 22.94 mmol) and diisopropylethylamine (4.2 mL, 25.23 mmol). The reaction mixture was stirred at 55 °C for 24 hours after which it was poured into ice water and the resulting solid was collected by filtration. The solid was dried (6.7 g, 91% yield) and used without further purification

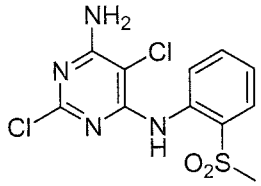
2,5,6-trichloro-N-(2-(methylsulfonyl)phenyl)pyrimidin-4-amine



To a solution of 2,5,6-trichloro-*N*-(2-(methylthio)phenyl)pyrimidin-4-amine (6.7 g, 20.89 mmol) in dichloromethane (100 mL) was added *m*CPBA (14.3 g, 83.58 mmol). The reaction mixture was stirred for 4 hours after which it was diluted with dichloromethane (100 mL). The organic layer was washed with satd. $NaHCO_3$ solution and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was

purified by flash column chromatography using a 95:5 v/v Hexane:Ethyl acetate as solvent to afford title compound (5.2 g, 71 %) as a white solid.

2,5-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-4,6-diamine



A sealed tube was charged with 2,5,6-trichloro-*N*-(2-(methylsulfonyl)phenyl)pyrimidin-4-amine (500 mg, 1.42 mmol), 2.0 M NH_3 in isopropyl alcohol (7.0 mL) and isopropyl alcohol (7.0 mL). The tube was sealed and the reaction mixture was stirred at 80 °C for 30 hours. The reaction mixture was poured into ice water and the resulting white solid was filtered and dried. Two isomers (380 mg, 80% yield), i.e. 2,5-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-4,6-diamine and 5,6-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine were produced in a 3 : 1 ratio.

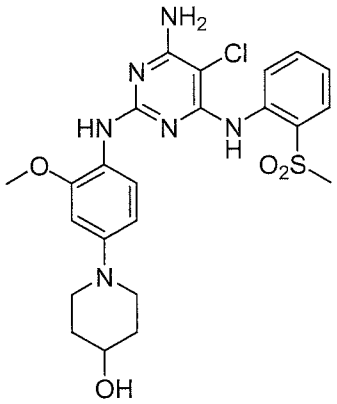
2,5-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-4,6-diamine

^{1}H NMR 600 MHz (DMSO-d_6) δ 9.16 (*s*, 1H), 8.21 (*d*, *J* = 7.8 Hz, 1H), 7.87 (*dd*, *J* = 1.2 Hz, *J* = 7.8Hz, 1H), 7.73 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.45(*bs*, 2H), 7.33 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 3.22 (*s*, 3H), MS m/z : 333.12 (M + 1).

5,6-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine

^{1}H NMR 600 MHz (DMSO-d_6) δ 9.35 (*s*, 1H), 8.52 (*d*, *J* = 8.4 Hz, 1H), 7.88 (*dd*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.71 (*dt*, J = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.35 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.01 (*bs*, 2H), 3.24 (*s*, 3H), MS m/z : 333.12 (M + 1).

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol



A sealed tube was charged with the isomers of 2,5-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-4,6-diamine and 5,6-dichloro-N^4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4-diamine (100 mg, 0.30 mmol), 1-(4-amino-3-methoxyphenyl)piperidin-4-ol (134 mg, 0.60 mmol), 4*N* HCl dioxane (0.15 mL) and 2-butanol (1.0 mL). The tube was sealed and the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was neutralized with satd. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMSO (3 mL). The resulting solution was subjected to purification by reverse-phase HPLC to yield the title compound as a TFA salt. The product containing fraction was neutralized with satd. $NaHCO_3$ solution and extracted with ethyl acetate dried over $MgSO_4$, filtered and concentrated. Two isomers, i.e. 1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol and 1-(4-(2-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-4-ylamino)-3-methoxyphenyl)piperidin-4-ol were produced.

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol

^{1}H NMR 600 MHz ($CDCl_3$) δ 8.93 (*s*, 1H), 8.40 (*d*, *J* = 8.4 Hz, 1H), 8.00 (*d*, *J* = 9.0 Hz, 1H), 7.89 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.54 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.15 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.06 (*s*, 1H), 6.50 (*m*, 1H), 6.41 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H),

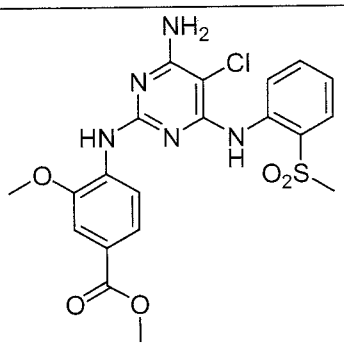
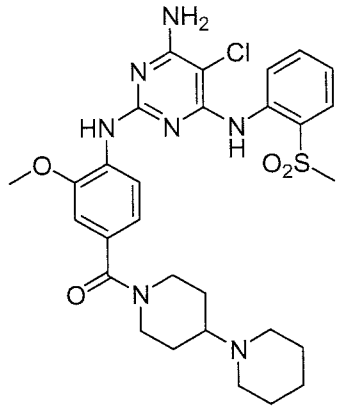
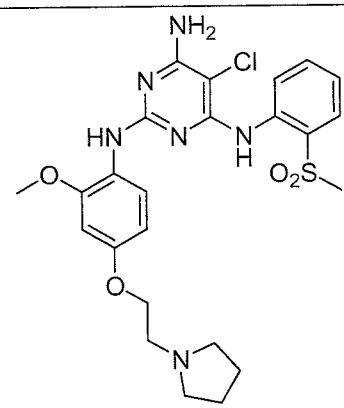
5.02 (*s*, 2H), 3.78 (*m*, 4H), 3.41 (*m*, 2H), 3.00 (*s*, 3H), 2.84(*m*, 2H), 1.98(*m*, 2H), 1.69 (*m*, 2H), MS m/z : 519.47 (M + 1).

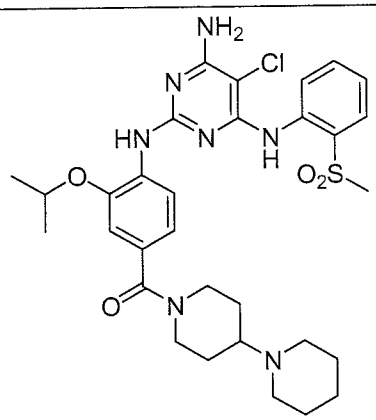
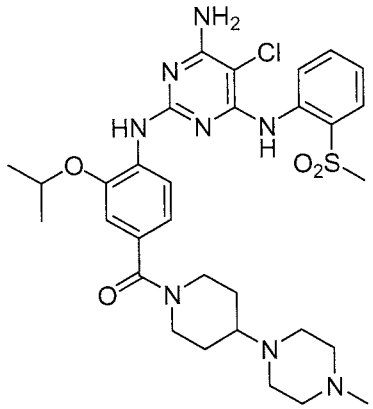
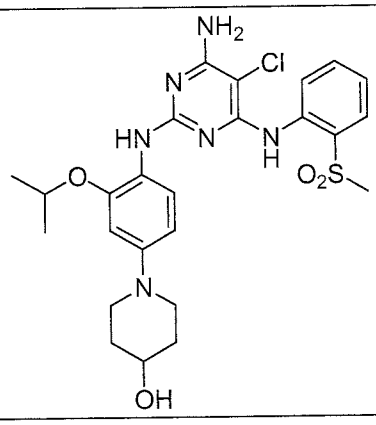
1-(4-(2-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-4-ylamino)-3-methoxyphenyl)piperidin-4-ol

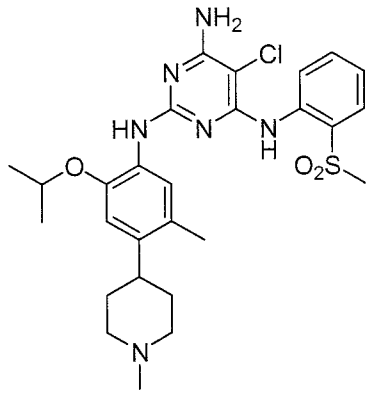
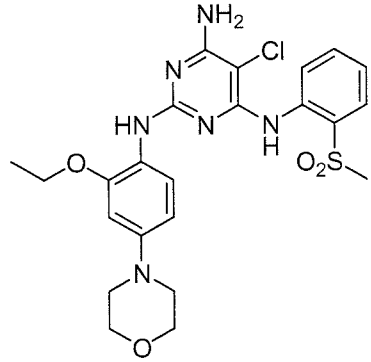
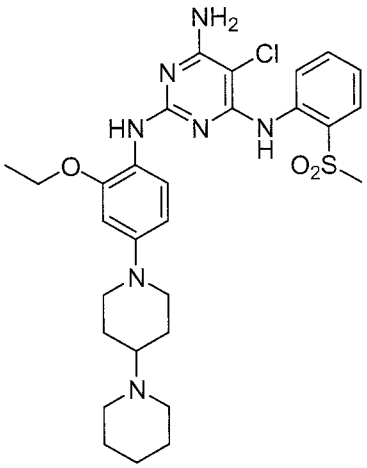
^{1}H NMR 600 MHz ($CDCl_3$) δ 8.87 (*s*, 1H), 8.36 (*d*, *J* = 8.4 Hz, 1H), 8.12 (*d*, *J* = 9.0 Hz, 1H), 7.87 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.53 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.36 (*s*, 1H), 7.11 (*dt*, J = 1.2 Hz, J = 7.8 Hz, 1H), 6.50 (*m*, 2H), 4.65 (*s*, 2H), 3.83 (*s*, 3H), 3.77 (*m*, 1H), 3.43 (*m*, 2H), 3.00 (*s*, 3H), 2.85(*m*, 2H), 1.96(*m*, 2H), 1.69 (*m*, 2H), MS m/z : 519.47 (M + 1).

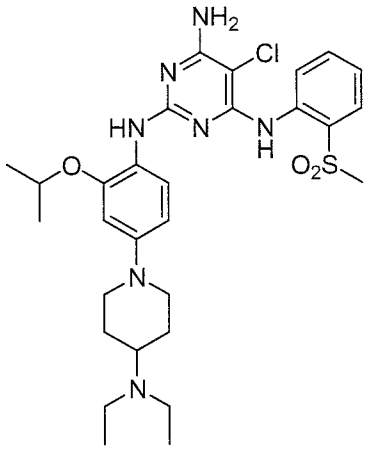
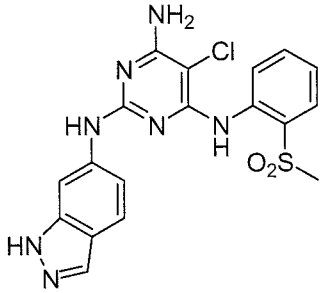
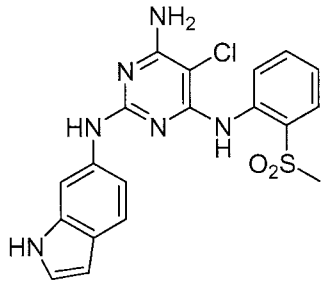
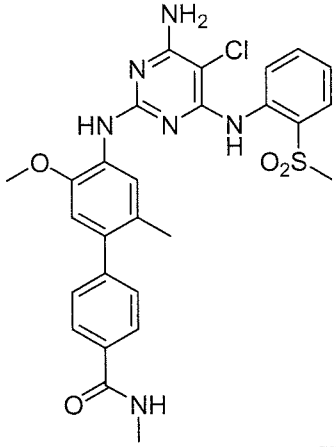
Table 1

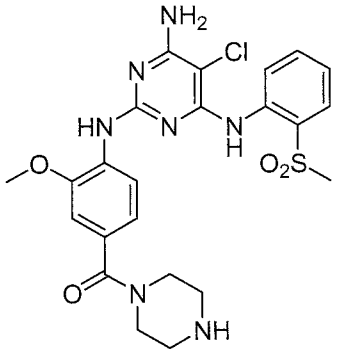
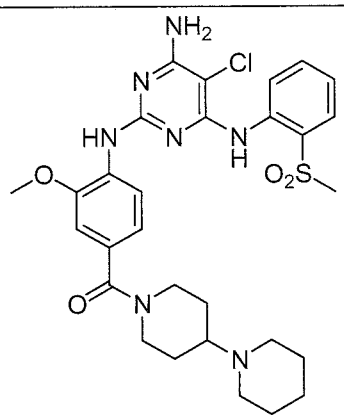
The following compounds were synthesized using the appropriate anilines:

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
1-1		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.14 (*s*, 1H), 9.02 (*s*, 1H), 8.44 (*d*, *J* = 8.4 Hz, 1H), 7.95 (*dd*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.75 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.70 (*s*, 1H), 7.62 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.20 (*t*, 1H), 6.93 (*d*, *J* = 7.2 Hz, 1H), 4.86 (*s*, 2H), 4.00 (*s*, 3H), 3.91(*s*, 3H), 3.07 (*s*, 3H), MS m/z : 478.21 (M + 1).
1-2		^{1}H NMR 600 MHz (CDCl3) δ 8.99 (*s*, 1H), 8.41 (*d*, *J* = 8.4 Hz, 1H), 8.35 (*d*, *J* = 7.8 Hz, 1H), 7.97 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.63 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.43 (*s*, 1H), 7.25 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.96 (*d*, *J* = 1.8 Hz, 1H), 6.89 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 5.07 (*s*, 2H), 3.89 (*s*, 3H), 3.07 (*s*, 3H), 2.61 (*m*, 2H), 2.52 (*m*, 7H), 1.50 (*m*, 6H), 1.49 (*m*, 2H), 1.44 (*m*, 2H), MS m/z : 614.43 (M + 1).
1-3		1H NMR 600 MHz ($CDCl_3$) δ 8.93 (*s*, 1H), 8.41 (*d*, *J* = 7.2 Hz, 1H), 8.11 (*bs*, 1H), 7.63 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.29 (*s*, 1H), 7.14 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.69 (*d*, *J* = 9.0 Hz, 1H), 6.39 (*dd*, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H), 5.19 (*s*, 2H), 4.03 (*m*, 2H), 3.77 (*s*, 3H), 3.02 (*s*, 3H), 2.91 (*m*, 2H), 2.70 (*m*, 4H), 1.89(*m*, 4H), MS m/z : 533.42 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
1-4		MS m/z : 642.52 (M + 1).
1-5		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.99 (*s*, 1H), 8.42 (*d*, *J* = 8.4 Hz, 1H), 8.36 (*d*, *J* = 7.8 Hz, 1H), 7.97 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.62 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.46 (*s*, 1H), 7.25 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.94 (*d*, *J* = 1.8 Hz, 1H), 6.87 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 5.07 (*s*, 2H), 4.64 (*m*, 1H), 3.07 (*s*, 3H), 2.88 (*m*, 3H), 2.63 (*m*, 6H), 2.47 (*m*, 4H), 2.45 (*s*, 3H), 1.90 (*m*, 2H), 1.48 (*m*, 2H), 1.38 (*d*, J = 6.0 Hz, 6H), MS m/z : 657.49 (M + 1).
1-6		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.76 (*s*, 1H), 8.49 (*d*, *J* = 8.4 Hz, 1H), 8.09 (*d*, *J* = 8.4 Hz, 1H), 7.95 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.58 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.19 (*t*, *J* = 8.4 Hz, 1H), 7.12 (*s*, 1H), 6.55 (*d*, *J* = 2.4 Hz, 1H), 6.44 (*dd*, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 5.05 (*s*, 2H), 4.56 (*m*, 1H), 3.84(*m*, 1H), 3.46 (*m*, 2H), 3.07 (*s*, 3H), 2.86 (*m*, 2H), 2.02 (*m*, 2H), 1.76 (*m*, 2H), 1.36 (*d*, *J* = 6.0 Hz, 6H), MS m/z : 547.44 (M + 1).

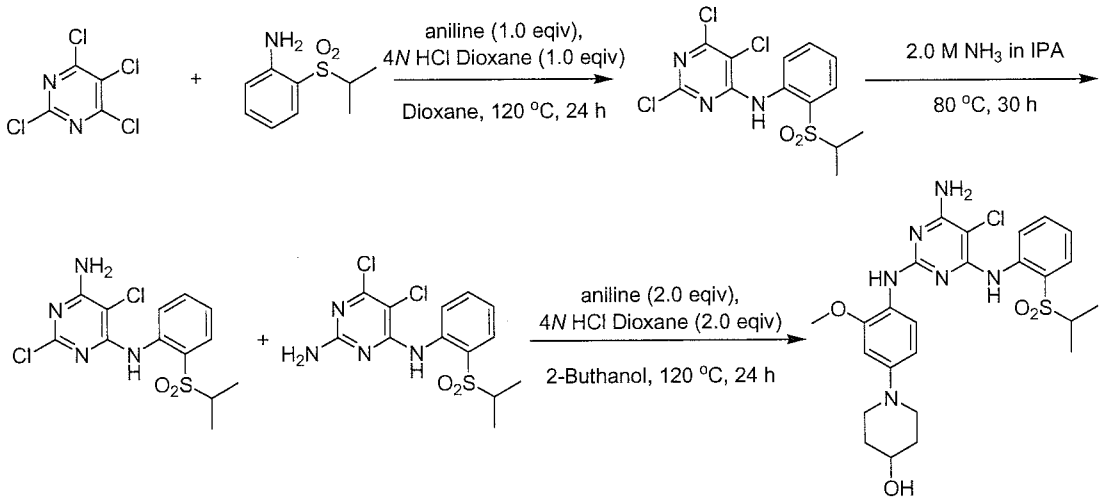
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
1-7		MS m/z : 599.47 (M + 1).
1-8		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.93 (*s*, 1H), 8.43 (*d*, *J* = 8.4 Hz, 1H), 8.06 (*d*, *J* = 9.0 Hz, 1H), 7.90 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.53 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.11 (*t*, 1H), 7.06 (*s*, 1H), 6.44 (*d*, *J* = 2.4 Hz, 1H), 6.35 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 4.93 (*s*, 2H), 4.04 (*m*, 2H), 3.80(*m*, 4H), 3.01(*m*, 7H), 1.38 (*m*, 3H), MS m/z : 519.47 (M + 1).
1-9		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.99 (*s*, 1H), 8.48 (*d*, *J* = 8.4 Hz, 1H), 8.11 (*d*, *J* = 9.0 Hz, 1H), 7.96 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.60 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.23 (*t*, 1H), 7.12 (*s*, 1H), 6.50 (*d*, *J* = 2.4 Hz, 1H), 6.42 (*dd*, *J* = 3.0 Hz, *J* = 8.4 Hz, 1H), 4.99 (*s*, 2H), 4.09 (*m*, 2H), 3.65(*m*, 2H), 3.09 (*m*, 5H), 2.72 (*m*, 3H), 2.16 (*m*, 2H), 1.68 (*m*, 6H), 1.56 (*m*, 4H), 1.43 (*t*, 3H), MS m/z : 600.54 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
1-10		MS m/z : 602.27 (M + 1).
1-11		MS m/z : 430.34 (M + 1).
1-12		MS m/z : 429.38 (M + 1).
1-13		^{1}H NMR 600 MHz (DMSO-d_6) δ 8.99 (*s*, 1H), 8.43 (*m*, 2H), 8.01 (*m*, 1H), 7.86 (*m*, 3H), 7.67 (*m*, 1H), 7.45 (*m*, 3H), 7.26 (*m*, 1H), 6.83 (*m*, 3H), 3.83 (*s*, 3H), 3.22 (*s*, 3H), 2.79 (*s*, 3H), 2.10 (*s*, 3H), MS m/z : 577.35 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
1-14		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.98 (*s*, 1H), 8.39 (*s*, 1H), 8.36 (*d*, *J* = 8.4 Hz, 1H), 7.90 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.60 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.32 (*s*, 1H), 7.16 (*t*, 1H), 6.95 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 6.81 (*d*, *J* = 8.4 Hz, 1H), 5.04 (*s*, 2H), 3.86 (*s*, 3H), 3.66 (*m*, 4H), 3.02 (*m*, 3H), 2.88 (*m*, 4H), MS m/z : 547.50 (M + 1).
1-15		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.99 (*s*, 1H), 8.41 (*d*, *J* = 8.4 Hz, 1H), 8.35 (*d*, *J* = 7.8 Hz, 1H), 7.97 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.63 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.43 (*s*, 1H), 7.25 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.96 (*d*, *J* = 1.8 Hz, 1H), 6.89 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 5.07 (*s*, 2H), 3.89 (*s*, 3H), 3.07 (*s*, 3H), 2.61 (*m*, 2H), 2.52 (*m*, 7H), 1.50 (*m*, 6H), 1.49 (*m*, 2H), 1.44 (*m*, 2H), MS m/z : 614.43 (M + 1).

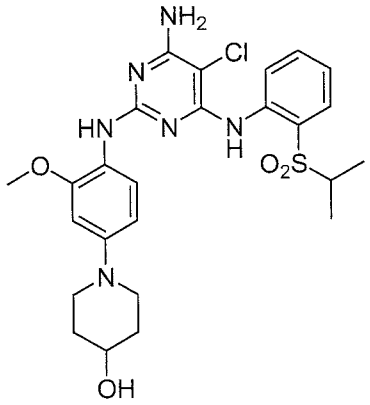
Alternatively, the compounds of Formula I, particularly Formula IA can be prepared through the preparation shown in the Reaction Scheme 2 below.

Scheme 2

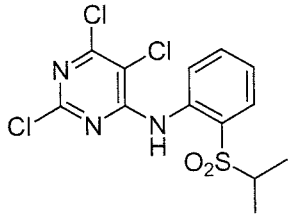


Example 2-0

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol



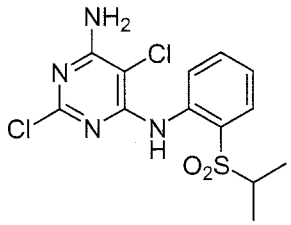
2,5,6-trichloro-N-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine



A sealed tube was charged with 2,3,5,6-tetrachloropyrimidine (2.18 g, 10.03 mmol), 2-(isopropylsulfonyl)benzenamine (2.0 mg, 10.03 mmol), 4*N* HCl dioxane (2.5 mL) and dioxane (50.0 mL). The tube was sealed and the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was neutralized with satd. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using a 95:5 v/v hexane:ethyl acetate as solvent to afford title compound (2.6 g, 68% yield) as a white solid.

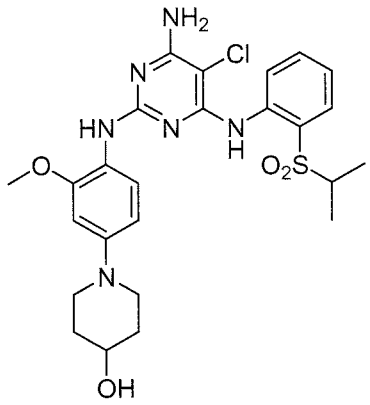
^{1}H NMR 600 MHz ($CDCl_3$) δ 10.18 (*s*, 1H), 8.53 (*dd*, *J* = 1.2, *J* = 8.4 Hz, 1H), 7.92 (*dd*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.38 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.35 (*dt*, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 3.21 (*m*, 1H), 1.31 (*d*, *J* = 6.6 Hz, 6H).

2,5-dichloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-4,6-diamine



A sealed tube was charged with 2,5,6-trichloro-N-(2-(methylsulfonyl)phenyl)pyrimidin-4-amine (900 mg, 1.42 mmol), 2.0 M NH_3 in isopropyl alcohol (10 mL) and isopropyl alcohol (10.0 mL). The tube was sealed and the reaction mixture was stirred at 80 °C for 30 hours. The reaction mixture was poured into ice water and the resulting white solid was filtered and dried, yielding (560 mg) mixture of two isomers 2,5-dichloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-4,6-diamine and 5,6-dichloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine.

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol



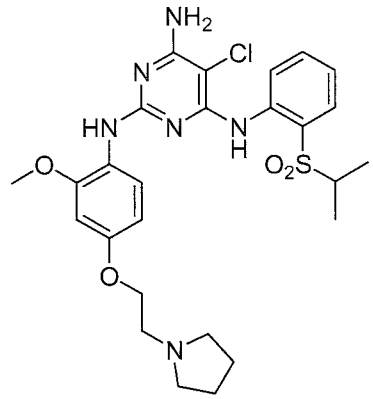
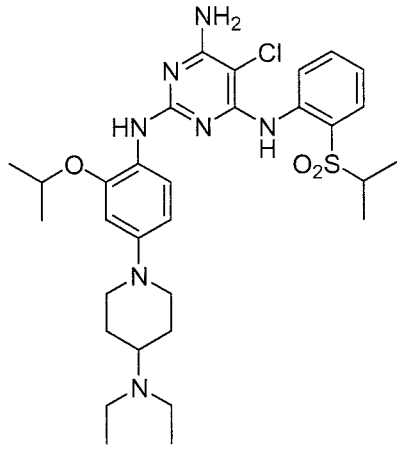
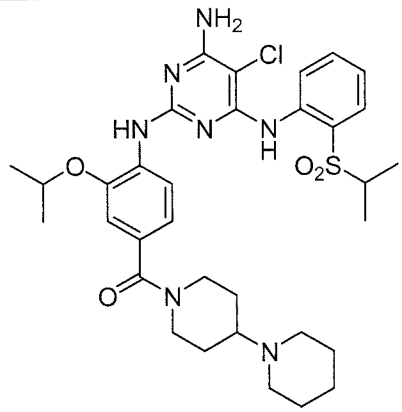
A sealed tube was charged with the isomers of 2,5-dichloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-4,6-diamine and 5,6-dichloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (100 mg, 0.28 mmol), 1-(4-amino-3-methoxyphenyl)piperidin-4-ol (123 mg, 0.56 mmol), 4*N* HCl dioxane (0.14 mL) and 2-butanol (1.0 mL). The tube was sealed and the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was neutralized with satd. $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in DMSO (3mL). The resulting solution was subjected to purification by reverse-phase HPLC to yield the title

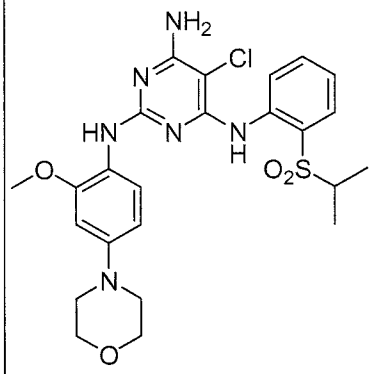
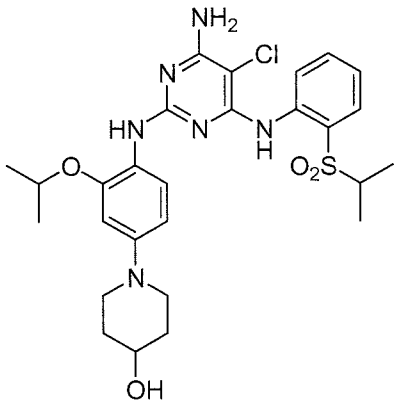
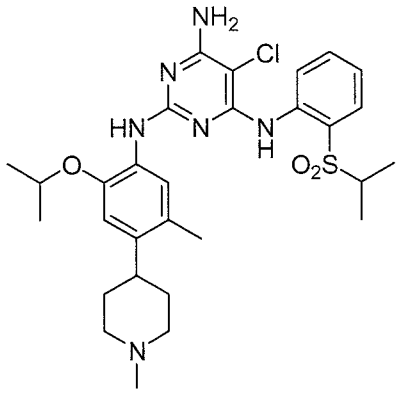
compound as a TFA salt. The product containing fraction was neutralized with satd. $NaHCO_3$ solution and extracted with ethyl acetate dried over $MgSO_4$, filtered and concentrated.

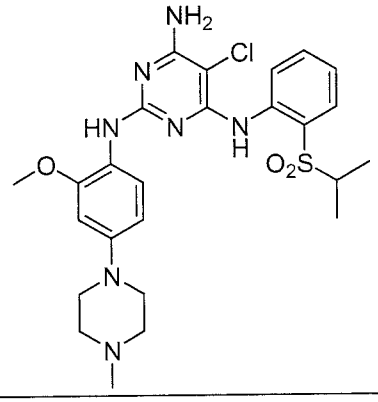
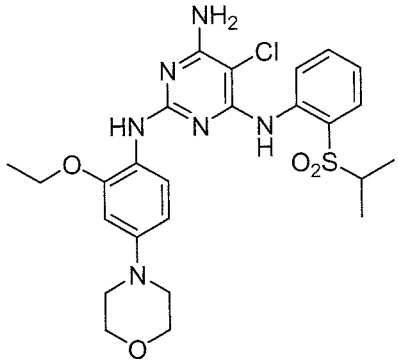
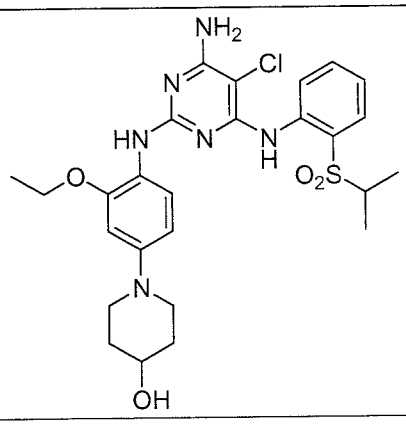
^1H NMR 600 MHz ($CDCl_3$) δ 9.19 (*s*, 1H), 8.47 (*d*, *J* = 8.4 Hz, 1H), 8.00 (*d*, *J* = 3.0 Hz, 1H), 7.81 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.52 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.13 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.01 (*s*, 1H), 6.48 (*d*, J = 2.4 Hz, 1H), 6.41 (*dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 4.90 (*s*, 2H), 3.79 (*m*, 4H), 3.41 (*m*, 2H), 3.20 (*m*, 1H), 2.84 (*m*, 2H), 1.97 (*m*, 2H), 1.69(*m*, 2H), 1.24 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 547.50 (M + 1)

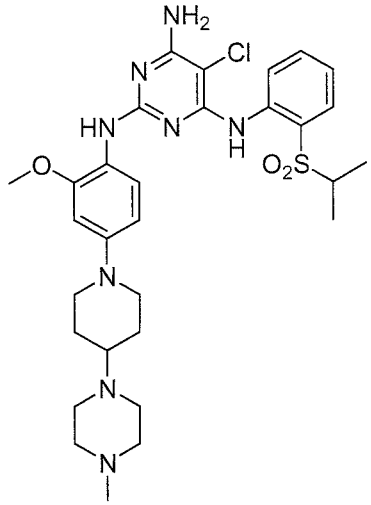
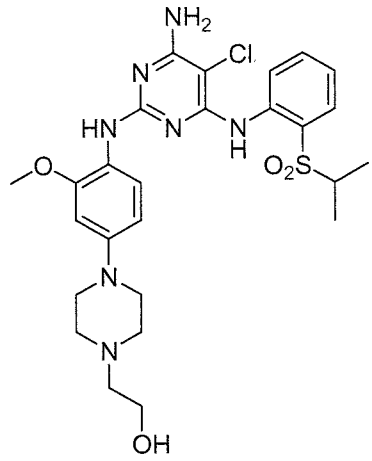
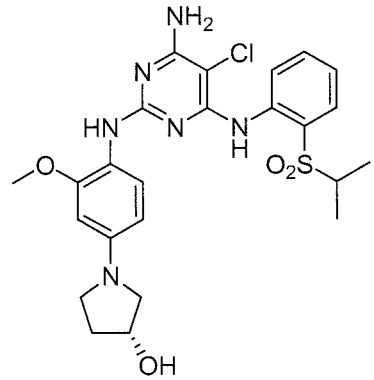
Table 2

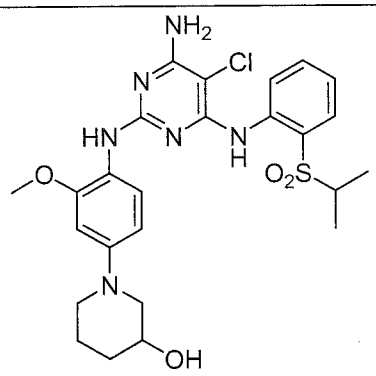
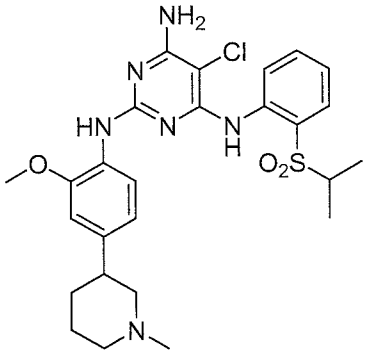
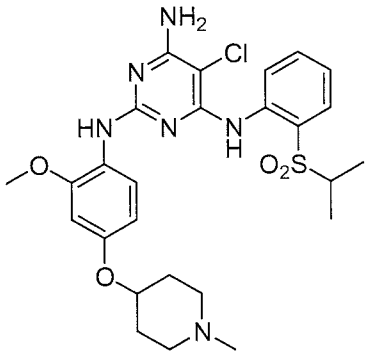
The following compounds were synthesized by repeating the procedures above using the appropriate anilines.

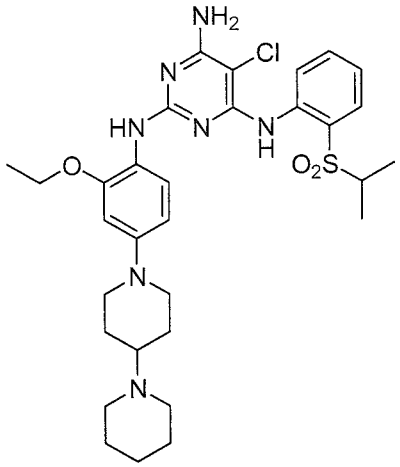
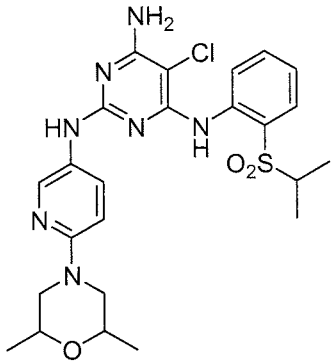
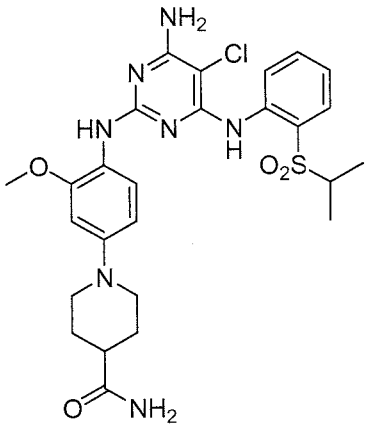
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-1		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.27 (*s*, 1H), 8.53 (*d*, *J* = 7.8 Hz, 1H), 8.09 (*d*, *J* = 3.0 Hz, 1H), 7.87 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.68 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.34 (*s*, 1H), 7.18 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.75 (*d*, *J* = 8.4 Hz, 1H), 6.46 (*dd*, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H), 5.09 (*s*, 2H), 4.00 (*t*, 2H), 3.83 (*s*, 3H), 3.26 (*m*, 1H), 2.88 (*m*, 2H), 2.64 (*m*, 4H), 1.81 (*m*, 4H), 1.30 (*d*, *J* = 7.2 Hz, 6H), MS m/z : 561.45 (M + 1).
2-2		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.24 (*s*, 1H), 8.55 (*d*, *J* = 9.0 Hz, 1H), 8.09 (*d*, *J* = 9.0 Hz, 1H), 7.87 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.58 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.19 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 6.54 (*d*, *J* = 7.8 Hz, 1H), 6.44 (*dd*, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 4.97 (*s*, 2H), 4.55 (*m*, 1H), 3.61 (*m*, 2H), 3.26 (*m*, 1H), 2.67 (*m*, 7H), 1.90 (m, 2H), 1.73 (m, 2H), 1.36 (*d*, *J* = 6.0 Hz, 6H), 1.30 (*d*, *J* = 7.2 Hz, 6H), 1.15 (*m*, 6H), MS m/z : 630.55 (M + 1).
2-3		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.21 (*s*, 1H), 8.40 (*d*, *J* = 7.8 Hz, 1H), 8.30 (*d*, *J* = 8.4 Hz, 1H), 7.83 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.55 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.40 (*s*, 1H), 7.19 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.88 (*d*, *J* = 1.2 Hz, 1H), 6.82 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 4.99 (*s*, 2H), 4.57 (*m*, 1H), 3.20 (*m*, 1H), 2.81 (*m*, 1H), 2.65 (*m*, 4H), 1.96 (*m*, 2H), 1.67 (*m*, 4H), 1.51 (*m*, 2H), 1.45 (*m*, 2H), 1.33 (*d*, *J* = 6.6 Hz, 6H), 1.24 (*d*, *J* = 7.2 Hz, 6H), 1.15 (*m*, 4H), MS m/z : 670.54 (M + 1).

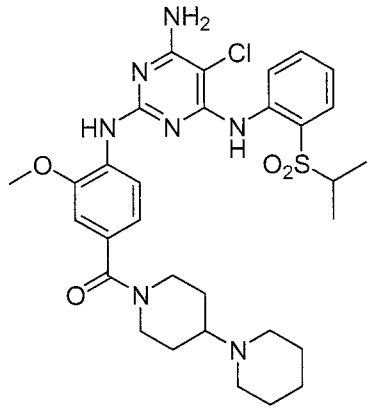
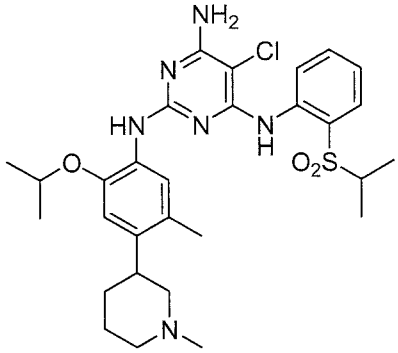
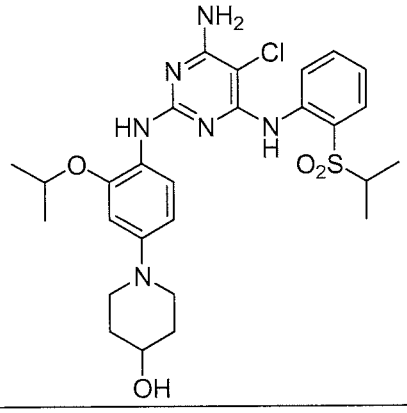
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-4		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.26 (*s*, 1H), 8.53 (*dd*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 8.10 (*d*, *J* = 8.4 Hz, 1H), 7.87 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.58 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.19 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.08 (*s*, 1H), 6.51 (*d*, *J* = 2.4 Hz, 1H), 6.44 (*m*, 1H), 4.99 (*s*, 2H), 3.87 (*m*, 7H), 3.27 (*m*, 1H), 3.11 (*m*, 4H), 1.30 (*d*, *J* = 7.2 Hz, 6H), MS m/z : 534.42 (M + 1).
2-5		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.24 (*s*, 1H), 8.54 (*d*, *J* = 8.4 Hz, 1H), 8.08 (*d*, *J* = 8.4 Hz, 1H), 7.87 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.58 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.19 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.11 (*s*, 1H), 6.55 (*d*, *J* = 3.0 Hz, 1H), 6.45 (*d*, *J* = 2.4 Hz, *J* = 7.8 Hz, 1H), 5.02 (*s*, 2H), 4.56 (*m*, 1H), 3.84 (*m*, 1H), 3.44 (*m*, 2H), 3.26 (*m*, 1H), 2.87 (*m*, 2H), 1.75 (*m*, 2H), 1.72 (*m*, 2H), 1.36 (*d*, *J* = 6.0 Hz, 6H), 1.30 (*d*, *J* = 7.2 Hz, 6H), MS m/z : 575.46 (M + 1).
2-6		MS m/z : 587.15 (M + 1).

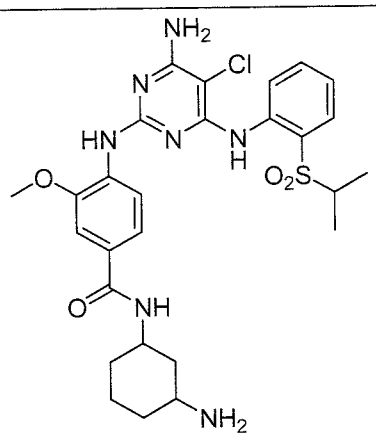
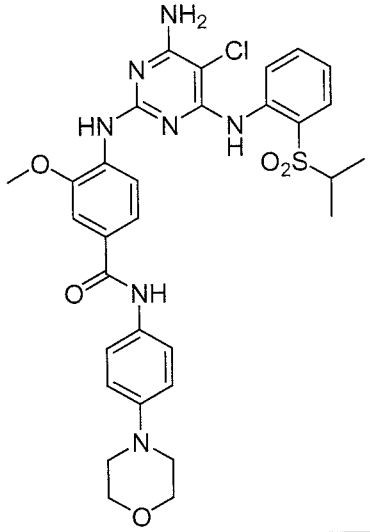
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-7		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.17 (*s*, 1H), 8.51 (*d*, *J* = 8.4 Hz, 1H), 7.74 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.60 (*m*, 2H), 7.42 (*s*, 1H), 7.22 (*t*, 1H), 6.60 (*m*, 3H), 6.42 (*dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 3.76 (*s*, 3H), 3.58 (*m*, 1H), 3.14 (*m*, 4H), 2.37 (*m*, 4H), 1.16 (*m*, 9H), MS m/z : 546.16 (M + 1).
2-8		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.17 (*s*, 1H), 8.49 (*d*, *J* = 8.4 Hz, 1H), 7.75 (*d*, *J* = 8.4 Hz, 1H), 7.69 (*d*, *J* = 8.4 Hz, 1H), 7.60 (*t*, 1H), 7.33 (*s*, 1H), 7.24 (*t*, 1H), 6.53 (*s*, 2H), 6.59 (*d*, *J* = 1.8 Hz, 1H), 6.41 (*dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 4.05 (*m*, 2H), 3.73 (*m*, 5H), 3.05 (*m*, 4H), 1.29 (*t*, 3H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 547.11 (M + 1).
2-9		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.16 (*s*, 1H), 8.50 (*d*, *J* = 7.8 Hz, 1H), 7.74 (*d*, *J* = 7.8 Hz, 1H), 7.63 (*d*, *J* = 8.4 Hz, 1H), 7.59 (*t*, 1H), 7.31 (*s*, 1H), 7.23 (*t*, 1H), 6.64 (*s*, 2H), 6.59 (*s*, 1H), 6.41 (*d*, *J* = 8.4 Hz, 1H), 4.66 (*m*, 1H), 4.02 (*m*, 2H), 3.59 (*m*, 1H), 3.46 (*m*, 2H), 2.78 (*m*, 2H), 1.8 (*m*, 2H), 1.48 (*m*, 2H), 1.28 (*t*, 3H), 1.15 (*d*, *J* = 6.0 Hz, 6H), MS m/z : 561.15 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-10		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.27 (*s*, 1H), 8.61 (*s*, 1H), 7.84 (*d*, *J* = 7.8 Hz, 1H), 7.66 (*m*, 2H), 7.50 (*s*, 1H), 7.32 (*t*, 1H), 6.70 (*m*, 3H), 6.52 (*d*, *J* = 8.4 Hz, 1H), 4.66 (*m*, 1H), 3.86 (*s*, 3H), 3.61(*m*, 1H), 3.77 (*m*, 2H), 2.74 (*m*, 3H), 2.40 (*m*, 4H), 2.24 (*s*, 3H), 1.94 (*m*, 2H), 1.61 (*m*, 2H), 1.25 (*m*, 9H), MS m/z : 629.31 (M + 1).
2-11		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.18 (*s*, 1H), 8.52 (*d*, *J* = 9.0 Hz, 1H), 7.74 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.60 (*m*, 2H), 7.41 (*s*, 1H), 7.22 (*t*, 1H), 6.60 (*s*, 2H), 6.59 (*d*, *J* = 2.4 Hz, 1H), 6.41 (*dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 4.42 (*m*, 1H), 3.76 (*s*, 3H), 3.54 (*m*, 2H), 3.10 (*m*, 4H), 2.56 (*m*, 4H), 2.47 (*m*, 2H), 1.15 (*d*, *J* = 7.2 Hz, 6H), MS m/z : 576.21 (M + 1).
2-12		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.19 (s, 1H), 8.54 (m, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.51 (m, 1H), 7.39 (m, 2H), 7.17 (t, 1H), 6.55 (s, 2H), 6.15 (s, 1H), 6.03 (m, 1H), 4.94 (m, 1H), 4.39 (m, 1H), 3.74 (s, 3H), 3.06 (m, 2H), 2.03 (m, 2H), 1.89 (m, 2H), 1.15 (d, J = 7.2 Hz, 6H), MS m/z 533.13 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-13		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.17 (*s*, 1H), 8.52 (*d*, *J* = 8.4 Hz, 1H), 7.74 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.57 (*m*, 2H), 7.40 (*s*, 1H), 7.23 (*dt*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 6.61 (*s*, 2H), 6.57 (*d*, *J* = 3.6 Hz, 1H), 6.40 (*dd*, *J* = 3.0 Hz, *J* = 9.0 Hz, 1H), 4.79 (*d*, *J* = 4.8 Hz, 1H), 3.76 (*s*, 3H), 3.62 (*m*, 1H), 3.54 (*m*, 1H), 3.43 (*m*, 1H), 2.62 (*m*, 1H), 1.89 (*m*, 1H), 1.76 (*m*, 1H), 1.56 (*m*, 1H), 1.27 (*m*, 2H), 1.15 (*d*, *J* = 7.2 Hz, 6H), MS m/z : 547.11 (M + 1).
2-14		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.16 (*s*, 1H), 8.47 (*d*, *J* = 8.4 Hz, 1H), 7.89 (*d*, *J* = 8.4 Hz, 1H), 7.74 (*m*, 1H), 7.64 (*t*, 1H), 7.46 (*s*, 1H), 7.26 (*t*, 1H), 6.87 (*m*, 1H), 6.72 (*m*, 3H), 3.81 (*s*, 3H), 2.90 (*m*, 3H), 2.73 (*m*, 1H), 2.29 (*m*, 4H), 1.80 (*m*, 3H), 1.62 (*m*, 1H), 1.43 (*m*, 1H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 545.22 (M + 1).
2-15		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.17 (*s*, 1H), 8.49 (*d*, *J* = 7.8 Hz, 1H), 7.74 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.63 (*d*, *J* = 8.4 Hz, 1H), 7.56 (*t*, 1H), 7.46 (*s*, 1H), 7.22 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 6.62 (*bs*, 2H), 6.60 (*d*, *J* = 2.4 Hz, 1H), 6.47 (*dd*, *J* = 3.0 Hz, *J* = 8.4 Hz, 1H), 4.32 (*m*, 1H), 3.75 (*s*, 3H), 2.62 (*m*, 2H), 2.20 (*m*, 6H), 1.90 (*m*, 2H), 1.65 (*m*, 2H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 561.28 (M + 1).

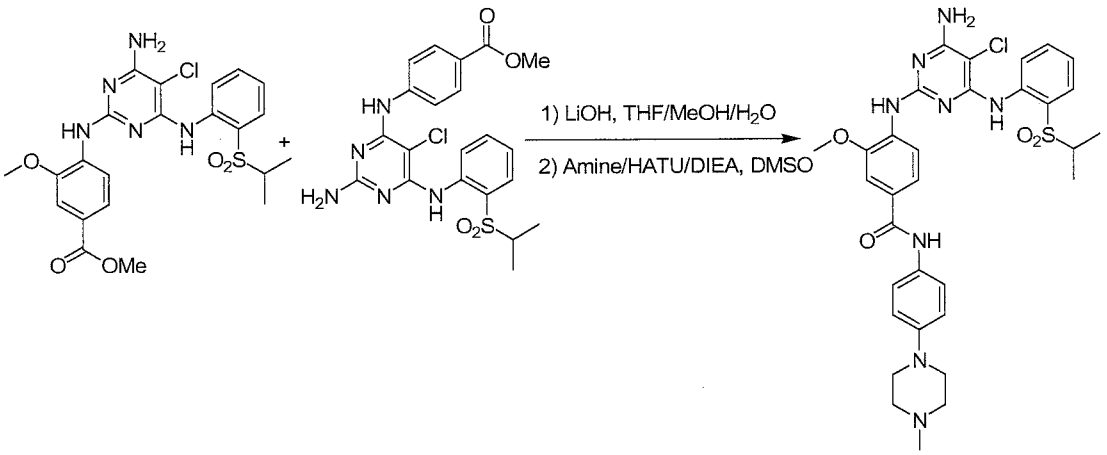
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-16		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.16 (*s*, 1H), 8.49 (*d*, *J* = 8.4 Hz, 1H), 7.75 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.63 (*d*, *J* = 9.0 Hz, 1H), 7.59 (*t*, 1H), 7.31 (*s*, 1H), 7.23 (*t*, 1H), 6.64 (*bs*, 2H), 6.57 (*d*, *J* = 1.8 Hz, 1H), 6.40 (*dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 4.04 (*q*, 2H), 3.65 (*m*, 2H), 2.60 (*m*, 2H), 2.47 (*m*, 4H), 2.32 (*m*, 1H), 1.79 (*m*, 2H), 1.54 (*m*, 7H), 1.37 (*m*, 2H), 1.28 (*t*, 3H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 628.31 (M + 1).
2-17		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.19 (*s*, 1H), 8.69 (*d*, *J* = 8.4 Hz, 1H), 8.31 (*m*, 2H), 7.75 (*d*, *J* = 7.8 Hz, 1H), 7.70 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.66 (*t*, 1H), 7.23 (*t*, 1H), 6.80 (*d*, *J* = 9.6 Hz, 1H), 6.24 (*bs*, 2H), 4.05 (*m*, 2H), 3.61 (*m*, 1H), 3.50 (*m*, 1H), 3.12 (*m*, 1H), 2.34 (*m*, 2H), 1.18 (*m*, 12H), MS m/z : 532.18 (M + 1).
2-18		MS m/z : 574.50 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-19		MS m/z : 642.17 (M + 1).
2-20		MS m/z : 587.23 (M + 1).
2-21		MS m/z : 575.24 (M + 1).

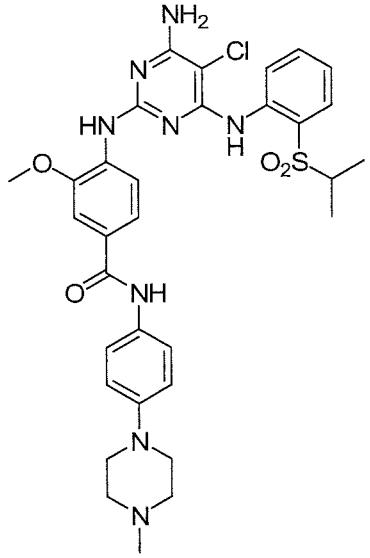
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
2-22		MS m/z : 587.21 (M + 1).
2-23		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.33 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 8.4, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.61 (m, 2H) 7.47 (d, J = 8.4 Hz, 2H), 7.41 (s, 1H), 7.21 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 5.58 (bs, 1H), 3.92 (s, 2H), 3.82 (m, 4H), 3.19 (m, 1H), 3.09 (m, 4H), 2.54 (s, 3H), 1.25 (d, J = 7.2 Hz, 6H), MS m/z 651.16 (M + 1).

Alternatively, the compounds of Formula I, particularly Formula IA can be prepared through the preparation shown in the Reaction Scheme 3 below.

Scheme 3.



Example 3-0
4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxy-N-(4-(4-methylpiperazin-1-yl)phenyl)benzamide



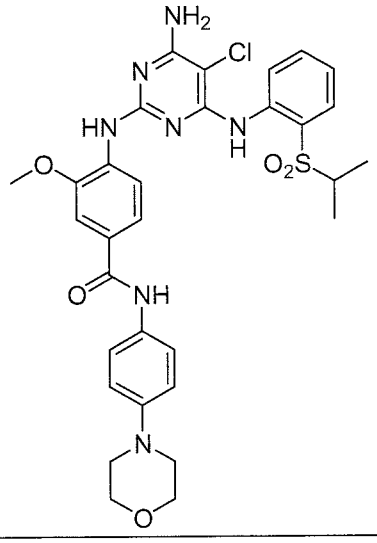
To a stirred solution of the isomers of methyl 4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxybenzoate and methyl 4-(2-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-4-ylamino)benzoate (779 mg, 1.55 mmol, prepared by the above procedure) in THF/MeOH (1:1, v/v, 50 mL) was added 10 mL of LiOH (350 mg, 8.33 mmol) aqueous solution. The resulting mixture was stirred at room temperature until the reaction was completed. Then the reaction was diluted with water and extracted with ethyl acetate. The water layer was acidified with 0.5 N HCl solution until PH = 5 and the solid was precipitated. The solid was collected by filtration and dried by air to give the isomers of 4-(2-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-4-ylamino)benzoic acid and 4-(4-amino-5-chloro-

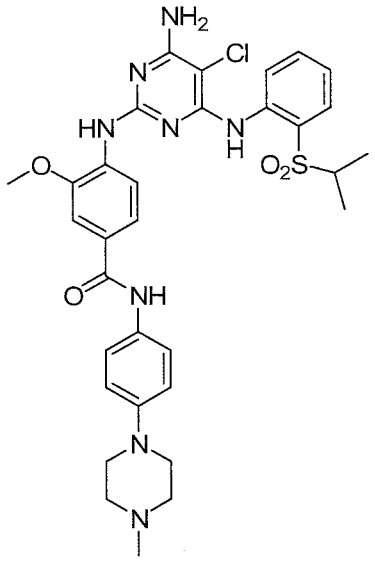
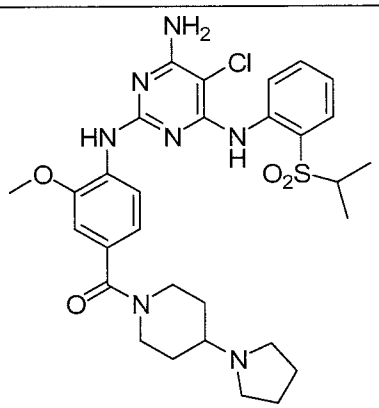
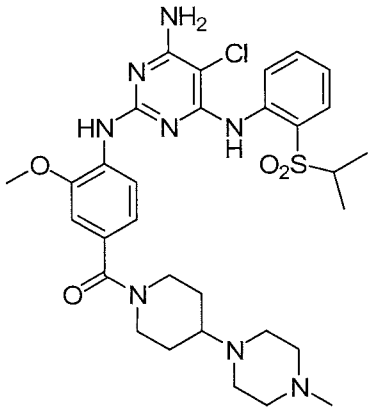
6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid (210 mg).

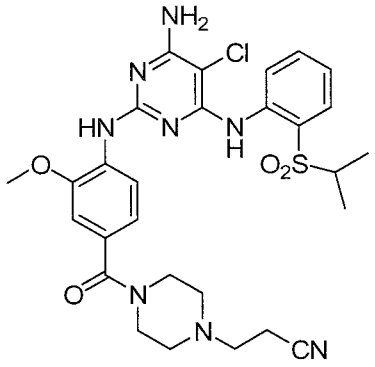
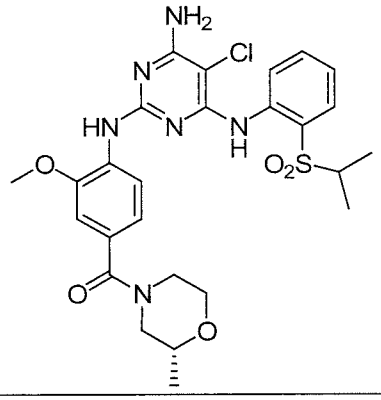
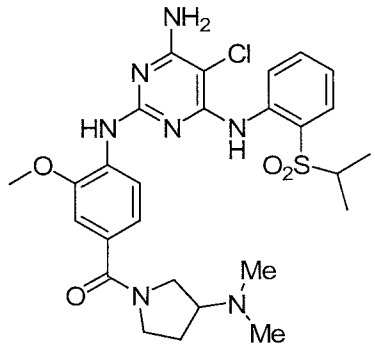
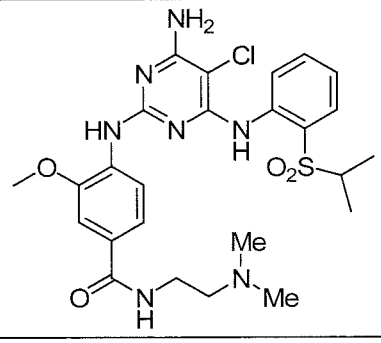
To a solution of the isomers of 4-(2-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-4-ylamino)benzoic acid and 4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxybenzoic acid (15 mg, 0.03 mmol), 4-(4-methylpiperazin-1-yl)benzenamine (19 mg, 0.1 mmol) and DIEA (27 μL, 0.15 mmol) in 1.0 mL of DMSO was added HATU (23 mg, 0.06 mmol). The mixture was stirred at room temperature until the reaction was completed determined by LC-MS. The resulting solution was subjected to purification by reverse-phase HPLC to yield the title compound as a TFA salt (17 mg).

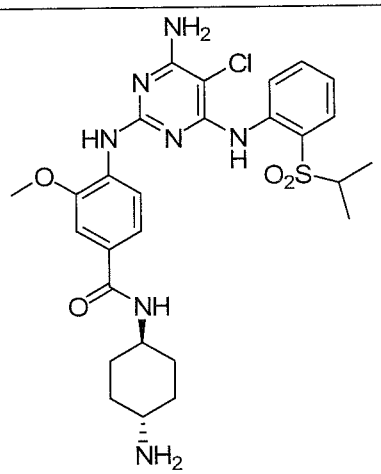
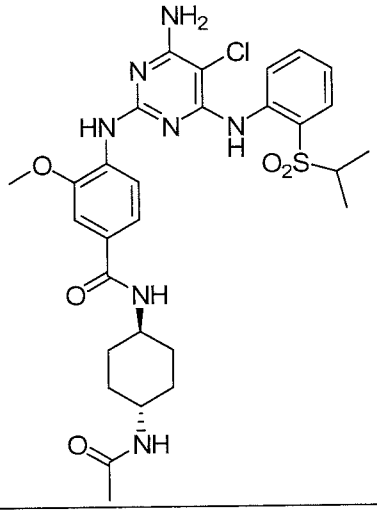
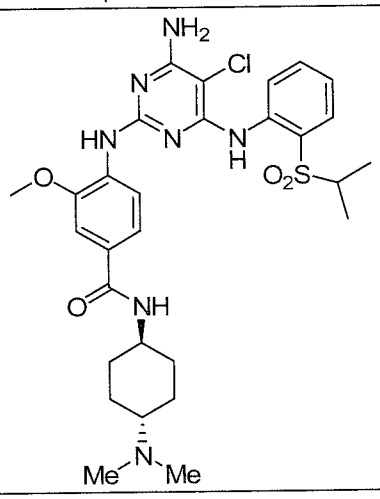
Table 3

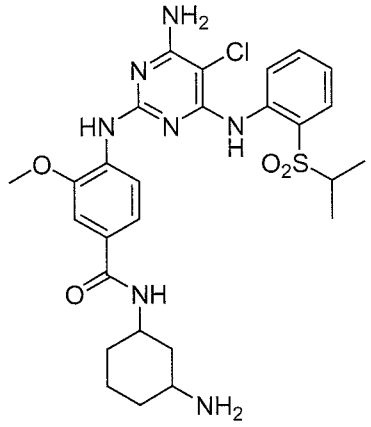
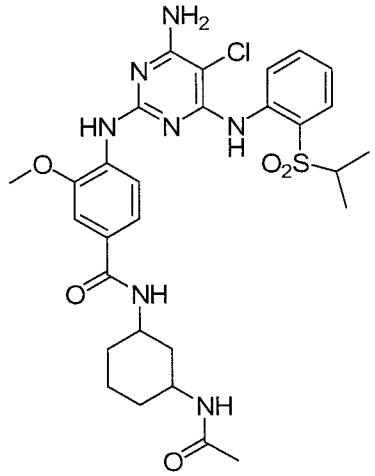
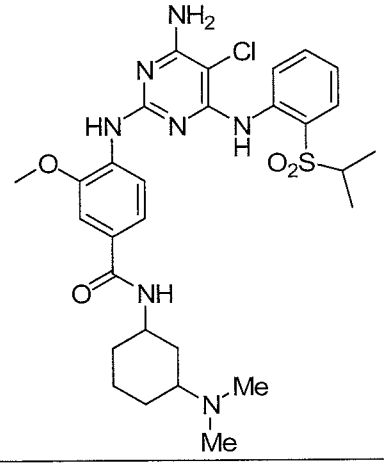
By repeating the procedures described in the above examples, using appropriate amines.

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
3-1		^{1}H NMR 600 MHz ($CDCl_3$) δ 9.33 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 8.4, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.61 (m, 2H) 7.47 (d, J = 8.4 Hz, 2H), 7.41 (s, 1H), 7.21 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 5.58 (s, br, 1H), 3.92 (s, 3H), 3.82-3.80 (m, 4H), 3.19-3.15 (m, 1H), 3.10-3.08 (m, 4H), 2.55 (s, 3H), 1.25 (d, J = 7.2 Hz, 6H), MS m/z 652.16 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
3-2		^{1}H NMR 600 MHz (CD_3OD) δ 8.24-8.20 (m, 2H), 7.91 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.77-7.74 (m, 1H), 7.59 (dd, *J* = 2.4, 6.6 Hz, 2H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.44-7.39 (m, 2H), 7.04-7.01 (m, 2H), 3.98 (s, 3H), 3.81 (d, *J* = 12.6 Hz, 2H), 3.61 (d, *J* = 11.4 Hz, 2H), 3.43-3.30 (m, 1H), 3.27 (t, *J* = 11.4 Hz, 2H), 3.05 (t, *J* = 12.0 Hz, 2H), 2.97 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 6H). MS m/z 665.16 (M + 1).
3-3		^{1}H NMR 600 MHz (CD_3OD) δ 8.19 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.72-7.70 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 1.2 Hz, 1H), 6.88 (dd, J = 1.2, 7.8 Hz, 1H), 3.93 (s, 3H), 3.72-3.64 (m, 2H), 3.46-3.42 (m, 1H), 3.34-3.28 (m, 3H), 3.20-3.10 (m, 2H), 3.10-2.90 (m, 2H), 2.30-2.12 (m, 4H), 2.08-1.98 (m, 2H), 1.72-1.60 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 6H). MS m/z 628.20 (M + 1).
3-4		^{1}H NMR 600 MHz (CD_3OD) δ 8.10 (d, *J* = 2.4 Hz, 1H), 7.93-7.91 (m, 2H), 7.71-7.69 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.87 (dd, J = 1.8, 7.8 Hz, 1H), 3.92 (s, 3H), 3.68-3.45 (m, 8H), 3.44-3.40 (m, 1H), 3.34-3.29 (m, 1H), 3.28-2.80 (m, 7H), 2.30-2.05 (m, 2H), 1.80-1.68 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 6H). MS m/z 657.24 (M + 1).

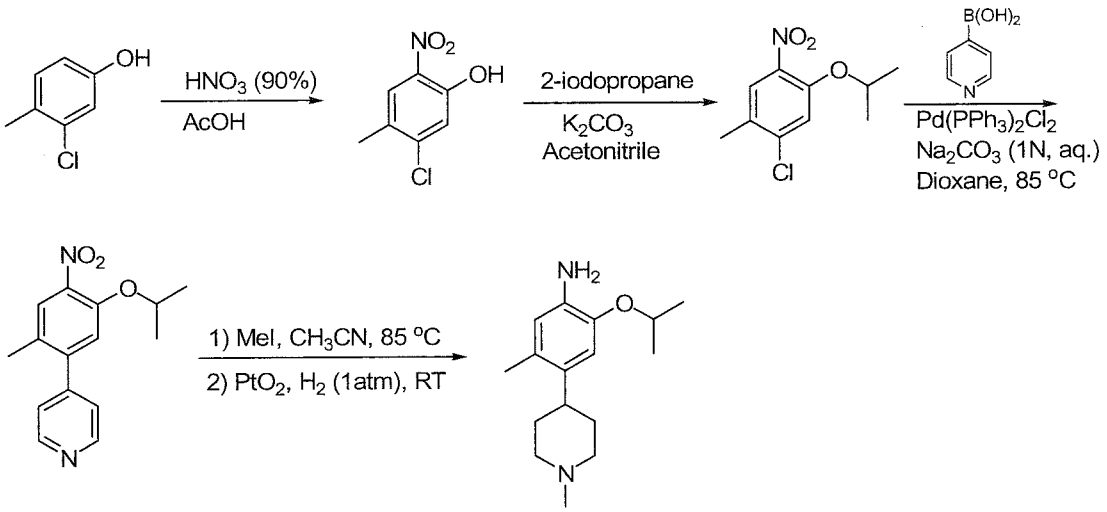
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
3-5		^{1}H NMR 600 MHz (CD_3OD) δ 8.16 (dd, J = 1.2, 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 1.2, 7.8 Hz, 1H), 7.73-7.70 (m, 1H), 7.44-7.41 (m, 1H), 7.12 (d, J = 1.8 Hz, 1H), 6.93 (dd, J = 1.8, 8.4 Hz, 1H), 3.94 (s, 3H), 3.92-3.84 (m, 4H), 3.48 (t, J = 7.2 Hz, 2H), 3.38-3.32 (m, 4H), 3.33-3.28 (m, 1H), 3.05 (t, J = 7.2 Hz, 2H), 1.23 (d, J = 7.2 Hz, 6H). MS m/z 613.09 (M + 1).
3-6		MS m/z 575.14 (M + 1).
3-7		^{1}H NMR 600 MHz (CD_3OD) δ 8.15 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 6.6 Hz, 1H), 7.92 (dd, J = 1.8, 8.4 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.44-7.41 (m, 1H), 7.19 (d, J = 1.8 Hz, 1H), 7.00 (dd, J = 1.2, 7.8 Hz, 1H), 4.10-3.98 (m, 2H), 3.93 (s, 3H), 3.83-3.66 (m, 3H), 3.34-3.30 (m, 1H), 3.05-2.85 (m, 6H), 2.48 (s, br, 1H), 2.22 (s, br, 1H), 1.22 (d, J = 6.6 Hz, 6H). MS m/z 588.07 (M + 1).
3-8		^{1}H NMR 600 MHz (CD_3OD) δ 8.21-8.18 (m, 2H), 7.93 (dd, J = 1.8, 7.8 Hz, 1H), 7.77-7.74 (m, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.44-7.41 (m, 1H), 7.35 (dd, J = 1.8, 9.0 Hz, 1H), 3.97 (s, 3H), 3.76 (t, J = 6.0 Hz, 2H), 3.38 (t, J = 6.0 Hz, 2H), 3.34-3.28 (m, 1H), 2.99 (s, 6H), 1.23 (d, J = 7.2 Hz, 6H). MS m/z 562.07 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
3-9		^{1}H NMR 600 MHz (CD_3OD) δ 8.17 (dd, J = 0.6, 8.4 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 1.2, 8.4 Hz, 1H), 7.75-7.72 (m, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.44-7.41 (m, 1H), 7.31 (dd, 1.2, 8.4 Hz, 1H), 3.95 (s, 3H), 3.90-3.88 (m, 1H), 3.33-3.30 (m, 1H), 3.38-3.20 (m, 1H), 2.15-2.08 (m, 4H), 1.60-1.48 (m, 4H), 1.22 (d, *J* = 6.6 Hz, 6H). MS m/z 588.14 (M + 1).
3-10		MS m/z 630.11 (M + 1).
3-11		MS m/z 616.06 (M + 1).

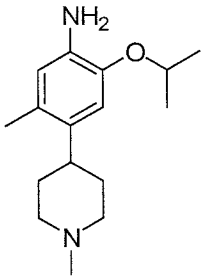
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
3-12		MS m/z : 588.14 (M + 1).
3-13		MS m/z : 630.25 (M + 1).
3-14		MS m/z : 616.25 (M + 1).

Alternatively still, the compounds of Formula I can be prepared through the preparation of intermediates shown in the Reaction Scheme 4 below

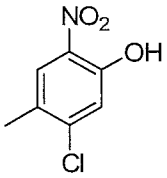
Scheme 4.



Example 4-1.
2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)benzenamine

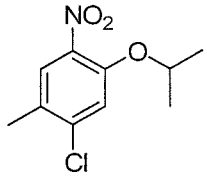


5-chloro-4-methyl-2-nitrophenol



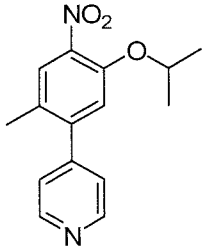
To a stirred solution of 3-chloro-4-methylphenol (4.9 g, 34 mmol) in 35 mL of glacial acetic acid was added 90% aqueous nitric acid (1.7 mL) in 20 min at 8 ~ 10 °C. The resulting mixture was stirred at 10 ~ 15 °C for 5 h. Then the mixture poured over ice water and the solid precipitated. The solid was collected by filtration and washed with water. Further purification by flash chromatography gave the title compound as bright yellow solid (2.67 g, 42%). ^{1}H NMR (600 M, $CDCl_3$) δ 10.42 (s, 1H), 7.97 (s, 1H), 7.19 (s, 1H), 2.35 (s, 3H).

1-chloro-5-isopropoxy-2-methyl-4-nitrobenzene



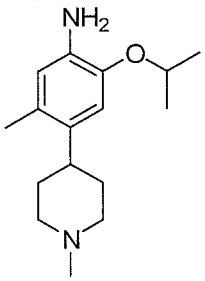
To a stirred solution of 5-chloro-4-methyl-2-nitrophenol (1.6 g, 8.5 mmol) in 30 mL of acetonitrile was added K_2CO_3 (2.37 g, 17 mmol) at room temperature. After 15 min, 2-iodopropane (1.7 mL, 17 mmol) was added and the resulting mixture was stirred at 85 °C for 20 h. Then the reaction was cooled down to room temperature and filtered. The filtrate was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give title compound (1.02 g, 52%), which was used without further purification. ^{1}H NMR (600 M, $CDCl_3$) δ 7.69 (s, 1H), 7.06 (s, 1H), 4.62-4.57 (m, 1H), 2.33 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H).

4-(5-isopropoxy-2-methyl-4-nitrophenyl)pyridine



A mixture of 1-chloro-5-isopropoxy-2-methyl-4-nitrobenzene (460 mg, 2.0 mmol), pyridin-4-ylboronic acid (300 mg, 2.4 mmol) and $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol) in dioxane/1.0 N Na_2CO_3 aqueous solution (1:1, v/v, 20 mL) was heated at 85 °C under an argon atmosphere. After 1 h, the solution was cooled to room temperature and filtered through a pad of celite and eluted with ethyl acetate. The combined filtrate was washed with brine and dried over anhydrous Na_2SO_4. The resulting crude product was concentrated and purified by flash chromatography to yield the title compound (458 mg, 84%). ^{1}H NMR (600 M, $CDCl_3$) δ 8.70 (dd, J = 1.8, 4.8 Hz, 2H), 7.70 (s, 1H), 7.22 (dd, J = 1.8, 4.8 Hz, 2H), 6.89 (s, 1H), 4.65-4.59 (m, 1H), 2.20 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H).

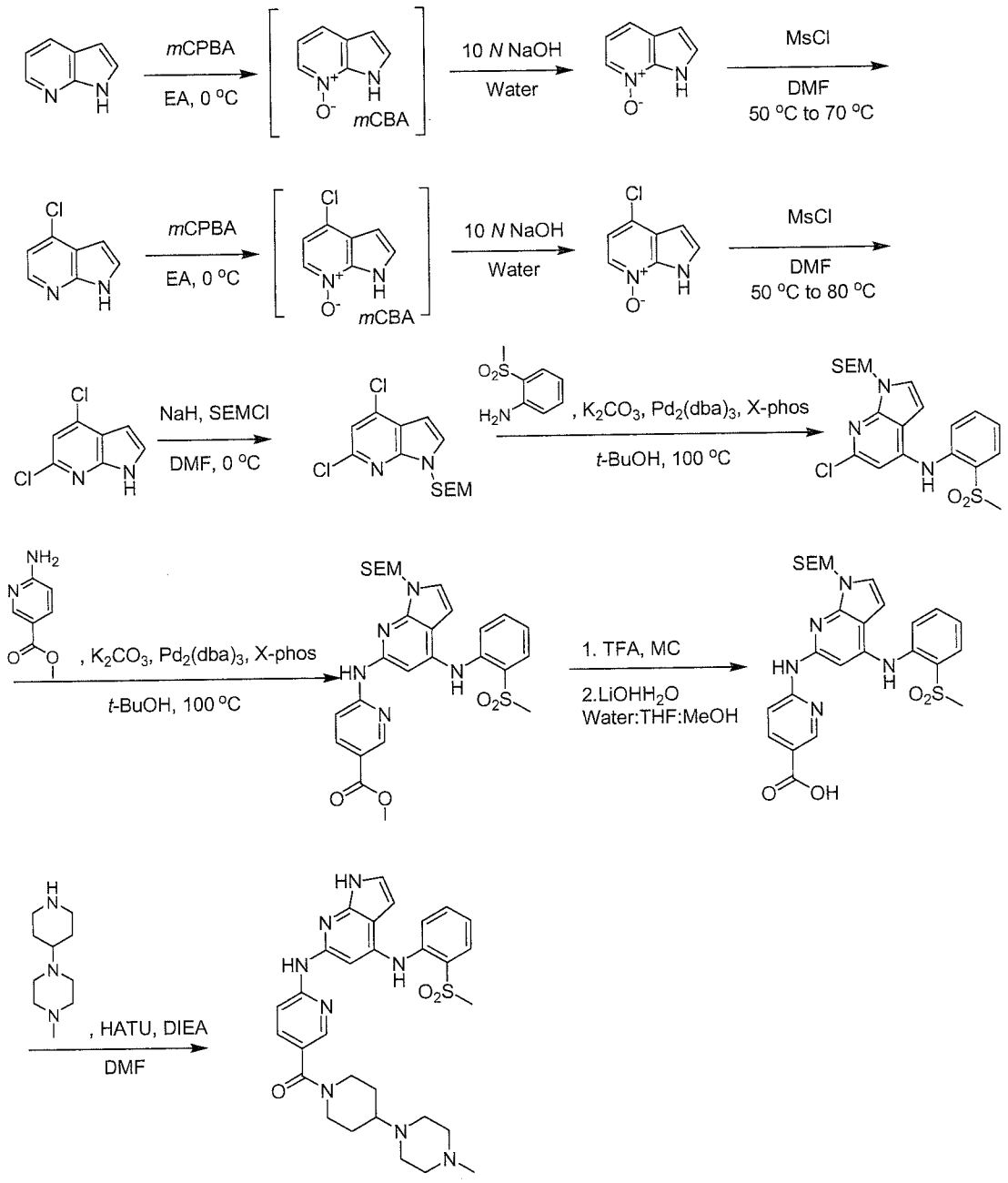
2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)benzenamine



A sealed tube was charged with 4-(5-isopropoxy-2-methyl-4-nitrophenyl)pyridine (445 mg, 1.64 mmol), iodomethane (0.2 mL, 3.28 mmol) and acetonitrile (10 mL). The reaction mixture was stirred at 85 °C for 12 h, then it was cooled down to room temperature. The reaction was concentrated and the residue was used in next step without further purification. The residue was dissolved in 20 mL of methanol. After hydrogenation on platinum oxide, one atmosphere of hydrogen for 20 h, the reaction mixture was filtered through a pad of celite and eluted with methanol. The combined filtrate was concentrated to afford the title compound, which was used without further purification (430 mg, 99%). ^{1}H NMR (600 M, $CDCl_3$) δ 6.75 (s, 1H), 6.50 (s, 1H), 4.55-4.49 (m, 1H), 3.68 (s, br, 2H), 3.53 (d, J = 12.0 Hz, 2H), 2.94-2.85 (m, 3H), 2.74 (s, 3H), 2.47-2.41 (m, 2H), 2.16 (s, 3H), 1.90 (d, J = 14.4 Hz, 2H), 1.31 (d, J = 6.0 Hz, 6H).

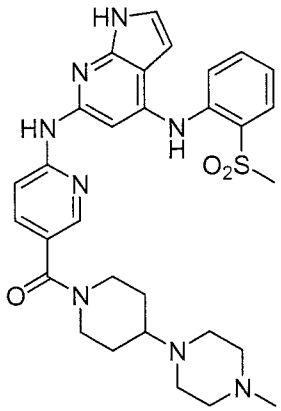
The compounds of Formula II, can be prepared through the preparation shown in the Reaction Scheme 5 below.

Scheme 5

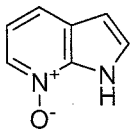


Example 5-0

(4-(4-methylpiperazin-1-yl)piperidin-1-yl)(6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)methanone

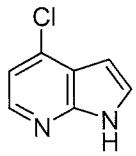


1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide



To a solution of 1*H*-pyrrolo[2,3-*b*]pyridine(20 g, 169.4 mmol) in ethyl acetate (250 mL) was added a solution of *m*-chloroperbenzoic acid (40.8 g, 237.0 mmol) in ethyl acetate(40 mL) at 0 °C for 30 min, followed by the addition of an additional 30 mL of ethyl acetate. After stirring at room temperature overnight, the reaction mixture was then cooled down to 0 °C. The resulting white solid was collected, washed with ethyl acetate, and dried. This white solid was suspended in water (100 mL) and treated with sat. K_2CO_3 slowly until a substantial amount of white solid was precipitated. This slurry mixture was slowly stirred overnight, cooled down to 0 °C. The resulting white solid was collected, washed with water and then dried to give 12.3 g (54% yield) of the title product.

4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine

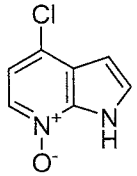


To a solution of 1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (12.3 g, 91.7 mmol) in *N,N*-dimethylformamide (40 mL) was added methanesulfonyl chloride (10.8 mL, 137.6 mmol) at 50 °C. The orange reaction mixture was stirred at 70 °C for 2 h and cooled down to 40 °C and then treated with 40 mL of water. The resulting suspension was cooled to 0 °C and

treated with 10.0 *N* NaOH solution to reach a pH of approximately 7. The resulting solid was collected, washed with water and dried to give 11.9 g (78% yield) of the title product.

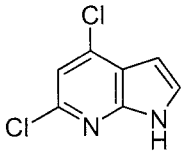
^{1}H NMR 600 MHz (DMSO-d_6) δ 12.01 (*s*, 1H), 8.15(*d*, *J* = 5.4 Hz, 1H), 7.56 (*dd*, *J* = 2.4 Hz, *J* = 3.0 Hz, 1H), 7.16 (*d*, *J* = 4.8 Hz, 1H), 6.48 (*dd*, *J* = 2.4 Hz, *J* = 3.6 Hz, 1 H), MS *m/z* 153.05 (M + 1).

4-chloro-1H-pyrrolo[2,3-b]pyridine 7-oxide



To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (8.0 g, 52.6 mmol) in ethyl acetate (80 mL) was added a solution of *m*-chloroperbenzoic acid (12.6 g, 52.63 mmol) in ethyl acetate(13 mL) at 0 °C for 30 min, followed by the addition of an additional 10 mL of ethyl acetate. After stirring at room temperature overnight, the reaction mixture was then cooled down to 0 °C. The resulting white solid was collected, washed with ethyl acetate, and dried. This white solid was suspended in water (35 mL) and treated with sat. K_2CO_3 slowly until a substantial amount of white solid precipitated. This slurry mixture was slowly stirred overnight and then cooled down to 0 °C. The resulting white solid was collected, washed with water and then dried to give 5.2 g (58% yield) of the title product.

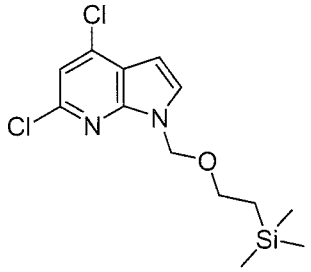
4,6-dichloro-1*H*-pyrrolo[2,3-*b*]pyridine



To a solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine 7-oxide (5.2 g, 30.9 mmol) in *N,N*-dimethylformamide (13.5 mL) was added methanesulfonyl chloride (3.42 mL, 43.3 mmol) at 50 °C. The orange reaction mixture was stirred at 80 °C for 3 h and cooled down to 40 °C and then treated with 13.5 mL of water. The resulting suspension was cooled to 0 °C and treated with 10 *N* NaOH solution to reach a pH of approximately 7. The resulting solid was collected, washed with water and dried to give 4.8 g (84% yield) of the title product.

^{1}H NMR 600 MHz (DMSO-d_6) δ 12.24 (*s*, 1H), 7.61(*d*, *J* = 3.6 Hz, 1H), 7.32 (*s*, 1H), 6.53 (*d*, *J* = 3.6 Hz, 1 H), MS *m/z* 187.01 (M + 1).

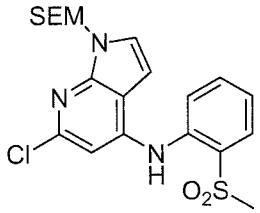
4,6-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine



To a solution of 4,6-dichloro-1*H*-pyrrolo[2,3-*b*]pyridine (1.50 g, 8.0 mmol) in *N,N*-dimethylformamide (26 mL) was added sodium hydride (481 mg, 12.0 mmol) at 0 °C. The reaction mixture was allowed to stir for 20 min. after which time 2-(trimethylsilyl)ethoxymethyl chloride (1.7 mL, 9.6 mmol) was added. The reaction mixture was further stirred at room temperature for a period of 3 hours after which time water and then ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using a 9:1 v/v Hexane:Ethyl acetate as solvent to afford title compound (2.1 g, 82% yield) as a yellow oil.

^{1}H NMR 600 MHz ($CDCl_3$) δ 7.41(*d*, *J* = 4.2 Hz, 1H), 7.21 (*s*, 1H), 6.66 (*d*, *J* = 4.2 Hz, 1 H), 5.67 (*s*, 2H), 3.58 (*t*, 2H), 0.96 (*t*, 2H), 0.00(*s*, 9H).

6-chloro-N-(2-(methylsulfonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-amine

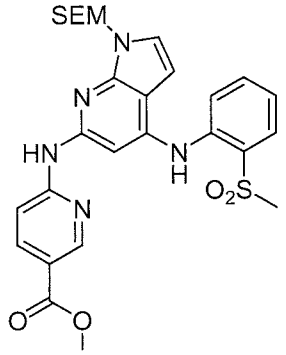


To a solution of 4,6-dichloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1.13 g, 3.57 mmol) in *t*-BuOH (18 mL) was added 2-(methylsulfonyl)benzenamine hydrochloride (742 mg, 3.57 mmol) and K_2CO_3 (1.97 g, 14.28 mmol). The reaction mixture was degassed using Argon for 10 min and then $Pd_2(dba)_2$ (196 mg, 0.214 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (153 mg, 0.32 mmol) were added. The reaction flask was placed into the preheated oil-bath at 100 °C. The

reaction mixture was further stirred at 100 °C for a period of 4 hours after which, it was filtered and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using a 9:1 v/v Hexane:Ethyl acetate as solvent to afford title compound (850 mg, 53% yield) as a yellow solid.

^{1}H NMR 600 MHz ($CDCl_3$) δ 8.38 (*s*, 1H), 8.07 (*d*, *J* = 7.8 Hz, 1H), 7.73 (*d*, *J* = 8.4 Hz, 1H), 7.70 (*t*, 1H), 7.32 (*m*, 2H), 7.00 (*s*, 1H), 6.52 (*d*, *J* = 3.0 Hz, 1H), 5.67 (*s*, 2H), 3.65 (*m*, 2H), 3.12 (*s*, 3H), 1.08 (*m*, 2H), 0.02 (*s*, 9H), MS m/z : 451.98 (M + 1).

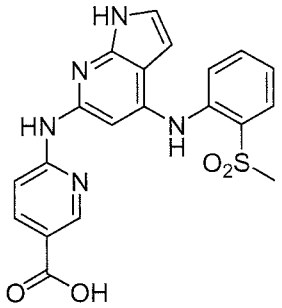
methyl 6-(4-(2-(methylsulfonyl)phenylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinate



To a solution of 6-chloro-N-(2-(methylsulfonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-amine (215 mg, 0.48 mmol) in *t*-BuOH (2 mL) was added methyl 6-aminonicotinate (80 mg, 0.52 mmol) and K_2CO_3 (217 mg, 1.57 mmol). The reaction mixture was degassed using Argon for 10 min after which $Pd_2(dba)_2$ (26 mg, 0.03 mmol) and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (22 mg, 0.05 mmol) were added. The reaction flask was put into the preheated oil-bath at 100 °C. The reaction mixture was further stirred at 100 °C for a period of 6 hours after which, it was filtered and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash column chromatography using a 9:1 v/v Hexane:Ethyl acetate as solvent to afford title compound (185 mg, 69% yield).

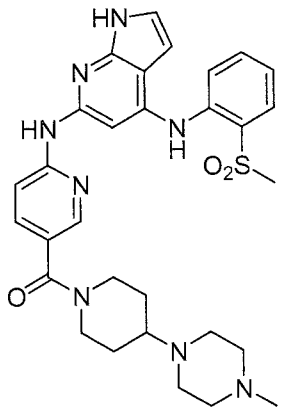
^{1}H NMR 600 MHz ($CDCl_3$) δ 8.92 (*d*, *J* = 3.6 Hz, 1H), 3.33 (*s*, 1H), 8.27 (*dd*, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 8.09 (*d*, *J* = 9.0 Hz, 1H), 8.06 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.86 (*s*, 1H), 7.77 (*d*, *J* = 8.4 Hz, 1H), 7.66 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.26 (*dt*, *J* = 0.6 Hz, *J* = 7.8 Hz, 1H), 7.18 (*d*, *J* = 3.6 Hz, 1H), 7.11 (*s*, 1H), 6.46 (*d*, *J* = 4.2 Hz, 1H), 5.67 (*s*, 2H), 3.97 (*s*, 3H), 3.69 (*m*, 2H), 3.35 (*s*, 3H), 1.02 (*m*, 2H), 0.00 (*s*, 9H), MS m/z : 568.13 (M + 1).

6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinic acid



To a solution of methyl 6-(4-(2-(methylsulfonyl)phenylamino)-1-((2-(trimethylsilyl)ethoxy)methyl) -1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinate (185 mg, 0.33 mmol) in methylene chloride (1.5 mL) was added trifluoroacetic Acid (0.13 mL, 1.63 mmol). The reaction mixture was stirred for 5h after which, the solvent was removed in vacuo. The crude product was redissolved in a mixture of methanol (0.5 mL) and THF (0.5 mL) followed by the addition of lithium monohydroxide (68 mg, 1.63 mmol) in water (0.5 mL). The reaction mixture was stirred for 6h after which, it was neutralized with 1N HCl solution and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was used without further purification.

(4-(4-methylpiperazin-1-yl)piperidin-1-yl)(6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)methanone

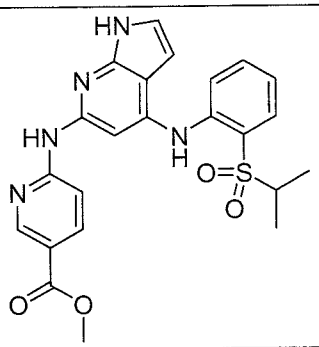


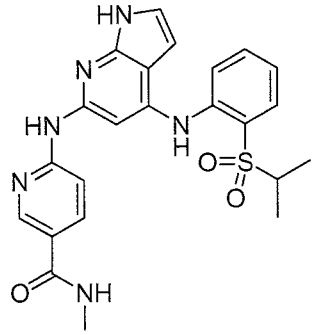
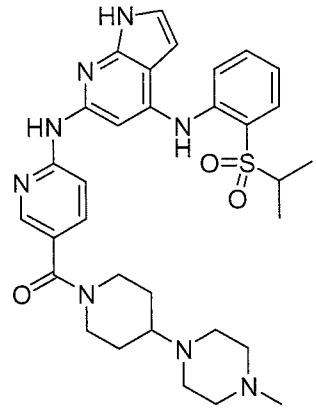
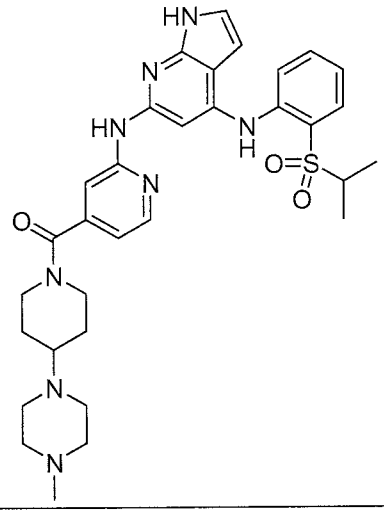
To a solution of 6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinic acid (50 mg, 0.12 mmol) in *N,N*-dimethylformamide (0.6 mL) was added HATU (67 mg, 0.18 mmol), DIEA (60 uL, 0.3 mmol) and 1-methyl-4-(piperidin-4-yl)piperazine (49 mg, 0.18 mmol). The reaction mixture was further stirred for a period of 6 hours after which, it was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by reverse-phase HPLC to yield the title compound as a TFA salt (63 mg, 78% yield).

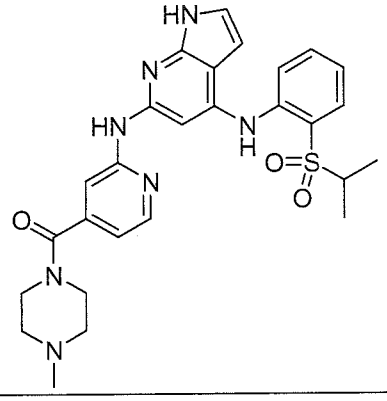
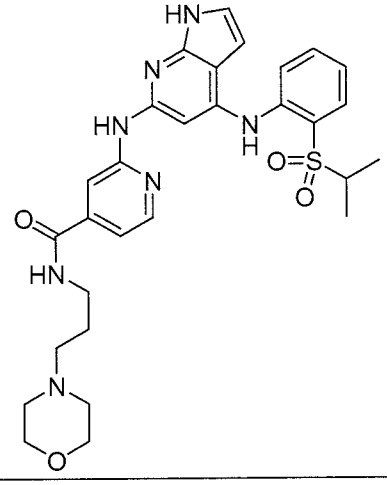
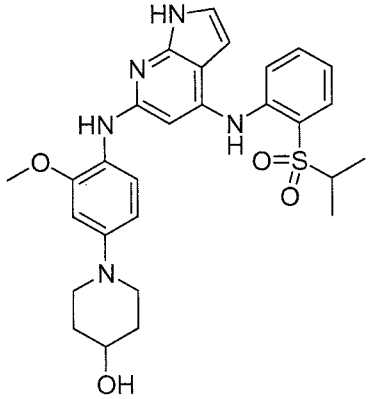
^{1}H NMR 600 MHz (DMSO-d_6) δ 12.09 (*s*, 1H), 11.19 (*s*, 1H), 9.61 (s, 1H), 8.40 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.90 (m, 2H), 7.69 (m, 2H), 7.22 (s, 1H), 7.15 (m, 1H), 6.54 (s, 1H), 5.98 (s, 1H), 3.42 (m, 2H), 3.23 (*m*, 5H), 3.10 (m, 2H), 2.81 (s, 3H), 2.52 (*m*, 2H), 2.48 (*m*, 4H), 1.95 (*m*, 2H), 1.54 (*m*, 2H), MS m/z : 589.48 (M + 1).

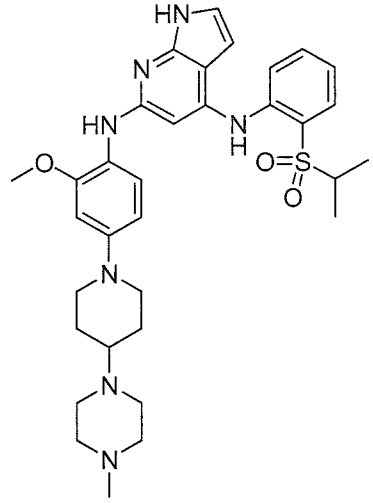
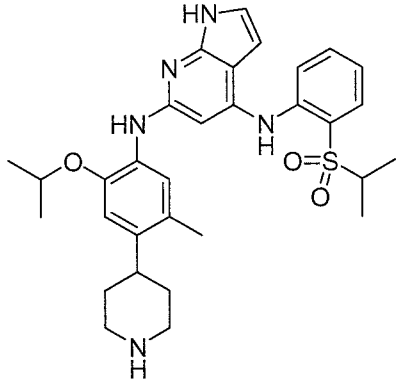
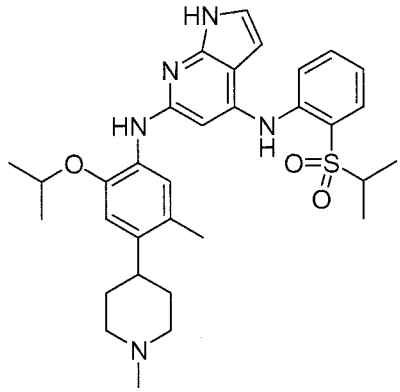
Table 3

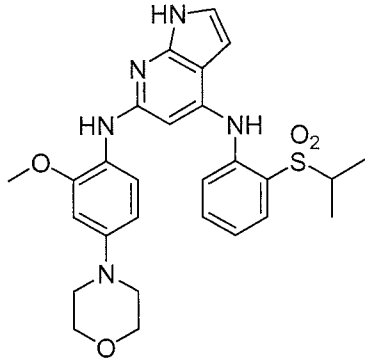
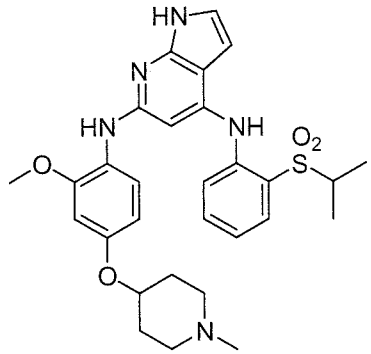
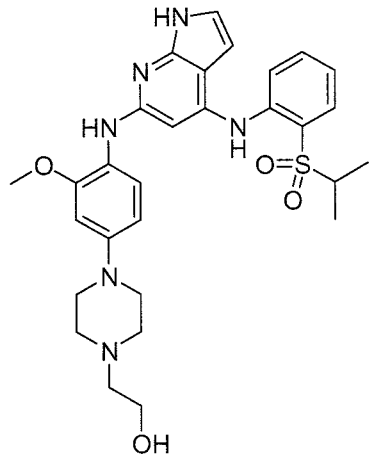
The following compounds were synthesized by following the procedures above with the appropriate anilines.

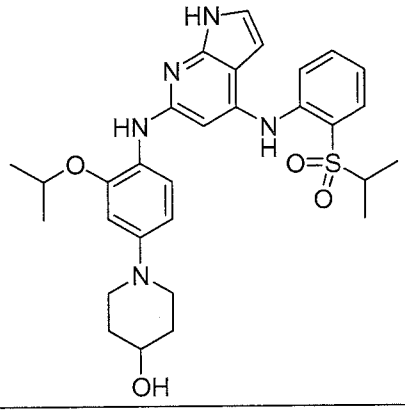
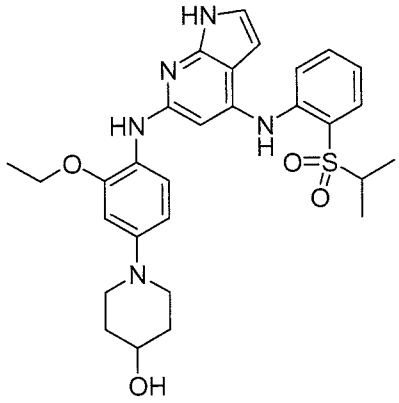
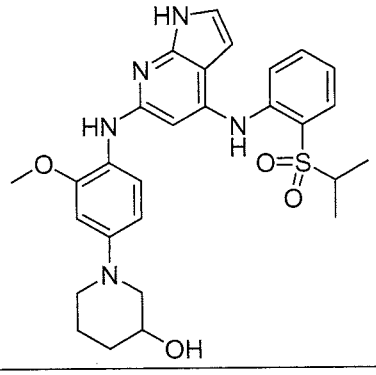
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-1		^{1}H NMR 600 MHz ($CDCl_3$) δ 10.64 (*s*, 1H), 10.05 (*s*, 1H), 8.83 (*s*, 1H), 8.51 (*s*, 1H), 8.12 (*m*, 1H), 7.84 (*d*, *J* = 7.8 Hz, 1H), 7.54 (m, 3H), 7.12 (t, 1H), 7.06(m, 1H), 7.03 (m, 1H), 6.32 (m, 1H), 3.85 (s, 3H), 3.20 (m, 1H), 1.12 (d, J = 6.6 Hz, 6H), MS *m/z* : 465.99 (M + 1).

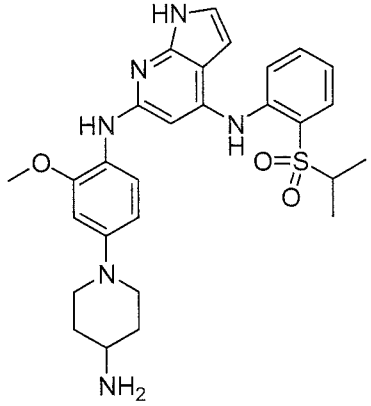
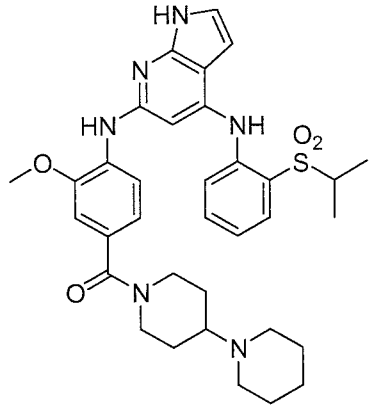
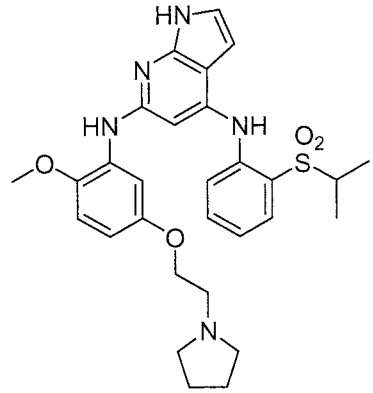
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-2		MS *m/z* : 464.97 (M + 1).
5-3		MS *m/z* : 617.19 (M + 1).
5-4		MS *m/z* : 617.19 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-5		MS *m/z* : 534.07 (M + 1).
5-6		MS *m/z* : 578.09 (M + 1).
5-7		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.51 (*s*, 1H), 7.83 (*d*, *J* = 1.8 Hz, 1H), 7.48 (*m*, 2H), 7.19 (*m*, 3H), 7.12 (*m*, 2H), 6.85 (*d*, J = 3.0 Hz, 1H), 6.49 (*m*, 1H), 6.19 (*m*, 2H), 3.84 (*m*, 1H), 3.78 (*s*, 3H), 3.46 (*m*, 2H), 3.19 (*m*, 1H), 2.90 (*m*, 2H), 1.99 (*m*, 2H), 1.69 (*m*, 2H), 1.19 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 536.33 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-8		^{1}H NMR 600 MHz ($CDCl_3$) δ 8.99 (*s*, 1H), 8.27 (*s*, 1H), 7.80 (*d*, *J* = 9.0 Hz, 1H), 7.51 (*d*, *J* = 7.2 Hz, 1H), 7.64 (*dt*, *J* = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.19 (*s*, 1H), 7.03 (*dt*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 6.76 (*d*, *J* = 2.4 Hz, 1H), 6.50 (*d*, *J* = 2.4 Hz, 1H), 6.47 (*m*, 2H), 6.34 (*s*, 1H), 6.15 (*d*, *J* = 2.4 Hz, 1H), 3.79 (*s*, 3H), 3.57 (*m*, 2H), 3.25 (*m*, 1H), 2.63 (*m*, 6H), 2.45 (*m*, 3H), 2.33 (*m*, 2H), 2.24 (*s*, 3H), 1.89 (*m*, 2H), 1.67 (*m*, 2H), 1.21 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 618.21 (M + 1).
5-9		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.13 (*s*, 1H), 8.44 (*s*, 1H), 7.92 (s, 1H), 7.80 (*d*, *J* = 6.6 Hz, 1H), 7.69 (*m*, 2H), 7.35 (*s*, 1H), 7.21 (*t*, 1H), 6.97 (*s*, 1H), 6.74 (*s*, 1H), 6.64 (*s*, 1H), 6.04 (*s*, 1H), 4.49 (*m*, 1H), 3.39 (*m*, 1H), 3.07 (*m*, 2H), 2.70 (*m*, 1H), 2.63 (*m*, 2H), 2.22 (*s*, 3H), 1.59 (*m*, 2H), 1.51 (*m*, 2H), 1.25 (*d*, *J* = 6.0 Hz, 6H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 562.19 (M + 1).
5-10		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.16 (*s*, 1H), 8.47 (*s*, 1H), 8.00 (*s*, 1H), 7.81 (*dd*, *J* = 1.8 Hz, *J* = 7.8 Hz, 1H), 7.70 (*m*, 2H), 7.41 (*s*, 1H), 7.23 (*dt*, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 7.00 (*m*, 1H), 6.77 (*s*, 1H), 6.67 (*s*, 1H), 6.06 (*m*, 1H), 4.51 (*m*, 1H), 3.39 (*m*, 1H), 3.16 (*m*, 2H), 2.98 (*m*, 2H), 2.87 (*m*, 1H), 2.71 (*s*, 3H), 2.26 (*s*, 3H), 1.59 (*m*, 2H), 1.51 (*m*, 2H), 1.28 (*d*, *J* = 6.0 Hz, 6H), 1.17 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 576.17 (M + 1).

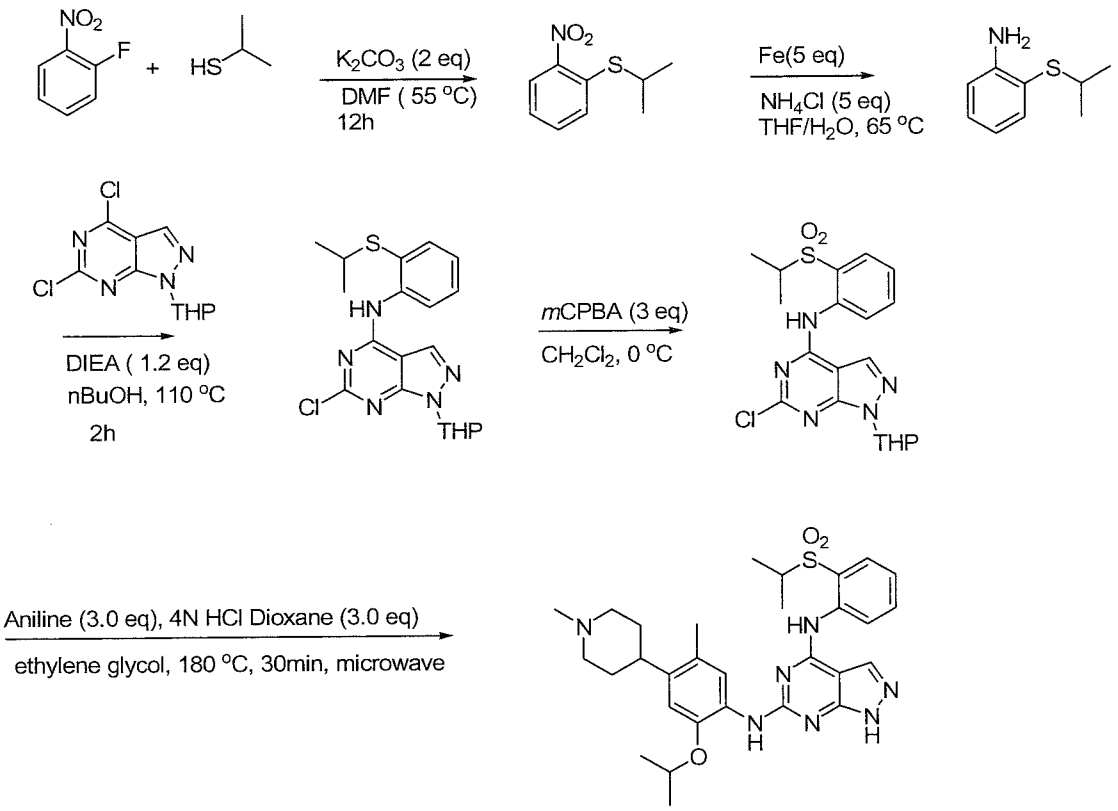
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-11		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.09 (*s*, 1H), 8.42 (*s*, 1H), 8.04 (*m*, 1H), 7.78 (*dd*, 1H), 7.64 (*m*, 3H), 7.20 (*t*, 1H), 6.92 (*m*, 1H), 6.52 (*m*, 2H), 6.44 (*dd*, 1H), 6.06 (*m*, 1H), 3.79 (*s*, 3H), 3.72 (*m*, 4H), 3.37 (*m*, 1H), 3.04 (*m*, 4H), 1.14 (*d*, *J* = 6.74 Hz, 6H), MS *m/z* : 522.25 (M + 1).
5-12		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.10 (*s*, 1H), 8.43 (*s*, 1H), 8.09 (*d*, *J* = 8.50 Hz, 1H), 7.78 (*dd*, 1H), 7.68 (*m*, 1H), 7.64 (*m*, 1H), 7.60 (*s*, 1H), 7.20 (*t*, 1H), 6.93 (*m*, 1H), 6.60 (*m*, 2H), 6.48 (*dd*, 1H), 6.07 (*m*, 1H), 4.30 (*m*, 1H), 3.79 (*s*, 3H), 3.40 (*m*, 1H), 2.67 (*m*, 2H), 2.23 (*m*, 5H), 1.91 (*m*, 2H), 1.64 (*m*, 2H), 1.14 (*d*, *J* = 6.74 Hz, 6H), MS *m/z* : 550.23 (M + 1).
5-13		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.08 (*s*, 1H), 8.42 (*s*, 1H), 8.00 (*d*, *J* = 7.6 Hz, 1H), 7.78 (*dd*, 1H), 7.67 (*m*, 2H), 7.53 (*s*, 1H), 7.19 (*t*, 1H), 6.92 (*m*, 1H), 6.58 (*m*, 2H), 6.42 (*dd*, 1H), 6.05 (*m*, 1H), 3.79 (*s*, 3H), 3.37 (*m*, 1H), 3.06 (*m*, 4H), 2.42 (*m*, 8H), 1.15 (*d*, *J* = 6.74 Hz, 6H), MS *m/z* : 565.27 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-14		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.20 (*s*, 1H) 8.52 (*s*, 1H), 8.03 (*d*, *J* = 8.8 Hz, 1H), 7.89 (*dd*, 1H), 7.78 (*m*, 1H), 7.70 (*d*, *J* = 7.6 Hz, 2H), 7.39 (*s*, 1H), 7.30 (*m*, 1H), 7.04 (*m*, 1H), 6.69 (*m*, 2H), 6.57 (*m*, 1H). 6.11 (*m*, 1H), 4.66 (*m*, 1H), 3.69 (*m*, 1H), 3.52 (*m*, 2H), 3.34 (*m*, 1H), 2.84 (*m*, 2H), 1.93 (*m*, 2H), 1.63 (*m*, 2H), 1.35 (*d*, *J* = 6.1 Hz, 6H), 1.26 (*d*, *J* = 6.7 Hz, 6H) MS *m/z* : 564.15 (M + 1).
5-15		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.14 (*s*, 1H) 8.52 (*s*, 1H), 8.14 (*d*, *J* = 8.6 Hz, 1H), 7.80 (*dd*, 1H), 7.68 (*m*, 1H), 7.50 (*d*, *J* = 7.6 Hz, 2H), 7.39 (*s*, 1H), 7.25 (*m*, 1H), 7.10 (*m*, 1H), 6.70 (*m*, 2H), 6.57 (*m*, 1H). 6.13 (*m*, 1H), 4.74 (*m*, 1H), 3.70 (*m*, 1H), 3.48 (*m*, 2H), 3.30 (*m*, 1H), 2.80 (*m*, 2H), 1.96 (*m*, 2H), 1.68 (*m*, 2H), 1.35 (*d*, *J* = 6.2 Hz, 3H), 1.24 (*d*, *J* = 6.7 Hz, 6H), MS *m/z* : 550.03 (M + 1).
5-16		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.08 (*s*, 1H) 8.43 (*s*, 1H), 7.98 (*d*, *J* = 8.8 Hz, 1H), 7.77 (*m*, 1H), 7.68 (*m*, 2H), 7.53 (*m*, 1H), 7.20 (*m*, 1H), 6.92 (*m*, 1H), 6.56 (*m*, 2H), 6.41 (*m*, 1H), 6.05 (*m*, 1H). 3.79 (*s*, 3H), 3.58 (*m*, 1H), 3.48 (*m*, 1H), 3.38 (*m*, 2H), 2.56 (*m*, 1H), 2.42 (*m*, 1H), 1.88 (*m*, 1H), 1.73 (*m*, 1H), 1.53 (*m*, 2H), 1.15 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 536.10 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
5-17		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.10 (*s*, 1H), 8.42 (*s*, 1H), 7.97 (*d*, *J* = 7.8 Hz, 1H), 7.78 (*dd*, 1H), 7.67 (*m*, 2H), 7.51 (s, 1H), 7.18 (*t*, 1H), 6.91 (*m*, 1H), 6.57 (*m*, 2H), 6.42 (*dd*, 1H), 6.05 (*m*, 1H), 3.78 (*s*, 3H), 3.51 (*m*, 2H), 3.36 (*m*, 1H), 2.62 (*m*, 3H), 1.78 (*m*, 2H), 1.32 (*m*, 2H), 1.14 (*d*, *J* = 6.6 Hz, 6H), MS *m/z* : 535.25 (M + 1).
5-18		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.27 (*s*, 1H), 8.61 (d, J = 8.21 Hz, 1H), 8.51 (s, 1H), 8.08 (*s*, 1H), 7.80 (*d*, J = 7.63 Hz, 1H), 7.70 (*m*, 2H), 7.22 (*t*, 1H), 7.02 (*m*, 1H), 6.96 (*s*, 1H), 6.91 (*d*, *J* = 8.21 Hz, 1H), 6.84 (*s*, 1H), 6.14 (s, 1H), 3.86 (*s*, 3H), 3.38 (*m*, 1H), 2.81 (*m*, 4H), 2.47 (*m*, 5H), 1.71 (*m*, 2H), 1.45 (*m*, 4H), 1.37 (*m*, 4H), 1.14 (*d*, *J* = 6.45 Hz, 6H), MS *m/z* : 631.27 (M + 1).
5-19		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.28 (*s*, 1H), 8.50 (*s*, 1H), 8.25 (*d*, *J* = 2.93 Hz, 1H), 7.87 (*s*, 1H), 7.80 (*m*, 1H), 7.70 (*m*, 2H), 7.22 (*m*, 1H), 7.02 (*t*, 1H), 6.84 (*d*, *J* = 8.8 Hz, 1H), 6.79 (*s*, 1H), 6.39 (*dd*, 1H), 6.14 (*m*, 1H), 4.07 (*m*, 2H), 3.78 (*s*, 3H), 3.38 (*m*, 1H), 3.06 (*m*, 2H), 2.79 (*m*, 2H), 2.48 (*m*, 2H), 1.76 (*m*, 4H), 1.15 (*d*, *J* = 6.74 Hz, 6H), MS *m/z* : 550.23 (M + 1).

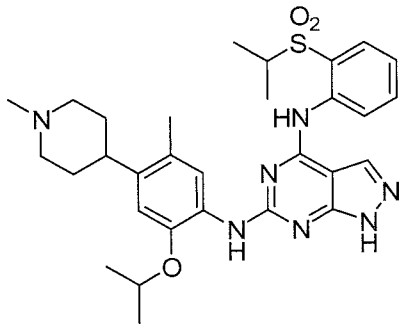
Similarly, the compounds of Formula III, can be prepared through the preparation shown in the Reaction Scheme 6 below.

Scheme 6

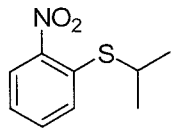


Example 6-0

N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine

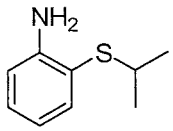


isopropyl(2-nitrophenyl)sulfane



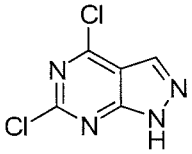
To a solution of 1-fluoro-2-nitrobenzene (3.0 g, 21.2 mmol) in DMF (60 mL) was added 2-propane thiol (2.2 mL, 23.4 mmol) and K_2CO_3 (6.8g, 42.4 mmol). The reaction was heated to 45 °C for 16 hours. The mixture was then diluted with 300mL of ethyl acetate, filtrated, washed five times with 60mL of water and brine. The organic phase was dried over sodium sulfate, filtered, concentrated. The resulting yellow solid (4.0 g, 95% yield) was used without further purification.

(isopropylthio)benzenamine



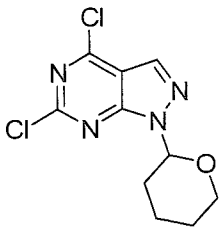
To a solution of isopropyl (2-nitrophenyl)sulfane(4.0 g, 20.3 mmol) in methanol (200 mL) was added Pd/C (0.40 g). The 500mL of flask was evacuated and charged with high purity hydrogen gas. The reaction was stirred for 20 hours. The mixture was filtrated through celite. After concentration, the residue was purified by flash chromatography using 10:1 methylene chloride –ethyl acetate as solvent to afford title compound (3.36 g, 20.1 mmol) as brown oil.

4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine



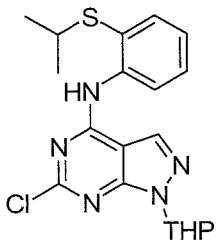
To a 100mL flask was added 4,6-dihydroxylpyrazolo(3,4-d)pyrimidine (2.0 g, 13.15 mmol), phosphorus oxychloride (12 mL, 131.5 mmol) and N, N-diethylaniline (4.0mL, 26.3 mmol). The reaction mixture was heated to 110 °C for 2 hours. After removal of phosphorus oxychloride, the dark residue was poured onto crushed ice water. The cold aqueous solution was extracted with diethyl ether (3 x 100mL). The organic layer was washed with water and brine, dried over sodium sulfate, concentrated to afford 1.30 g of a crude tan product, which was used without further purification.

4,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine



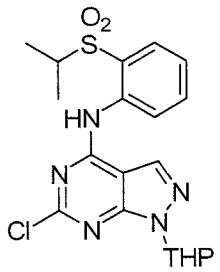
To a solution of 4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine (1.30 g, 6.88 mmol) in methylene chloride (20 mL) and THF (20 mL) was added TsOH (0.13 g, 0.688 mmol) and 3,4 –dihydro-2H-pyran (0.93 mL, 10.32 mmol). The solution was stirred for 4 hours. After removal of solvent, the residue was dissolved in methylene chloride (100 mL), washed with twice with a satd. aqueous solution of Na_2CO_3, water and brine. The methylene chloride solution was dried over sodium sulfate and concentrated. The resulting yellow oil was treated with 1 mL of ethyl acetate and 10 mL of hexane to induce solidification. The resulting 1.20 grams of white solid was used without further purification.

6-chloro-N-(2-(isopropylthio)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



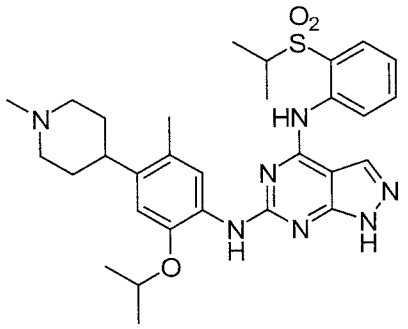
To a 25 mL of flask charged with 4,6-dichloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (0.955 g, 3.50 mmol) and (isopropylthio)benzenamine (1.168 g,7.0 mmol) in n-butanol (3 mL) was added DIEA (0.69 mL, 4.2 mmol). The reaction mixture was heated to 110 °C for 2 hours. After removal of solvent, the residue was purified by flash chromatography using 3:1 hexane-ethyl acetate as solvent to afford title compound (1.20 g, 2.97 mmol) as white solid.

6-chloro-N-(2-(isopropylsulfonyl)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine



To a solution of 6-chloro-N-(2-(isopropylthio)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1.20 g, 2.97 mmol) in dichloromethane (80 mL) was added *m*CPBA (2.00 g, 8.92 mmol). The reaction mixture was stirred for 4 hours after which, it was diluted with dichloromethane (100 mL). The organic layer was washed with satd. $NaHCO_3/Na_2S_2O_3$, satd. $NaHCO_3$ solution and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting light yellow solid (1.20 g, 2.75 mmol) was used without further purification.

N^6-(2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)phenyl)-N^4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine



A microwave tube was charged with 6-chloro-N-(2-(isopropylsulfonyl)phenyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (40 mg, 0.0917 mmol), 2-isopropoxy-5-methyl-4-(1-methylpiperidin-4-yl)benzenamine (72.3 mg, 0.275 mmol) 4N HCl in Dioxane (0.069 mL, 0.276 mmol) and ethylene glycol (1.5 mL). The tube was sealed and the reaction mixture was stirred at 180 °C for 30 min in a microwave reactor. The reaction mixture was purified by reverse-phase preparative HPLC. The crude TFA salt of product was neutralized with a satd. aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was

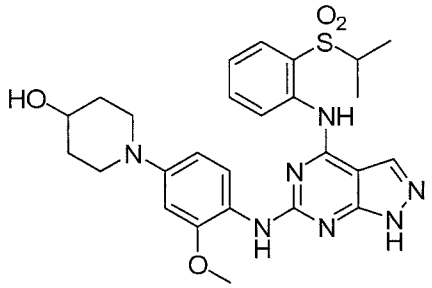
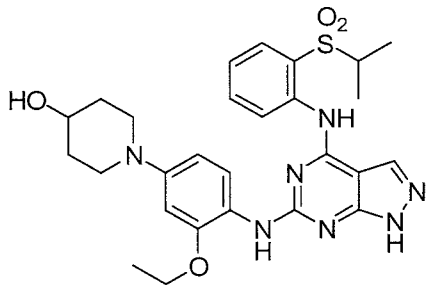
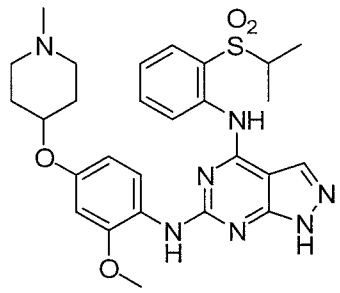
purified by flash chromatography using 30:1:0.3 methylene chloride-methanol-triethylamine as solvent to afford the title compound (20.0 mg, 0.037 mmol).

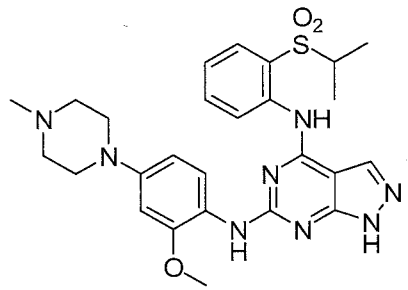
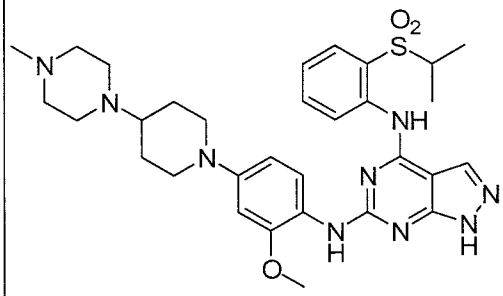
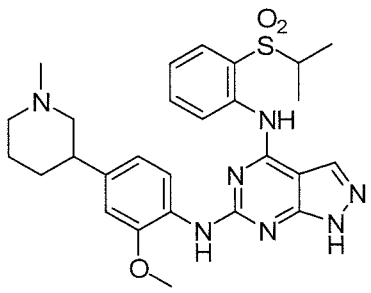
^{1}H NMR 600 MHz (CD_3OD) δ 8.46 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.38 (m, 1H), 6.78 (s, 1H), 4.58 (m,1H), 3.49 (d, J = 12 Hz, 2H), 3.30 (m, 1H), 3.00 (m, 3H), 2.80 (s,3H), 2.21 (s, 3H), 1.94 (m, 4H), 1.35 (d, J = 6.6 Hz, 6H), 1.20 (d, J = 6.6 Hz, 6H).

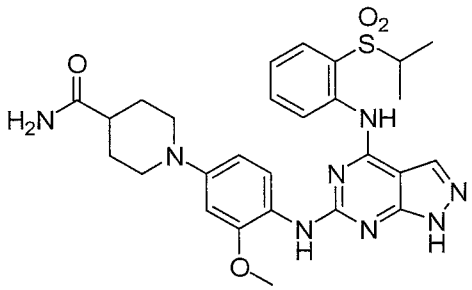
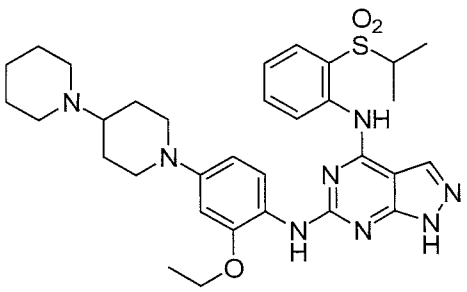
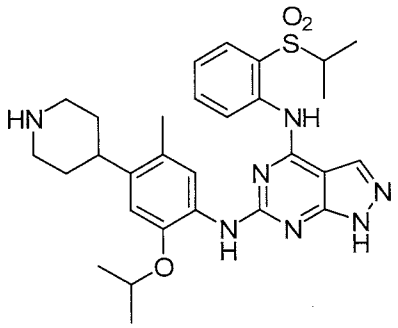
MS m/z : 536.60 (M + 1)

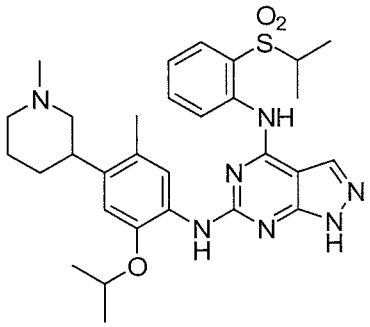
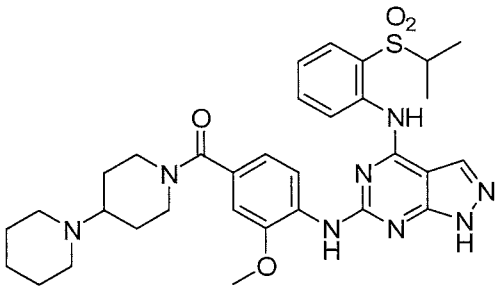
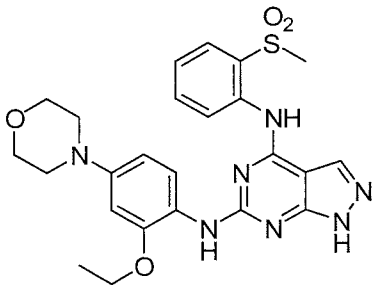
Table 4

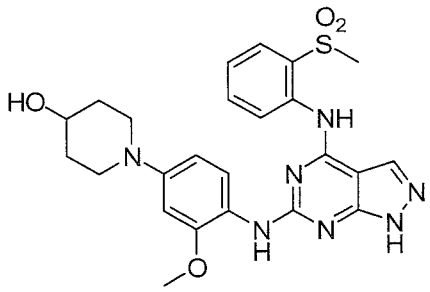
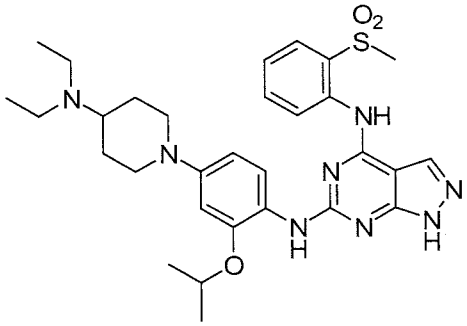
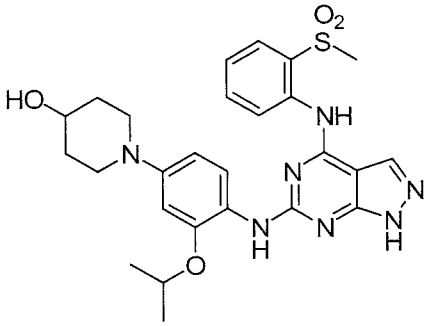
The following compounds were synthesized using the procedures described above with the appropriate anilines:

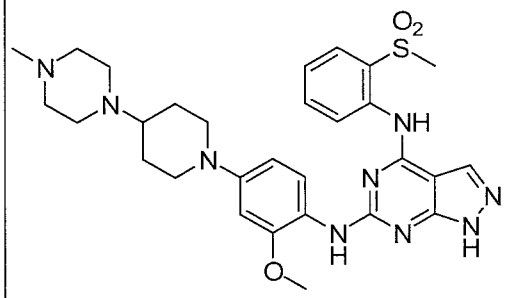
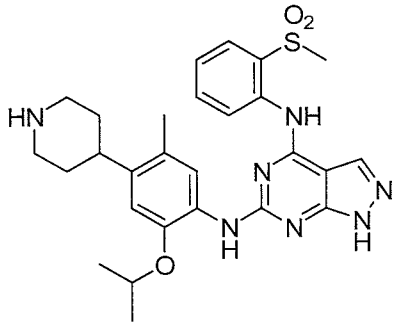
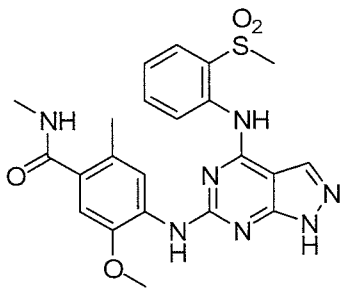
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-1		^{1}H NMR 600 MHz (CD_3OD) δ 8.18 (*m*,1H), 8.10 (*b*, 1H), 8.02 (*m*, 1H), 7.83 (*m*, 1H), 7.58 (*m*, 1H), 7.20 (*m*, 1H), 6.86 (*m*, 1H), 4.05 (m, 1H), 3.97 (s, 3H), 3.80 (*m*, 2H), 3.50 (*m*, 2H), 2.20 (*m*, 2H), 1.98 (*m*, 2H), 1.18 (d, *J* = 6.6 Hz, 6H), MS m/z : 538.63 (M + 1).
6-2		^{1}H NMR 600 MHz (CD_3OD) δ 8.18 (*m*,1H), 8.08 (*b*, 1H), 8.02 (*m*,1H), 7.83 (*m*,1H), 7.58 (*m*, 1H), 7.16 (*m*, 1H), 6.94 (*m*, 1H), 4.20 (q, *J*=7.2 Hz, *J* = 6.6 Hz, 2H), 4.04 (*m*, 1H), 3.78 (*m*, 3H), 3.49 (*m*, 2H), 2.20 (*m*, 2H), 1.96 (*m*, 2H), 1.47(*t*, *J* = 7.2 Hz, *J*=6.6 Hz, 3H), 1.19 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 552.66 (M + 1).
6-3		MS m/z : 552.66 (M + 1).

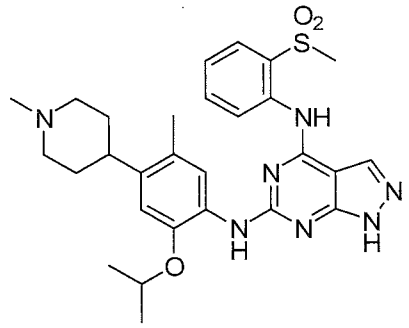
Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-4		^{1}H NMR 600 MHz (CD_3OD) δ 8.10 (*m*, 1H), 7.79 (*m*, 1H), 7.60 (*m*, 1H), 7.44 (*m*, 1H), 7.24 (*m*, 1H), 6.74 (*m*, 1H), 6.58 (*m*, 1H), 3.85 (*s*, 3H), 3.65 (*m*, 2H), 3.09 (*m*, 1H), 2.98 (*s*, 3H), 1.18 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 537.65 (M + 1).
6-5		^{1}H NMR 600 MHz (CD_3OD) δ 8.23 (*m*, 1H), 8.10 (*m*, 1H), 8.02(*dd*, *J* = 1.2 Hz, *J*= 7.8Hz, 1H), 7.80 (*m*, 1H), 7.66 (*m*, 1H), 7.60 (*m*, 1H), 6.96 (*m*, 1H), 6.72 (*m*, 1H), 3.89 (*s*, 3H), 3.80 (*m*, 2H), 3.45 (*m*, 4H), 3.30-3.10 (*m*, 8H), 2.90 (*s*, 3H), 2.20 (*m*, 2H), 1.98 (*m*, 2H), 1.16 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 620.78 (M + 1).
6-6		^{1}H NMR 600 MHz (CD_3OD) δ 8.13 (*m*, 1H), 8.02 (*m*, 1H), 7.90 (*m*, 1H), 7.80 (*m*, 1H), 7.76 (*m*, 1H), 7.60 (*m*, 1H), 6.96 (*m*, 1H), 6.73 (*m*, 1H), 3.91 (*s*, 3H), 3.56 (*m*, 3H), 3.12 (*m*, 1H), 3.04 (*m*, 2H), 2.91 (*s*, 3H), 2.0 (*m*, 4H), 1.18 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 536.66 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-7		^{1}H NMR 600 MHz (CD_3OD) δ 8.16 (*m*, 2H), 8.02 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.97 (*m*, 1H), 7.84 (*m*, 1H), 7.60 (*m*, 1H), 7.14 (*m*, 1H), 6.88 (*m*, 1H), 3.94 (*s*, 3H), 3.76 (*m*, 2H), 3.45 (*m*, 2H), 2.68 (*m*, 1H), 2.15 (*m*, 4H), 1.18 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 536.66 (M + 1).
6-8		^{1}H NMR 600 MHz (CD_3OD) δ 8.26 (*m*, 1H), 8.1 (*m*, 1H), 8.00(*d*, *J* = 7.8 Hz, 1H), 7.80 (*m*, 1H), 7.58 (*m*, 1H), 7.37 (*m*, 1H), 6.68 (*m*, 1H), 6.50 (*m*, 1H), 4.10 (*q*, *J* = 6.6 Hz, *J* = 7.2 Hz, 2H), 3.86 (*m*, 2H), 3.58 (*m*, 2H), 3.35 (*m*, 1H), 3.06 (*m*, 2H), 2.86 (*m*, 2H), 2.42 (*m*, 2H), 2.00 (*m*, 2H), 1.85 (*m*, 6H), 1.34 (*t*, *J* = 6.6 Hz, *J* = 7.2 Hz, 3H), 1.19 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 619.79 (M + 1).
6-9		^{1}H NMR 600 MHz (CD_3OD) δ 8.26 (*m*, 1H), 8.10 (*m*, 1H), 8.04 (*m*, 1H), 7.80 (*m*, 1H), 7.60 (*m*, 1H), 7.54 (*m*, 1H), 6.86 (*m*, 1H), 4.63 (*m*, 1H), 3.50 (*m*, 2H), 3.30 (*m*, 1H), 3.17 (*m*, 2H), 3.10 (*m*, 1H), 2.18 (*s*, 3H), 1.97 (*m*, 4H), 1.30 (*d*, *J* = 6.0 Hz, 6H), 1.18 (*d*, *J* = 6.6 Hz, 6H), MS m/z : 564.71(M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-10		^{1}H NMR 600 MHz (CD_3OD) δ 8.46 (*d*, J = 7.8 Hz,1H), 8.20 (*m*, 1H), 7.93 (*dd*, J = 1.2 Hz, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.70 (m, 1H), 7.39 (m, 1H), 6.80 (*s*, 1H), 4.57 (*m*, 1H), 3.30 (*m*, 1H), 3.00 (*m*, 2H), 2.89 (*m*, 1H), 2.36 (*s*, 3H), 2.18 (*s*, 3H), 2.10 (*m*, 2H), 1.80 (*m*, 4H), 1.50 (*m*, 2H), 1.34 (*d*, *J* = 7.8Hz, 6H), 1.21 (*d*, *J* = 6.6 Hz, 6H) MS m/z : 578.74(M + 1).
6-11		m/z : 633.78(M + 1).
6-12		^{1}H NMR 600 MHz (CD_3OD) δ 8.39 (*d*, *J* = 7.8 Hz, 1H), 8.02 (*dd*, *J* = 1.8 Hz, *J* = 8.4 Hz, 1H), 7.96 (*m*, 1H), 7.80 (*m*, 1H), 7.70 (*m*, 1H), 7.40 (*t*, *J* = 7.8 Hz, 1H), 6.62 (*d*, *J* = 2.4 Hz, 1H), 6.65 (*dd*, *J* = 2.4 Hz, *J* = 9.0 Hz), 4.10 (*q*, *J* = 7.2 Hz, 2H), 3.84 (*m*, 4H), 3.10 (*m*, 7H), 1.40 (*t*, *J* = 6.6 Hz, 3H) MS m/z : 510.58 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-13		^{1}H NMR 600 MHz (CD_3OD) δ 8.40 (d, *J* = 7.8 Hz, 1H), 8.04 (*dd*, *J* = 1.2 Hz, *J* = 7.8Hz, 1H), 7.94 (*m*, 1H), 7.82 (*m*, 1H), 7.70 (*m*, 1H), 7.40 (*m*, 1H), 6.68 (*d*, *J* = 2.4 Hz,1H), 6.51(*m*, 1H) 3.88 (*s*, 3H), 3.75 (*m*, 1H), 3.50 (*m*, 2H), 2.90 (*m*, 2H), 3.10 (*s*, 3H), 2.00 (*m*, 2H), 1.70 (*m*, 2H), MS m/z : 510.58 (M + 1).
6-14		^{1}H NMR 600 MHz (CD_3OD) δ 8.38 (*d*, *J* = 7.8 Hz, 1H), 8.02 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.98 (*m*, 1H), 7.80 (*m*, 1H), 7.70 (*m*, 1H), 7.40 (*m*, 1H), 6.65 (*d*, *J* = 3.0 Hz, 1H), 6.48 (*dd*, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H), 4.60 (*m*, 1H), 3.65 (*m*, 2H), 3.12 (*s*, 3H), 2.78 (*m*, 5H), 2.68 (*m*, 2H), 1.96 (*m*, 2H), 1.70 (*m*, 2H), 1.33 (*d*, *J* = 6.6 Hz, 6H), 1.14 (*t*, *J* = 7.2 Hz). MS m/z : 593.76 (M + 1).
6-15		^{1}H NMR 600 MHz (CD_3OD) δ 8.47 (*d*, *J* = 7.8 Hz, 1H), 8.02 (*dd*, *J* = 1.2Hz, *J* = 7.8 Hz, 1H), 7.97 (*m*, 1H), 7.82 (*m*, 1H), 7.71 (*m*, 1H), 7.43 (*m*, 1H), 6.68 (*d*, *J* = 2.4 Hz, 1H), 6.50 (*m*, 1H), 4.60 (*m*, 1H), 3.75 (*m*, 1H), 3.48 (*m*, 2H), 3.10 (*s*, 3H), 2.85 (*m*, 2H), 1.98 (*m*, 2H), 1.70 (*m*, 2H), 1.32 (d, *J* = 6.6 Hz, 6H) MS m/z : 538.63 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-16		^{1}H NMR 600 MHz (CD_3OD) δ 8.60 (*d*, *J* = 2.4 Hz, 1H), 7.96 (*m*, 2H), 7.88 (*s*, 1H), 7.66 (*m*, 1H), 7.30 (*m*, 1H), 6.67(*d*, *J* = 3.0 Hz, 1H), 6.52 (*m*, 1H), 3.88 (*s*, 3H), 3.70 (*m*, 2H), 3.12 (*s*, 3H), 2.70 (*m*, 9H), 2.40 (*m*, 2H), 2.34 (*s*, 3H), 2.0 (*m*, 2H), 1.70 (*m*, 2H), MS m/z : 592.73 (M + 1).
6-17		MS m/z : 536.66 (M + 1).
6-18		^{1}H NMR 600 MHz (CD_3OD) δ 8.15 (*dd*, *J* = 1.2 Hz, *J* = 7.8 Hz, 1H), 7.93 (*m*, 1H), 7.83 (*t*, J = 7.8 Hz, 1H), 7.66 (*t*, *J* = 7.8 Hz,1H), 7.42 (*m*, 2H), 6.90 (*s*, 1H), 3.87 (*s*, 3H), 3.13(*s*, 3H), 2.96 (*s*, 3H), 2.04 (*s*, 3H), MS m/z : 482.53 (M + 1).

Compound Number	Structure	Physical Data ^{1}H NMR 600 MHz and/or MS (m/z)
6-19		^{1}H NMR 600 MHz (CD_3OD) δ 8.38 (*d*, *J* = 7.8 Hz, 1H), 8.05 (*dd*, *J* = 1.8 Hz, 1H), 8.02 (*m*, 1H), 7.85 (*m*, 1H), 7.73 (*m*, 1H), 7.44 (*m*, 1H), 6.84 (*s*, 1H), 4.60 (*m*, 1H), 3.11 (*s*, 3H), 3.05 (*m*, 2H), 2.74 (*m*, 1H), 2.37 (*s*, 3H), 2.24 (*m*, 2H), 2.18 (*s*, 3H), 1.78 (*m*, 4H), 1.30 (*d*, *J* = 6.0 Hz, 6H), MS m/z : 550.69 (M + 1).

BIOLOGICAL EXAMPLES

Inhibition of ALK activity

Cell Lines. Murine pro-B cell line Ba/F3, the human t(2,5)-positive Karpas-299 and TEL-ALK transformed Ba/F3 are maintained in RPMI medium 1640 supplemented with 10% FBS (Sigma–Aldrich, St. Louis, MO). Ba/F3 cells are grown in the presence of 10% of WEHI media. Cell lines expressing luciferase alone or in combination with TEL-kinase fusion constructs are generated by retroviral transduction of cells with pMSCV-IRES puro/Luc vector.

Cell Proliferation Assays. Luciferase-expressing Ba/F3 cells, Karpas-299, Tel_ALK transformed Ba/F3 stably expressing NPM-ALK and TEL-ALK, are plated in 384-well plates (5,000 cells per well) and incubated with serial dilutions of ALK inhibitors or DMSO for 48 hours. Luciferase expression is used as a measure of cell proliferation/ survival and was evaluated with the Bright-Glo Luciferase Assay System (Promega, Madison, WI). Fifty percent inhibition values (IC_{50}) are generated by using XLFit software. In order to monitor inhibition of NPM-ALK biochemically, STAT-3 and 5 phosphorylation are monitored using phosphorylation specific antibodies (Cell Signaling). To monitor the ability of the compounds to inhibit EML4-ALK, an activating ALK translocation identified in lung cancer,

a proliferation assay using an established cell line (NCI-H3122) containing the fusion kinase is employed.

***In Vivo* Experiments.** For compound efficacy studies in a murine model, treatment is initiated 72 h after tail vein injection of $1x10^6$ Ba/F3 NPM-ALK (a murine pre-B cell line engineered to stably express NPM-ALK) or Karpas-299 (a human-derived NPM-ALK cell line), or expressing cells into female Fox Chase SCIDBeige mice. Mice (10 animals per group) are administered either the test compound dissolved in 90% PEG 300 /10% 1-methyl-2- pyrrolidinone (Sigma) at 1, 3, and 10 mg/kg once daily for three weeks or the vehicle solution at the same dosing schedule. Disease progression and compound efficacy is monitored weekly with bioluminescence using a xenogen imaging system. To determine the efficacy of the test compound on established disease, dosing is initiated on day 10, at which time the disease confirmed to be widespread by bioluminescence xenogen imaging. For monitoring pharmacodynamics, mice with established lymphomas are administered vehicle solution or test compound (typically 10 mg/kg) for 3 days. At the end of treatment, mice are sacrificed, and lymph nodes are extracted for immunoblotting and histological analysis.

The inhibition of ALK tyrosine kinase activity may also be measured using known methods, for example using the recombinant kinase domain of the ALK in analogy to the VEGF-R kinase assay described in J. Wood *et al. Cancer Res.* 60, 2178-2189 (2000).

The antiproliferative action of the compounds of the invention can also be determined in the human KARPAS-299 lympoma cell line (described in WG Dirks *et al. Int. J. Cancer* 100, 49-56 (2002) using the same methodology described above).

Compounds 1-3, 1-13, 1-14, 2-1, 2-4, 2-7, 2-10, 2-14, 2-15, 3-14, 5-1, 5-7, 5-8, 5-9, 5-10, 5-11, 5-14, 6-1, 6-2, 6-5, 6-6, 6-9, 6-16, 6-18 are representative examples of inhibitors of NPM-ALK dependent cellular proliferation EC50's of 1 uM or less.

Inhibition of NTRK 3 activity

A cell-based assay consists of using a ETV6-NTRK3 transformed Ba/F3 cell line. This cell line may be used to discover compounds that are differentially cytotoxic as compared to parental Ba/F3 cells grown in the presence of IL-3. Compounds that are selectively cytotoxic to Ba/F3 ETV6-NTRK3 are confirmed using a biochemical NTRK3 kinase assay. Cellular inhibition of NTRK3 is confirmed using phosphospecific antibodies.

Biochemical Kinase Enzyme Assay For Mps1:

In a LanthaScreen™ kinase assay, kinase, fluorescein-labeled substrate, and ATP are allowed to react. Then EDTA (to stop the reaction) and terbium-labeled antibody (to detect phosphorylated product) are added. In a LanthaScreen™ kinase reaction, the antibody associates with the phosphorylated fluorescein labelled substrate resulting in an increased TR-FRET value. The TR-FRET value is a dimensionless number that is calculated as the ratio of the acceptor (fluorescein) signal to the donor (terbium) signal. The amount of antibody that is bound to the tracer is directly proportional to the amount of phosphorylated substrate present, and in this manner, kinase activity can be detected and measured by an increase in the TR-FRET value

Kinase binding assay for Mps1:

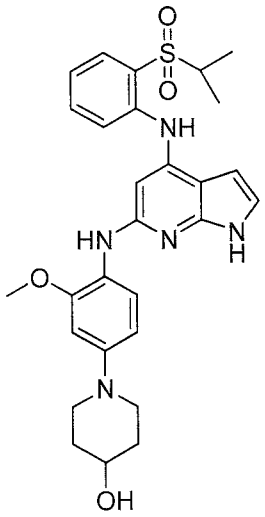
Kinase binding can be determined for Mps1 using Fluorescence Polarization (FP). FP is described, for example, in Huang et al. (2003*) J. Biomol. Screen* 8(1): 34-38; Checovich et al (1995) *Nature* 375:254-256; Heyduk et al. (1996) *Meth. Enzymol.* 274: 492-503; Jameson et al. (1995) *Meth. Enzymol.* 246: 283-300; Nasir et al. (1999) *Comb. Chem. High Throughput Screen.* 2: 177-190; and Owicki et al. (2000) *J. Biomol. Screen* 5: 297-306.

Results of Vaious Binding Assays

Binding assays for the following compound show kinases that are inhibited Numbers in the table are Kd (disassociation constants) in nanomolar.

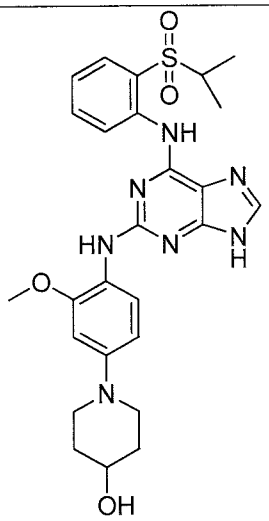
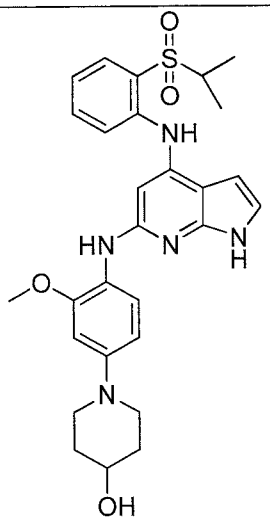
Representative Binding Assay Data

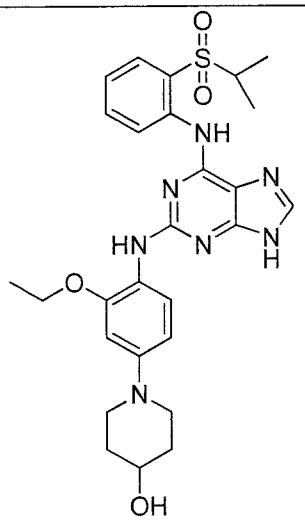
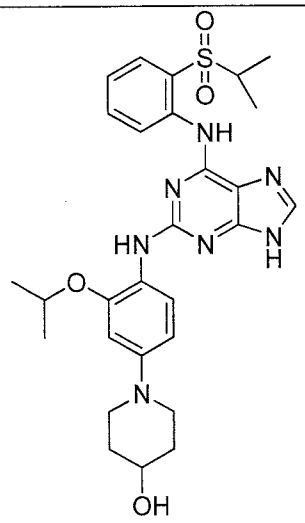
ALK	67
CLK1	420
IGFR1	870
INSR	410
PTK2	400
PTK2B	310
TTK	35

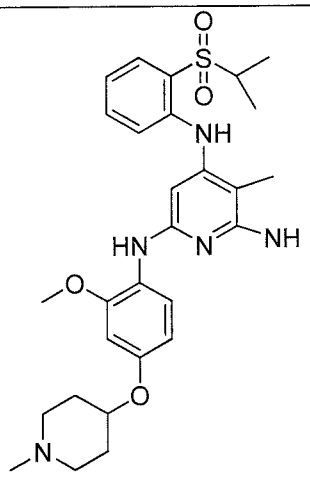
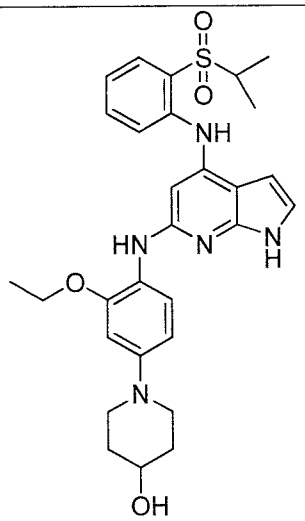


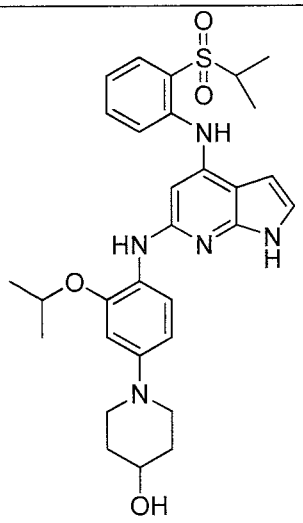
CLK1 (CDC like kinase 1), IGFR1 (insulin like growth factor receptor kinase 1); InsR (insulin receptor kinase), PTK2 (also known at FAK or focal adhesion kinase), PTK2B (also known as FAK2 or focal adhesion kinase 2), and TTK (also known as Mps 1) are shown to be inhibited.

Representative Mps1 Activity Data:

Structure	Activity (IC_{50})	Binding Kd (nM)
	79	9.6
	367.4	61.5

Structure	Activity (IC_{50})	Binding Kd (nM)
	224.7	29.9
	184.2	38

Structure	Activity (IC_{50})	Binding Kd (nM)
	663.8	115.5
	1066	299

Structure	Activity (IC_{50})	Binding Kd (nM)
	2282	698.9

* * *

Having thus described in detail preferred embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

REFERENCES

WO 2006021457 - Kawahara, Eiji; Miyake, Takahiro; Roesel, Johannes. Preparation of pyrimidine compounds as FAK and/or ALK inhibitors. PCT Int. Appl. (2006), 83 pp.

WO 2006021454 - Imbach, Patricia; Kawahara, Eiji; Konishi, Kazuhide; Matsuura, Naoko; Miyake, Takahiro; Ohmori, Osamu; Roesel, Johannes; Teno, Naoki; Umemura, Ichiro. Preparation of bis(arylamino)pyrimidine derivatives as antitumor agents. PCT Int. Appl. (2006), 118 pp.

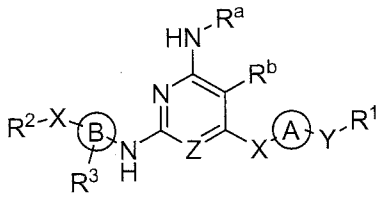
WO 2005016894 - Garcia-echeverria, Carlos; Kanazawa, Takanori; Kawahara, Eiji; Masuya, Keiichi; Matsuura, Naoko; Miyake, Takahiro; Ohmori, Osamu; Umemura, Ichiro; Steensma, Ruo; Chopiuk, Greg; Jiang, Jiqing; Wan, Yongqin; Ding, Qiang; Zhang, Qiong; Gray, Nathanael Schiander; Karanewsky, Donald. Preparation of 2,4-pyrimidinediamines useful in the treatment of neoplastic diseases, inflammatory and immune system disorders. PCT Int. Appl. (2005), 285 pp.

WO 2005097765 - Leahy, James William; Lewis, Gary Lee; Nuss, John M.; Ridgway, Brian Hugh; Sangalang, Joan C. Preparation of thiazoles and analogs as anaplastic lymphoma kinase modulators. PCT Int. Appl. (2005), 346 pp.

WHAT IS CLAIMED IS:

What is claimed is:

1. A compound having the formula:



(I)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

Z is N or CH;

A is aryl or heteroaryl optionally substituted with one or more R^4 groups;

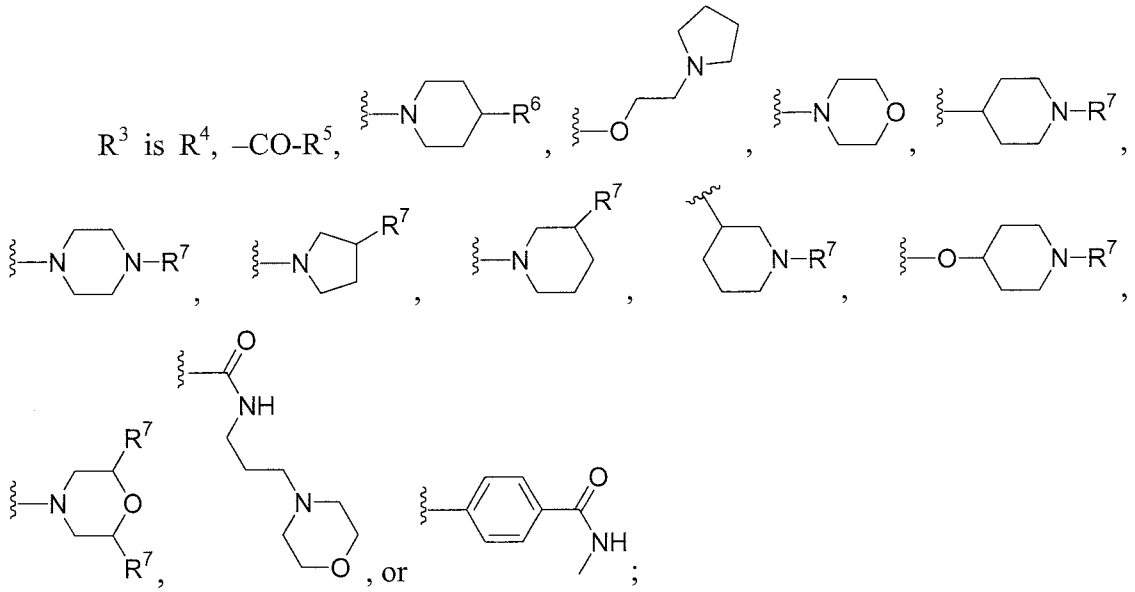
B is phenyl when Z is N; or B is phenyl, pyrazolyl or thiazolyl when Z is CH; wherein B is optionally substituted with one or more R^4 groups;

Y is $-SO_2-$, $-SO_2NH-$, $-NH-SO_2-$, -NH-C(O)-, $-C(O)-NH-$, -O-, or $-NR_2-$;

each occurrence of X is independently NH, O or S;

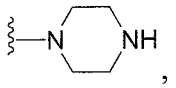
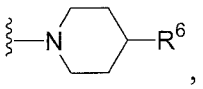
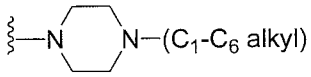
R^1 is H, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl;

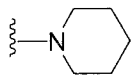
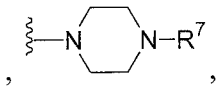
R^2 is H, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl;

R^3 is R^4, –CO-R^5, 

R^a is hydrogen and R^b is halogen, or R^a and R^b, taken together with the atoms to which they are bound form i) a pyrazolo ring fused to the pyrimidine ring when Z is N or ii) a pyrrolo ring fused to the the pyrimidine ring when Z is CH, said pyrazolo or pyrrolo ring optionally bearing one or two R^4 groups;

Each occurrence of R^4 is independently halogen, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxyl, nitro, azido, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide, ureido, amidino, guanidine, sulfonyl, sulphonylamino, aminosulphonyl;

Each occurrence of R^5 is independently is C_1-C_6 alkoxy,  , hydroxy,  ,  , dialkylamino, or -N-R^7;

Each occurrence of R^6 is independently is hydroxy,  ,  , or -$CONH_2$; and

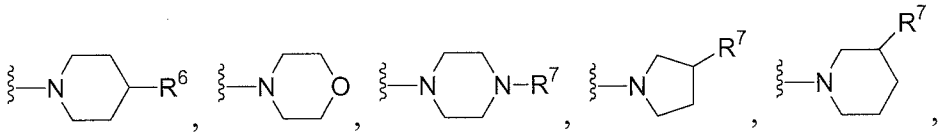
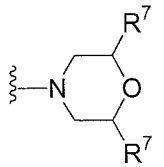
Each occurrence of R^7 is independently is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxyl, or C_1-C_6 hydroxyalkyl;

With the provisos that

(i) when Z is N, B is phenyl, and –X-R^2 is –NH-R^2,

then –X-R^2 is bound in the meta or para position on the phenyl group and R^3 and R^4, if present on B, are not bound to the meta or para position and are not -COR^5, C_1-C_6 alkyl, halo-(C_1-C_6 alkyl), C_1-C_6 cycloalkyl, halo-(C_1-C_6 cycloalkyl), heterocyclyl, heterocyclylC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heteroaryl or heteroarylC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide or amidino ;

(ii) when Z is N, B is phenyl, and –X-R^2 is not –NH-R^2,

then R^3 is bound to the meta or para position and is  ,  or

or R^3 and R^4, if present on B, are each bound to the meta or para position and are independently nitro, azido, ureido, guanidine, sulphonylamino;

and

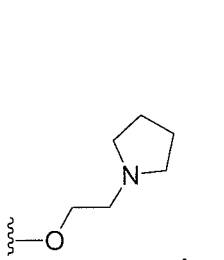
(iii) when Z is CH, and R^a and R^b are taken together with the atoms to which they are bound to form a pyrrolo ring fused to the pyridine ring,

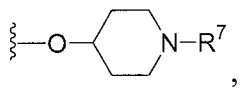
then

(a) $-X-R^2$ is not isopropoxy bound to the othro postion and R^3 or R^4, if present on B, is methyl, ethyl, methoxy, ethoxy, chloro or bromo any of which is bound to the ortho postion

or

(b) R^3 is bound to the meta or para position and is



,


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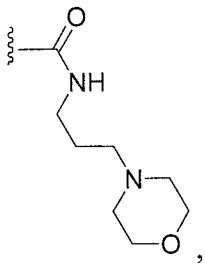
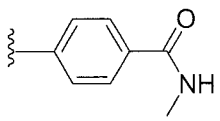
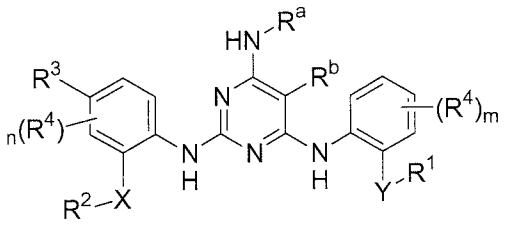


, or


or R^3 and R^4, if present on B, are each bound to the meta or para position and are independently is C_{1-6}alkoxy, C_{1-6}alkylthio, hydroxyl, nitro, azido, cyano, acyloxy, carboxy, ester, carbamoyl, carboxamide, ureido, amidino, guanidine, sulfonyl, sulphonylamino, aminosulphonyl; $-CO-R^5$, or phenyl substituted with aminosulphonyl, amino, alkynyl or carboxamide.

2. The compound of claim 1, having the formula:



(IA)

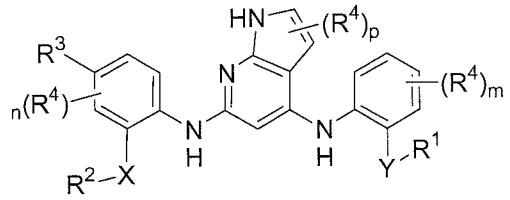
Wherein :

n is an integer from 0-3;

m is an integer from 0-4;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^a and R^b are as defined in claim 1.

3. The compound of claim 1, having the formula:



(II)

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

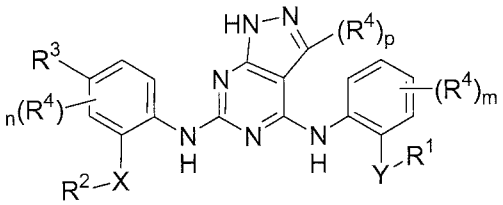
n is an integer from 0-3;

m is an integer from 0-4;

p is an integer from 0-2;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 are as defined in claim 1

4. The compound of claim 1, having the formula



(III)

N is an integer from 0-3;

M is an integer from 0-4;

P is an integer from 0-1;

and Y, X, R^1, R^2, R^3, R^4, R^5, R^6, R^7 are as defined in claim 1

5. The compound of claim 1, wherein X is O.

6. The compound of claim 5, wherein R^2 is methyl, ethyl, propyl, isopropyl, cyclopropyl or cyclobutyl.

7. The compound of claim 6, wherein R^2 is methyl.

8. The compound of claim 1, wherein Y is SO_2.

9. The compound of claim 8, wherein R^1 is methyl, ethyl, propyl, isopropyl, cyclopropyl or cyclobutyl.

10. The compound of claim 9, wherein R^1 is isopropyl.

11. The compound of any one of claims 1-4, wherein X is O, R^2 is methyl, Y is SO_2 and R^1 is isopropyl.

12. A compound having the IUPAC name:

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-4-ol;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N2-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-morpholinophenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(methylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

1-(4-(6-amino-5-chloro-2-(2-(isopropylsulfonyl)phenylamino)pyrimidin-4-ylamino)-3-isopropoxyphenyl)piperidin-4-ol;

5-chloro-N2-(2-ethoxy-4-morpholinophenyl)-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

N2-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-5-chloro-N4-(2-(methylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)pyrimidine-2,4,6-triamine;

5-chloro-N2-(2-ethoxy-4-morpholinophenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-ethoxyphenyl)piperidin-4-ol;

5-chloro-N4-(2-(isopropylsulfonyl)phenyl)-N2-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)pyrimidine-2,4,6-triamine;

2-(4-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazin-1-yl)ethanol;

(R)-1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)pyrrolidin-3-ol;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidin-3-ol;

N2-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-5-chloro-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4,6-triamine;

1-(4-(4-amino-5-chloro-6-(2-(isopropylsulfonyl)phenylamino)pyrimidin-2-ylamino)-3-methoxyphenyl)piperidine-4-carboxamide;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

13. A compound having the IUPAC name:

1-(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-3-methoxyphenyl)piperidin-4-ol;

1-(3-ethoxy-4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N4-(2-(isopropylsulfonyl)phenyl)-N6-(2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

N4-(2-(isopropylsulfonyl)phenyl)-N6-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)-3-methoxyphenyl)piperidine-4-carboxamide;

N6-(4-(1,4'-bipiperidin-1'-yl)-2-ethoxyphenyl)-N4-(2-(isopropylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

N6-(2-ethoxy-4-morpholinophenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(3-methoxy-4-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N6-(4-(4-(diethylamino)piperidin-1-yl)-2-isopropoxyphenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

1-(3-isopropoxy-4-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrazolo[3,4-d]pyrimidin-6-ylamino)phenyl)piperidin-4-ol;

N6-(2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidin-1-yl)phenyl)-N4-(2-(methylsulfonyl)phenyl)-1H-pyrazolo[3,4-d]pyrimidine-4,6-diamine;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

14. A compound having the IUPAC name:

methyl 6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)nicotinate;

6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-N-methylnicotinamide;

(6-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)(4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone;

1,4'-bipiperidin-1'-yl(4-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-3-methoxyphenyl)methanone;

(2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-4-yl)(4-(4-methylpiperazin-1-yl)piperidin-1-yl)methanone;

(2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-4-yl)(4-methylpiperazin-1-yl)methanone;

2-(4-(2-(isopropylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)-N-(3-morpholinopropyl)isonicotinamide;

(4-(4-methylpiperazin-1-yl)piperidin-1-yl)(6-(4-(2-(methylsulfonyl)phenylamino)-1H-pyrrolo[2,3-b]pyridin-6-ylamino)pyridin-3-yl)methanone;

or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof.

15. A pharmaceutical composition comprising a compound according to any one of claims 1, 3 or 4 or a physiologically acceptable salt, solvate, hydrate or stereoisomer thereof and a pharmaceutically acceptable diluent or carrier.

16. The pharmaceutical composition of claim 15 wherein the compound is present in a therapeutically effective amount.

17. The pharmaceutical composition of claim 16 further comprising at least one further active compound.

18. The pharmaceutical composition of claim 17, wherein the further active compound is an anti-hyperproliferative agent.

19. A packaged pharmaceutical composition comprising a container, the pharmaceutical composition of claim 15 and instructions for using the pharmaceutical composition to treat a disease or condition in a mammal.

20. A method of inhibiting kinase activity in a cell comprising contacting a cell with one or more compounds of any one of claims 1, 3 or 4.

21. The method of claim 20 wherein the kinase activity inhibited is Anaplastic Lymphoma Kinase activity.

22. The method of claim 20 wherein the kinase activity inhibited is hepatocyte growth factor receptor tyrosine kinase (c-Met) activity.

23. The method of claim 20 wherein the kinase activity inhibited is monopolar spindle (Mps1) kinase activity.

24. A method of treating a hyperproliferative disorder in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of any one of claims 1, 3 or 4.

25. The method of claim 24 wherein the hyperproliferative disorder is cancer.

26. The method of claim 25 wherein the cancer is a cancer of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid or a distant metastasis of a solid tumor.

27. The method of claim 26 wherein the cancer is a lymphoma, sarcoma, melanoma or leukemia.

28. A method of treating an angiogenesis disorder in a mammal comprising administering to a mammal in need thereof, a therapeutically effective amount of one or more compounds of any one of claims 1, 3 or 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/74472

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/04; A61K 31/70 (2008.04)
USPC - 514/49
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 514/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/256-257; 259.5, 269, 274, 406 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patent/Scholar
Search terms: anaplastic lymphoma kinase, c-met, monopolar spindle kinase, pyrimidine, piperidine, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/016894 A1 (Garcia-Echeverria et al.) 24 February 2005 (24.02.2005) p1, para 2-4; p2, para 1-3, 6-7; p3, para 3; p6, para 1; p21, para 5; p22, para 1; p28, para 2 and 4; p29, para 2	1-28
Y	US 2007/0032515 A1 (Anand et al.) 08 February 2007 (08.02.2007) para [0018], [0025]-[0026], [0028]-[0029], [0032], [0035]-[0037], [0123], [0125]	1-28
Y	US 2007/0191344 A1 (Choidas et al.) 16 August 2007 (16.08.2007) para [0013], [0318]	22
Y	US 7,241,769 B2 (Stadtmueller et al.) 10 July 2007 (10.07.2007) col 1, ln 5-16; col 1, ln 65 to col 2, ln 16	23

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 December 2008 (05.12.2008)	31 DEC 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)