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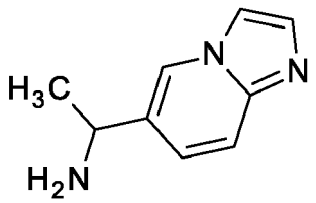
(54) SYNTHETIC INTERMEDIATE USEFUL IN THE PREPARATION OF TRIAZOLOPYRIDINE C-MET INHIBITORS

(57) The specification relates to a compound of the formula:



and salt thereof.

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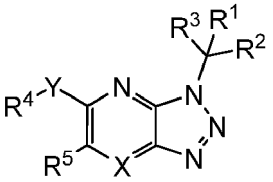
Description

[0001] The c-Met protein, also known as the hepatocyte growth factor (HGF) receptor, is a transmembrane 190 kDa heterodimer with tyrosine kinase activity, encoded by the c-met oncogene. The HGF/c-Met signalling pathway has been shown to demonstrate various cellular responses, including mitogenic, proliferative, morphogenic and angiogenic activities. The inhibition of the HGF/c-Met pathway has significant potential for the treatment of cancer.

[0002] Provided is at least one compound of formula 1:



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and/or at least one pharmaceutically acceptable salt thereof wherein

X is N, Y is selected from -O-, -S-, and -N(R^7)- and R^1 is selected from aryl and heteroaryl, each of which is optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$,-NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$,-N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or

X is N, Y is absent and R^1 is a fused bicyclic heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$,-N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or

X is C(R^6), Y is selected from -O-, -S-, and -N(R^7)- or Y is absent, and R^1 is heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$,-S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle;

R^2 and R^3 are independently selected from hydrogen and alkyl, or R^2 and R^3, together with the carbon to which they are attached, form a ring chosen from 3- to 7-membered cycloalkyl and 3- to 7-membered heterocycle;

R^4 is selected from halo, alkyl, cycloalkyl, heterocycle, aryl and heteroaryl, each of which, except for halo, is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

cycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryloxy optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

aryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and -S(O)$_nNR^{13}R^{14}$;

R^5 is selected from hydrogen, halo, OH, NH_2, CF_3, -CF_2H, alkyl, alkenyl, and alkynyl;

R^6 is selected from hydrogen, -OH, $-NH_2$, $-NHC(O)R^{11}$, halo and alkyl;
R^7 is selected from hydrogen and lower alkyl;
each n is independently 0, 1, or 2;
R^{11}, R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocycle, each of which except for hydrogen, is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy, or R^{13} and R^{14}, with the nitrogen to which they are attached, combine to form a heterocycle ring, which is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy and further optionally includes one or two additional heteroatoms in the heterocycle ring wherein the one or two additional heteroatoms are selected from -O-, -S-, and $-N(R^{15})-$; and
R^{15} is selected from hydrogen, lower alkyl, $-C(O)R^{11}$, $-C(O)OR^{11}$, $-C(O)NR^{13}R^{14}$, $-S(O)_nR^{12}$, and $-S(O)_nNR^{13}R^{14}$
provided that
R^1 is not optionally substituted phenyl or optionally substituted 4-pyridinyl;
when X is N, R^2 is hydrogen or methyl, R^3 and R^5 are hydrogen, and Y is absent, then R^1 is not quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl; and
when X is N, R^2, R^3 and R^5 are hydrogen, and Y is -O- or $-N(R^7)-$, and R^1 is quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl; then R^4 is optionally substituted heteroaryl.

[0003] Also provided is a composition comprising at least one compound and/or at least one pharmaceutically acceptable salt described herein and at least one pharmaceutically acceptable carrier.

[0004] Also provided is a method of inhibiting the activity of c-Met comprising contacting the receptor with an effective amount of at least one compound and/or at least one pharmaceutically acceptable salt described herein.

[0005] Also provided is a method of treating cancer responsive to inhibition of c-Met comprising administering to a subject in need thereof an effective amount of at least one compound and/or at least one pharmaceutically acceptable salt described herein.

[0006] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations and terms have the indicated meanings throughout:

[0007] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0008] The term "alkyl" herein refers to a straight or branched hydrocarbon, containing 1-10 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, n-butyl, *i*-butyl, and *t*-butyl. "Lower alkyl" refers to a straight or branched hydrocarbon, containing 1-4 carbon atoms.

[0009] By "alkoxy" is meant a straight or branched alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. Alkoxy groups will usually have from 1 to 6 carbon atoms attached through the oxygen bridge. ""Lower alkoxy" refers to a straight or branched alkoxy, wherein the alkyl portion contains 1-4 carbon atoms.

[0010] The term "alkenyl" herein refers to a C_{2-10} straight or branched hydrocarbon, containing one or more C=C double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, 2-propenyl, and 2-butenyl.

[0011] The term "alkynyl" herein refers to a C_{2-10} straight or branched hydrocarbon, containing one or more C≡C triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butynyl.

[0012] The term "cycloalkyl" refers to a saturated and partially unsaturated cyclic hydrocarbon group having 3 to 12 carbons. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. The ring may be saturated or have one or more double bonds (i.e. partially unsaturated), but not fully conjugated.

[0013] "Aryl" encompasses:

5- and 6-membered carbocyclic aromatic rings, for example, benzene;
bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and
tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

[0014] For example, aryl includes 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence

are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Aryl, however, does not encompass or overlap in any way with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings are fused with a heterocyclic aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[0015] The term "halo" includes fluoro, chloro, bromo, and iodo, and the term "halogen" includes fluorine, chlorine, bromine, and iodine.

[0016] The term "heteroaryl" refers to

5- to 8-membered aromatic, monocyclic rings containing one or more, for example, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon;

8- to 12-membered bicyclic rings containing one or more, for example, from 1 to 4, or, in some embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring; and

11- to 14-membered tricyclic rings containing one or more, for example, from 1 to 4, or in some embodiments, from 1 to 3, heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one heteroatom is present in an aromatic ring.

[0017] For example, heteroaryl includes a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings contains one or more heteroatoms, the point of attachment may be at the heteroaromatic ring or the cycloalkyl ring.

[0018] When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0019] Examples of heteroaryl groups include, but are not limited to, (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 1-pyrazolyl, 2,3-pyrazolyl, 2,4-imidazolinyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, thienyl, benzothienyl, furyl, benzofuryl, benzoimidazolinyl, indolinyl, pyridizinyl, triazolyl, quinolinyl, pyrazolyl, and 5,6,7,8-tetrahydroisoquinoline.

[0020] Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylidene. Heteroaryl does not encompass or overlap with aryl as defined above.

[0021] Substituted heteroaryl also includes ring systems substituted with one or more oxide ($-O^-$) substituents, such as pyridinyl N-oxides.

[0022] By "heterocycle" is meant a single aliphatic ring, usually with 3 to 7 ring atoms, containing at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms. "Heterocycle" also refers to 5- to 7-membered heterocyclic ring containing one or more heteroatoms selected from N, O, and S fused with 5- and 6-membered carbocyclic aromatic ring, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have one or more double bonds (i.e. partially unsaturated). The heterocycle can be substituted by oxo. The point of the attachment may be carbon or heteroatom in the heterocyclic ring.

[0023] Suitable heterocycles include, for example (as numbered from the linkage position assigned priority 1), 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, and 2,5-piperazinyl. Morpholinyl groups are also contemplated, including 2-morpholinyl and 3-morpholinyl (numbered wherein the oxygen is assigned priority 1). Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl and 1,1-dioxo-1-thiomorpholinyl.

[0024] By "optional" or "optionally" is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

[0025] The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo (i.e., =O) then 2 hydrogens on the atom are replaced. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation as an agent having at least practical utility. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion.

[0026] In some embodiments, "substituted with one or more groups" refers to two hydrogens on the designated atom

or group being independently replaced with two selections from the indicated group of substituents. In some embodiments, "substituted with one or more groups" refers to three hydrogens on the designated atom or group being independently replaced with three selections from the indicated group of substituents. In some embodiments, "substituted with one or more groups" refers to four hydrogens on the designated atom or group being independently replaced with four selections from the indicated group of substituents.

[0027] Compounds described herein include, but are not limited to, their optical isomers, racemates, and other mixtures thereof. In those situations, the single enantiomers or diastereomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates or mixtures of diastereomers. Resolution of the racemates or mixtures of diastereomers can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. In addition, such compounds include Z- and E- forms (or *cis*- and *trans*- forms) of compounds with carbon-carbon double bonds. Where compounds described herein exist in various tautomeric forms, the term "compound" is intended to include all tautomeric forms of the compound. Such compounds also include crystal forms including polymorphs and clathrates. Similarly, the term "salt" is intended to include all isomers, racemates, other mixtures, Z- and E-forms, tautomeric forms and crystal forms of the salt of the compound.

[0028] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, phosphate, diphosphate, hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, $HOOC-(CH_2)_n-COOH$ where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0029] In addition, if a compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[0030] A "solvate," such as a "hydrate," is formed by the interaction of a solvent and a compound. The term "compound" is intended to include solvates, including hydrates, of compounds. Similarly, "salts" includes solvates, such as hydrates, of salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates.

[0031] A "chelate" is formed by the coordination of a compound to a metal ion at two (or more) points. The term "compound" is intended to include chelates of compounds. Similarly, "salts" includes chelates of salts.

[0032] A "non-covalent complex" is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term "compound'.

[0033] The term "hydrogen bond" refers to a form of association between an electronegative atom (also known as a hydrogen bond acceptor) and a hydrogen atom attached to a second, relatively electronegative atom (also known as a hydrogen bond donor). Suitable hydrogen bond donor and acceptors are well understood in medicinal chemistry (G. C. Pimentel and A. L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen Bond Geometry in Organic Crystals", Accounts of Chemical Research, 17, pp. 320-326 (1984)).

[0034] As used herein the terms "group", "radical" or "fragment" are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments of molecules.

[0035] The term "active agent" is used to indicate a chemical substance which has biological activity. In some embodiments, an "active agent" is a chemical substance having pharmaceutical utility.

[0036] "Treating" or "treatment" or "alleviation" refers to administering at least one compound and/or at least one pharmaceutically acceptable salt described herein to a subject that has cancer, or has a symptom of cancer, or has a predisposition toward cancer, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect cancer, the symptoms of cancer, or the predisposition toward cancer.

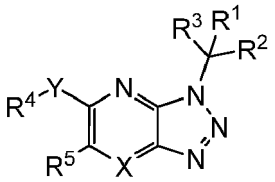
[0037] The term "effective amount" refers to an amount of at least one compound and/or at least one pharmaceutically acceptable salt described herein effective to "treat" a disease or disorder in a subject. In the case of cancer, the effective amount may cause any of the changes observable or measurable in a subject as described in the definition of "treating," "treatment" and "alleviation" above. For example, the effective amount can reduce the number of cancer or tumor cells; reduce the tumor size; inhibit or stop tumor cell infiltration into peripheral organs including, for example, the spread of tumor into soft tissue and bone; inhibit and stop tumor metastasis; inhibit and stop tumor growth; relieve to some extent one or more of the symptoms associated with the cancer, reduce morbidity and mortality; improve quality of life; or a combination of such effects. An effective amount may be an amount sufficient to decrease the symptoms of a disease

responsive to inhibition of c-Met activity. For cancer therapy, efficacy in vivo can, for example, be measured by assessing the duration of survival, time to disease progression (TTP), the response rates (RR), duration of response, and/or quality of life. Effective amounts may vary, as recognized by those skilled in the art, depending on route of administration, excipient usage, and co-usage with other agents.

[0038] The term "inhibition" indicates a decrease in the baseline activity of a biological activity or process. "Inhibition of c-Met activity" refers to a decrease in the activity of c-Met as a direct or indirect response to the presence of at least one at least one compound and/or at least one pharmaceutically acceptable salt described herein, relative to the activity of c-Met in the absence of the at least one compound and/or the at least one pharmaceutically acceptable salt thereof. The decrease in activity may be due to the direct interaction of the at least one compound and/or at least one pharmaceutically acceptable salt described herein with c-Met, or due to the interaction of the at least one compound and/or at least one pharmaceutically acceptable salt described herein, with one or more other factors that in turn affect c-Met activity. For example, the presence of at least one compound and/or at least one pharmaceutically acceptable salt described herein, may decrease c-Met activity by directly binding to the c-Met, by causing (directly or indirectly) another factor to decrease c-Met activity, or by (directly or indirectly) decreasing the amount of c-Met present in the cell or organism.

[0039] The details of one or more embodiments of the invention are set forth below.

[0040] Provided is at least one compound of formula 1:



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and/or at least one pharmaceutically acceptable salt thereof wherein

X is N, Y is selected from -O-, -S-, and -N(R^7)- and R^1 is selected from aryl and heteroaryl, each of which is optionally substituted with one or more groups selected from halo,-CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$,-NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$,-N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or

X is N, Y is absent and R^1 is a fused bicyclic heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$,-N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or

X is C(R^6), Y is selected from -O-, -S-, and -N(R^7)- or Y is absent, and R^1 is heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$,-S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle;

R^2 and R^3 are independently selected from hydrogen and alkyl, or R^2 and R^3, together with the carbon to which they are attached, form a ring chosen from 3- to 7-membered cycloalkyl and 3- to 7-membered heterocycle;

R^4 is selected from halo, alkyl, cycloalkyl, heterocycle, aryl and heteroaryl, each of which, except for halo, is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

cycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryloxy optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
aryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
heteroaryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and -S(O)$_nNR^{13}R^{14}$;

R^5 is selected from hydrogen, halo, OH, NH_2, CF_3, -CF_2H, alkyl, alkenyl, and alkynyl;
R^6 is selected from hydrogen, -OH, -NH_2, -NHC(O)R^{11}, halo and alkyl;
R^7 is selected from hydrogen and lower alkyl;
each n is independently 0, 1, or 2;
R^{11}, R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocycle, each of which except for hydrogen, is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy, or R^{13} and R^{14}, with the nitrogen to which they are attached, combine to form a heterocycle ring, which is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy and further optionally includes one or two additional heteroatoms in the heterocycle ring wherein the one or two additional heteroatoms are selected from -O-, -S-, and -N(R^{15})-; and
R^{15} is selected from hydrogen, lower alkyl,-C(O)R^{11}, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and -S(O)$_nNR^{13}R^{14}$ provided that
R^1 is not optionally substituted phenyl or optionally substituted 4-pyridinyl;
when X is N, R^2 is hydrogen or methyl, R^3 and R^5 are hydrogen, and Y is absent, then R^1 is not quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl; and
when X is N, R^2, R^3 and R^5 are hydrogen, and Y is -O- or -N(R^7)-, and R^1 is quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl; then R^4 is optionally substituted heteroaryl.

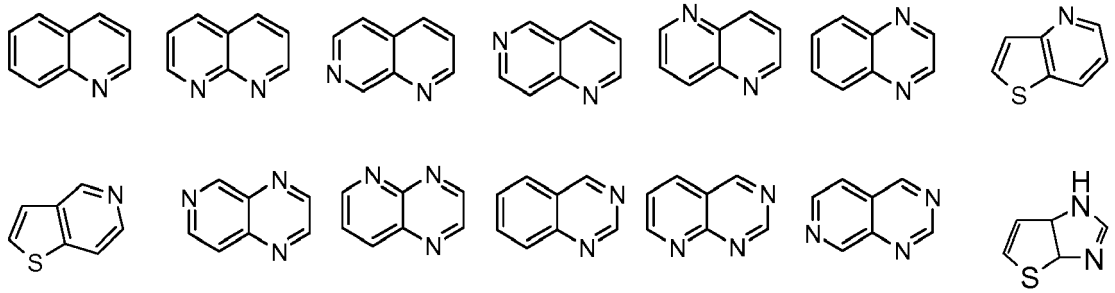
[0041] In some embodiments, X is N. In some embodiments, X is C(R^6). In some embodiments, R^6 is selected from hydrogen, halo and lower alkyl. In some embodiments, R^6 is hydrogen.

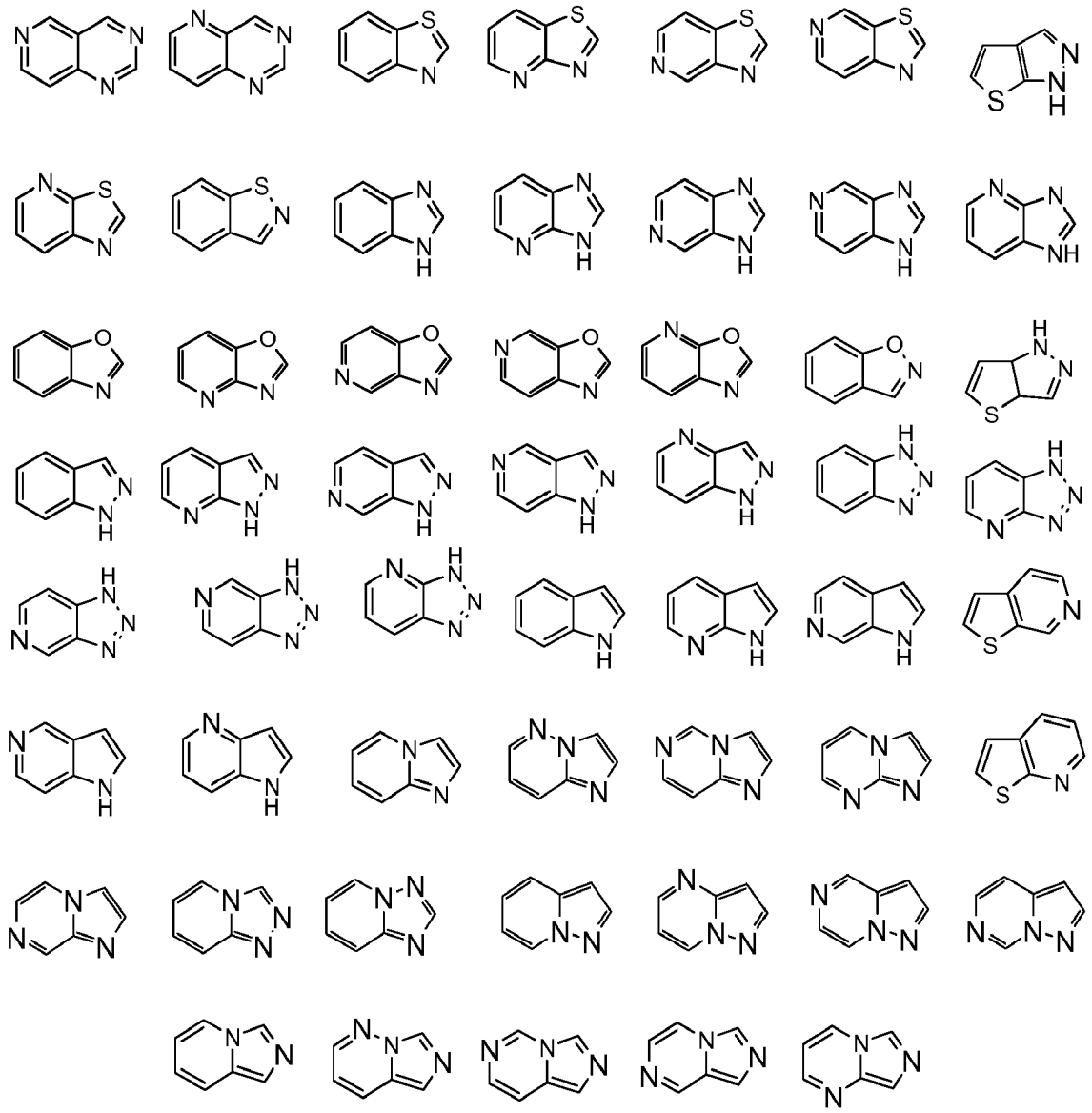
[0042] In some embodiments, Y is -O-. In some embodiments, Y is -S-. In some embodiments, Y is -N(R^7)-. In some embodiments, R^7 is hydrogen or methyl. In some embodiments, R^7 is hydrogen. In some embodiments, Y is absent.

[0043] In some embodiments, R^1 is 8-10 membered heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle. In some embodiments, R^1 is 8-10 membered heteroaryl optionally substituted with one or more groups selected from halo, lower alkyl, lower alkyl substituted with hydroxy, and lower alkyl substituted with lower alkoxy.

[0044] In some embodiments, R^1 is selected from quinolin-6-yl, thieno[3,2-c]pyridin-2-yl, benzo[d]thiazol-6-yl, and imidazo[1,2-a]pyridin-6-yl, each of which is optionally substituted with one or more groups selected from halo, lower alkyl, lower alkyl substituted with hydroxy, and lower alkyl substituted with lower alkoxy. In some embodiments, R^1 is selected from quinolin-6-yl optionally substituted with one or more groups selected from halo, lower alkyl, lower alkyl substituted with hydroxy, and lower alkyl substituted with lower alkoxy.

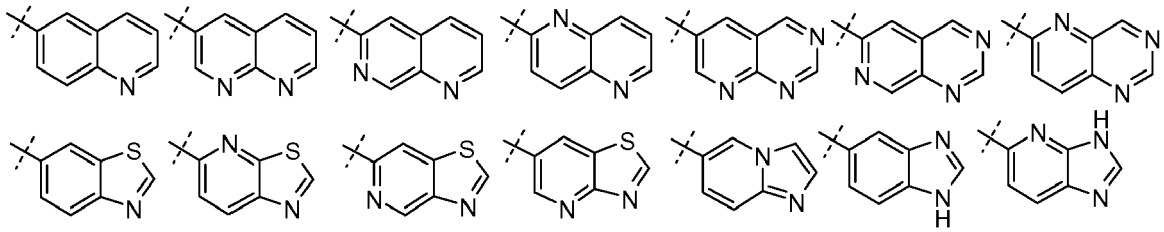
[0045] In some embodiments, R^1 is a ring system selected from

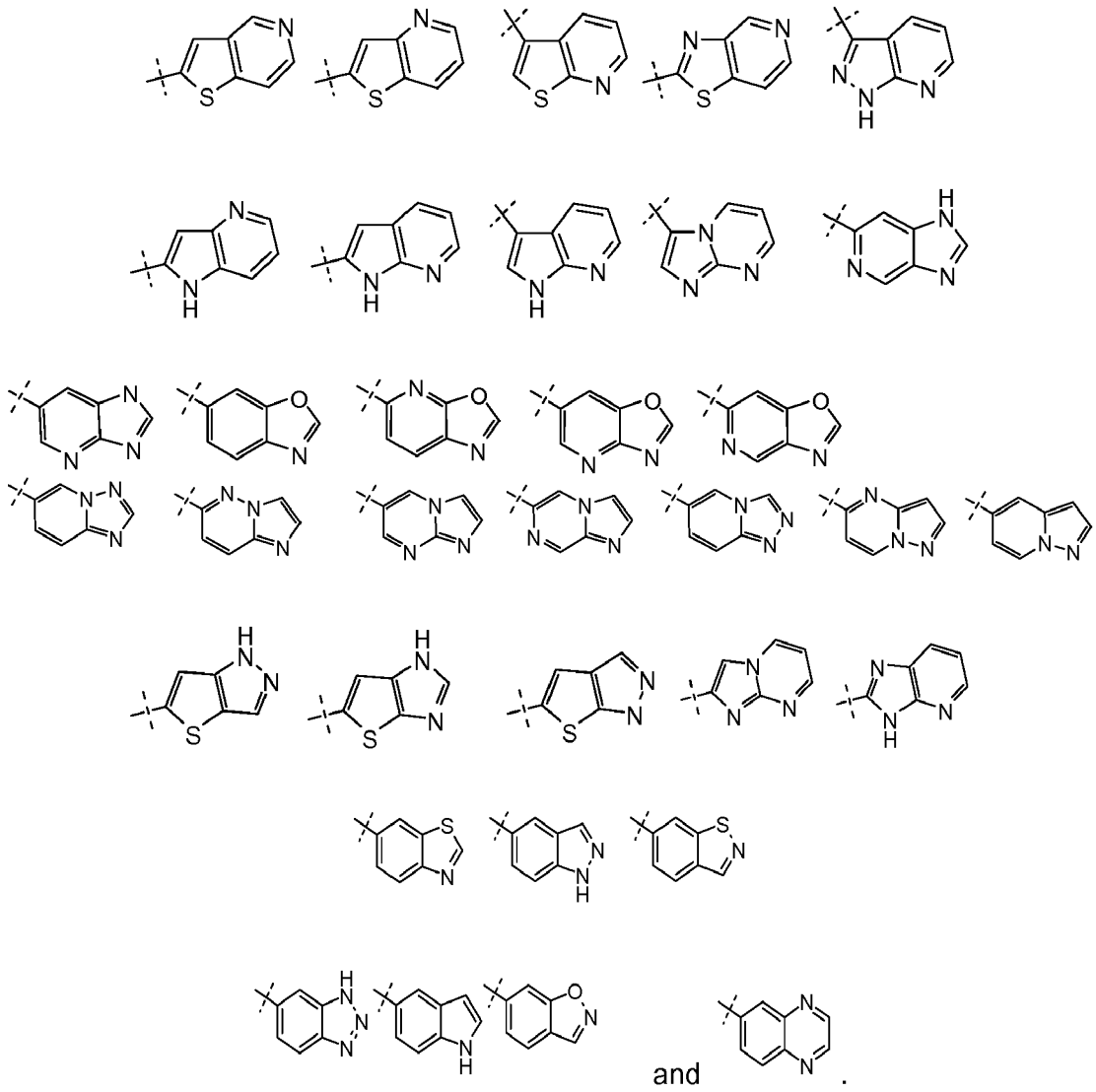




wherein each of said ring systems is optionally substituted with one or more groups selected from halo, CF_3, $-CF_2H$, cycloalkyl, $-C(O)R^{11}$, $C(O)OR^{11}$, -CN, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$,$-NR^{13}C(O)R^{11}$, $-NR^{13}S(O)_nR^{12}$, $-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-NO_2$, $-S(O)_nR^{12}$, $-S(O)_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with $-NR^{13}R^{14}$, and lower alkyl substituted with heterocycle. For avoidance of doubt, each of said ring systems may be appended to the carbon bearing R^2 and R^3 at any open valence on either of the rings in the ring systems.

[0046] In some embodiments, R^1 is a ring system selected from





wherein each of said ring systems is optionally substituted with one or more groups selected from halo, CF_3, $-CF_2H$, cycloalkyl, $-C(O)R^{11}$, $C(O)OR^{11}$, -CN, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$,$-NR^{13}C(O)R^{11}$, $-NR^{13}S(O)_nR^{12}$, $-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-NO_2$, $-S(O)_nR^{12}$, $-S(O)_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with $-NR^{13}R^{14}$, and lower alkyl substituted with heterocycle. For avoidance of doubt, each of said ring systems depicted above is appended to the carbon bearing R^2 and R^3 at the position indicated.

[0047] In some embodiments, R^2 and R^3 are independently selected from hydrogen and C_1-C_6 alkyl or R^2 and R^3, together with the carbon to which they are attached, form a 3-membered cycloalkyl. In some embodiments, R^2 is hydrogen and R^3 is selected from hydrogen and C_1-C_6 alkyl. In some embodiments, R^2 is hydrogen and R^3 is selected from hydrogen and methyl. In some embodiments, R^2 and R^3 are hydrogen. In some embodiments, R^2 and R^3, together with the carbon to which they are attached, form a 3-membered cycloalkyl.

[0048] In some embodiments, R^4 is aryl optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, $-C(O)OR^{11}$, $-C(O)NR^{13}R^{14}$,$-NR^{13}R^{14}$, $-OC(O)R^{11}$, $-NR^{13}C(O)R^{11}$, $-NR^{13}S(O)_nR^{12}$,$-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, and $-NR^{13}C(O)NR^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryloxy optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

aryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, -NR^{13}C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n R^{12}$, and -S(O)$_n$N$R^{13}R^{14}$.

[0049] In some embodiments, R^4 is aryl optionally substituted with one or more groups selected from halo, hydroxy, -NR^{13}S(O)$_n R^{12}$, lower alkoxy, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkoxy substituted with hydroxy, and lower alkoxy substituted with lower alkoxy..

[0050] In some embodiments, R^4 is phenyl optionally substituted with one or more groups selected from lower alkoxy, lower alkoxy substituted with hydroxy, and lower alkoxy substituted with lower alkoxy.

[0051] In some embodiments, R^4 is heterocycle optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, and -NR^{13}C(O)N$R^{13}R^{14}$,
lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,
heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, -NR^{13}C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n R^{12}$, and -S(O)$_n$N$R^{13}R^{14}$.

[0052] In some embodiments, R^4 is selected from pyrrolidin-1-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, morpholin-4-yl, and 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl, each of which is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, and -NR^{13}C(O)N$R^{13}R^{14}$,
lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,
heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, -NR^{13}C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n R^{12}$, and -S(O)$_n$N$R^{13}R^{14}$.

[0053] In some embodiments, R^4 is selected from pyrrolidin-1-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, morpholin-4-yl, and 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl, each of which is optionally substituted with one or more groups selected from halo, CF_3, -CF_2H, hydroxy, lower alkyl, lower alkyl substituted with hydroxy, and lower alkyl substituted with lower alkoxy.

[0054] In some embodiments, R^4 is heteroaryl optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, and -NR^{13}C(O)N$R^{13}R^{14}$,
lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,
heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, -NR^{13}C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n R^{12}$, and -S(O)$_n$N$R^{13}R^{14}$.

[0055] In some embodiments, R^4 is selected from 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, oxazol-2-yl, thiazol-2-yl, isoxazol-3-yl, isoxazol-5-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, thiophen-2-yl, thiophen-3-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl, each of which is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$,-N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, and -NR^{13}C(O)N$R^{13}R^{14}$,
lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,
heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n R^{12}$,-NR^{13}S(O)$_n$N$R^{13}R^{14}$, -NR^{13}C(O)OR^{12}, -NR^{13}C(O)N$R^{13}R^{14}$,-C(O)N$R^{13}R^{14}$, -S(O)$_n R^{12}$, and -S(O)$_n$N$R^{13}R^{14}$.

[0056] In some embodiments, R^4 is selected from 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, oxazol-2-yl, thiazol-2-yl, isoxazol-3-yl, isoxazol-5-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, thiophen-2-yl, thiophen-3-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl, each of which is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, $-C(O)OR^{11}$, $-C(O)NR^{13}R^{14}$,$-NR^{13}R^{14}$, $-OC(O)R^{11}$, $-NR^{13}C(O)R^{11}$, $-NR^{13}S(O)_nR^{12}$,$-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, and $-NR^{13}C(O)NR^{13}R^{14}$, and

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

[0057] In some embodiments, R^4 is selected from 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, oxazol-2-yl, thiazol-2-yl, isoxazol-3-yl, isoxazol-5-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, thiophen-2-yl, thiophen-3-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl, each of which is optionally substituted with one or more groups selected from lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, and halo.

[0058] In some embodiments, R^4 is lower alkyl.

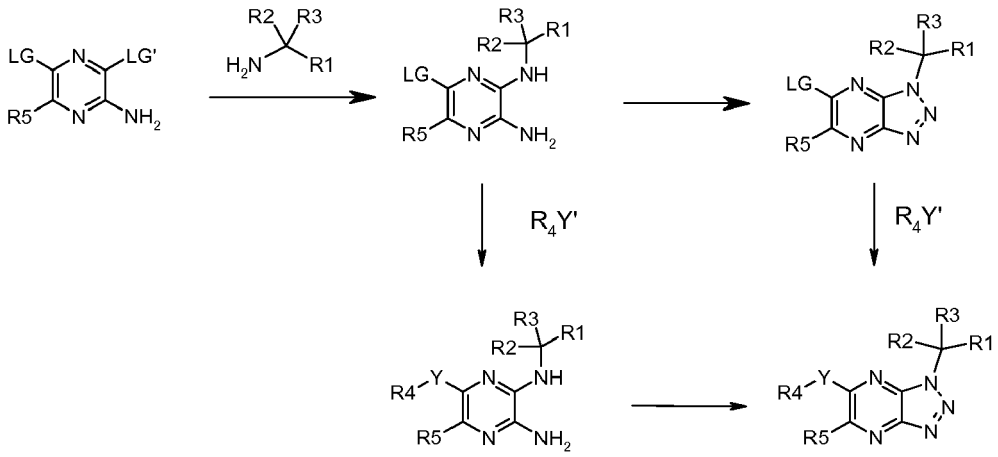
[0059] In some embodiments, R^5 is hydrogen.

[0060] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

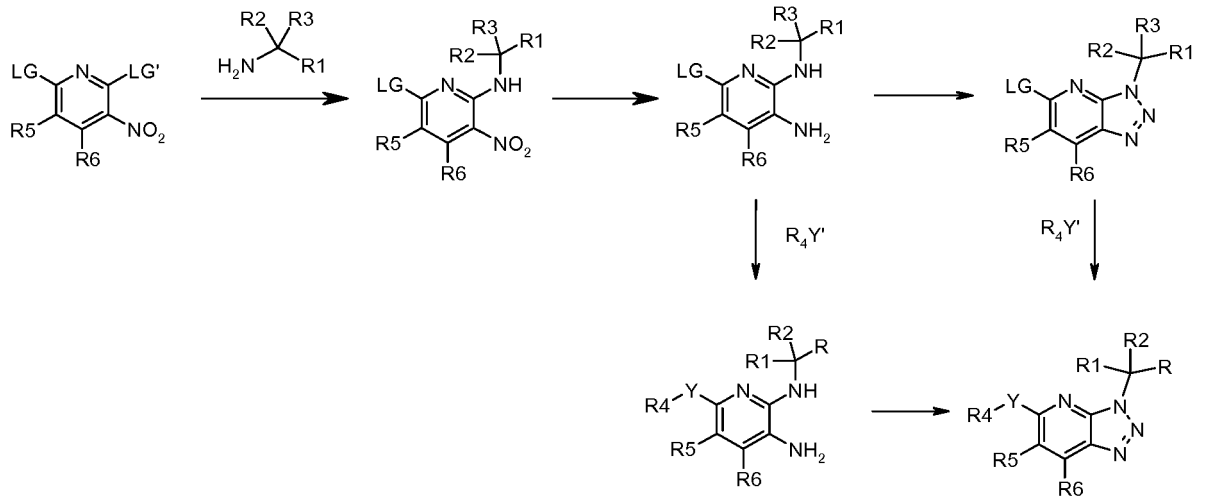
[0061] Also provided is at least one compound selected from compounds 1 to 332 and/or at least one pharmaceutically acceptable salt described herein.

[0062] The compounds described herein, and/or the pharmaceutically acceptable salts thereof, can be synthesized from commercially available starting materials by methods well known in the art. The following schemes illustrate methods for most of compound preparation. In each of the schemes, LG and LG' are leaving groups that can be same or different. Y' is $-NHR^7$, -OH, -SH, $-B(OH)_2$, or $B(OR')_2$, and R^1, R^2, R^3, R^4, R^5 and Y are as defined herein.

Scheme I



Scheme II



[0063] The compounds thus obtained can be further modified at their peripheral positions to provide the desired compounds. Synthetic chemistry transformations are described, for example, in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

[0064] Before use, the at least one compound and/or at least one pharmaceutically acceptable salt described herein, can be purified by column chromatography, high performance liquid chromatography, crystallization, or other suitable methods.

[0065] Also provided is a composition containing at least one compound and/or at least one pharmaceutically acceptable salt described herein, and at least one pharmaceutically acceptable carrier.

[0066] A composition comprising at least one compound and/or at least one pharmaceutically acceptable salt described herein, can be administered in various known manners, such as orally, parenterally, by inhalation spray, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0067] An oral composition can be any orally acceptable dosage form including, but not limited to, tablets, capsules, emulsions, and aqueous suspensions, dispersions and solutions. Commonly used carriers for tablets include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added to tablets. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added.

[0068] A sterile injectable composition (e.g., aqueous or oleaginous suspension) can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the pharmaceutically acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or di-glycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents.

[0069] An inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0070] A topical composition can be formulated in form of oil, cream, lotion, ointment and the like. Suitable carriers for the composition include vegetable or mineral oils, white petrolatum (white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohols (greater than C12). In some embodiments, the pharmaceutically accept-

able carrier is one in which the active ingredient is soluble. Emulsifiers, stabilizers, humectants and antioxidants may also be included as well as agents imparting color or fragrance, if desired. Additionally, transdermal penetration enhancers may be employed in these topical formulations. Examples of such enhancers can be found in U.S. Patents 3,989,816 and 4,444,762.

[0071] Creams may be formulated from a mixture of mineral oil, self-emulsifying beeswax and water in which mixture the active ingredient, dissolved in a small amount of an oil, such as almond oil, is admixed. An example of such a cream is one which includes about 40 parts water, about 20 parts beeswax, about 40 parts mineral oil and about 1 part almond oil. Ointments may be formulated by mixing a solution of the active ingredient in a vegetable oil, such as almond oil, with warm soft paraffin and allowing the mixture to cool. An example of such an ointment is one which includes about 30% by weight almond and about 70% by weight white soft paraffin.

[0072] A pharmaceutically acceptable carrier refers to a carrier that is compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which form specific, more soluble complexes with the at least one compound and/or at least one pharmaceutically acceptable salt described herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10.

[0073] Suitable *in vitro* assays can be used to preliminarily evaluate the efficacy of the at least one compound and/or at least one pharmaceutically acceptable salt described herein, in inhibiting the activity of c-Met. The at least one compound and/or at least one pharmaceutically acceptable salt described herein, can further be examined for efficacy in treating cancer by *in vivo* assays. For example, the compounds described herein, and/or the pharmaceutically acceptable salts thereof, can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects can be accessed. Based on the results, an appropriate dosage range and administration route for animals, such as humans, can also be determined.

[0074] Also provided is a method of inhibiting the activity of c-Met. The method comprises contacting the receptor with an amount of at least one compound and/or at least one pharmaceutically acceptable salt described herein effective to inhibit the activity of c-Met.

[0075] The at least one compound and/or at least one pharmaceutically acceptable salt described herein can be used to achieve a beneficial therapeutic or prophylactic effect, for example, in subjects with cancer. As used herein, the term "cancer" refers to a cellular disorder characterized by uncontrolled or disregulated cell proliferation, decreased cellular differentiation, inappropriate ability to invade surrounding tissue, and/or ability to establish new growth at ectopic sites. The term "cancer" includes, but is not limited to, solid tumors and bloodborne tumors. The term "cancer" encompasses diseases of skin, tissues, organs, bone, cartilage, blood, and vessels. The term "cancer" further encompasses primary and metastatic cancers.

[0076] Non-limiting examples of solid tumors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; skin cancer, including e.g., malignant melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; soft tissue sarcoma; and thyroid carcinoma.

[0077] Non-limiting examples of hematologic malignancies include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; β-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom's macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts (RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes.

[0078] In some embodiments, the examples of the cancer to be treated include, but are not limited to, lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, stomach cancer, kidney cancer, liver cancer, brain cancer, bone cancer, and leukemia.

[0079] In some embodiments, the at least one compound and/or at least one pharmaceutically acceptable salt described herein, is administered in conjunction with another therapeutic agent. In some embodiments, the other therapeutic agent is one that is normally administered to patients with the disease or condition being treated. The at least one compound and/or at least one pharmaceutically acceptable salt described herein, may be administered with the other therapeutic agent in a single dosage form or as a separate dosage form. When administered as a separate dosage form, the other therapeutic agent may be administered prior to, at the same time as, or following administration of the at least one

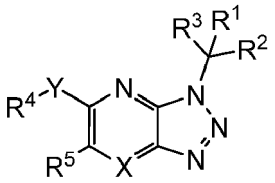
compound and/or at least one pharmaceutically acceptable salt described herein.

[0080] In some embodiments, at least one compound and/or at least one pharmaceutically acceptable salt described herein, is administered in conjunction with an anti-neoplastic agent. As used herein, the term "anti-neoplastic agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer. Nonlimiting examples anti-neoplastic agents include: radiotherapy; immunotherapy; DNA damaging chemotherapeutic agents; and chemotherapeutic agents that disrupt cell replication.

[0081] Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

[0082] Chemotherapeutic agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors (e.g., bortezomib); NF-kappa B inhibitors, including inhibitors of I kappa B kinase; antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed or activated in cancers, the inhibition of which downregulates cell replication.

[0083] Provided in embodiment A is at least one compound of formula 1:



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and/or at least one pharmaceutically acceptable salt thereof wherein

X is N, Y is selected from -O-, -S-, and -N(R^7)- and R^1 is selected from aryl and heteroaryl, each of which is optionally substituted with one or more groups selected from halo, -CF_3,-CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$,-S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or

X is N, Y is absent and R^1 is a fused bicyclic heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, - C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}$R14, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle; or X is C(R^6), Y is selected from -O-, -S-, and -N(R^7)- or Y is absent, and R^1 is heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl,-C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle;

R^2 and R^3 are independently selected from hydrogen, and alkyl, or R^2 and R^3, together with the carbon to which they are attached, form a ring chosen from 3- to 7-membered cycloalkyl and 3- to 7-membered heterocycle;

R^4 is selected from halo, alkyl, cycloalkyl, heterocycle, aryl and heteroaryl, each of which, except for halo, is optionally substituted with one or more groups selected from lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

cycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycloalkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, heteroaryloxy optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
aryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
heteroaryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,
halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$;
R^5 is selected from hydrogen, halo, OH, NH_2, CF_3, -CF_2H, alkyl, alkenyl, and alkynyl;
R^6 is selected from hydrogen, -OH, -NH_2, -NHC(O)R^{11}, halo and alkyl;
R^7 is selected from hydrogen and lower alkyl;
each n is independently 0, 1, or 2;
R^{11}, R^{12}, R^{13}, and R^{14} are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocycle, each of which except for hydrogen, is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy, or R^{13} and R^{14}, with the nitrogen to which they are attached, combine to form a heterocycle ring, which is optionally substituted with one or more groups selected from halo, lower alkyl, hydroxy, and lower alkoxy and further optionally includes one or two additional heteroatoms in the heterocycle ring wherein the one or two additional heteroatoms are selected from -O-, -S-, and -N(R^{15})-; and
R^{15} is selected from hydrogen, lower alkyl,-C(O)R^{11}, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and -S(O)$_nNR^{13}R^{14}$;
provided that
R^1 is not optionally substituted phenyl or optionally substituted 4-pyridinyl;
when X is N, R^2 is hydrogen or methyl, R^3 and R^5 are hydrogen, and Y is absent, then R^1 is not quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl; and
when X is N, R^2, R^3 and R^5 are hydrogen, and Y is -O- or -N(R^7)-, and R^1 is quinolin-6-yl, 7-fluoroquinolin-6-yl, 3-quinazolin-6-yl, 2-3-dihydro-benzofuran-5-yl, or 2,3-dihydro-benzo[1,4]dioxin-6-yl, then R^4 is optionally substituted heteroaryl.

[0084] In a further embodiment B is provided at least one compound of embodiment A, and/or at least one pharmaceutically acceptable salt thereof, wherein X is N.

[0085] In a further embodiment C is provided at least one compound of embodiment A, and/or at least one pharmaceutically acceptable salt thereof, wherein X is C(R^6).

[0086] In a further embodiment D is provided at least one compound of embodiment C, and/or at least one pharmaceutically acceptable salt thereof, wherein R^6 is selected from hydrogen and lower alkyl.

[0087] In a further embodiment E is provided at least one compound of embodiment D, and/or at least one pharmaceutically acceptable salt thereof, wherein R^6 is hydrogen.

[0088] In a further embodiment F is provided at least one compound of any one of embodiments A to E, and/or at least one pharmaceutically acceptable salt thereof, wherein Y is -O-.

[0089] In a further embodiment G is provided at least one compound of any one of embodiments A to E, and/or at least one pharmaceutically acceptable salt thereof, wherein Y is -S-.

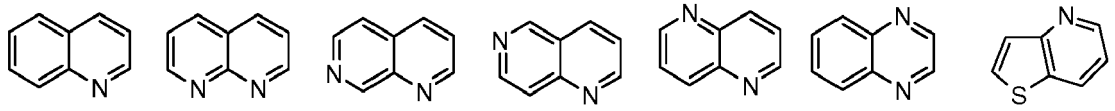
[0090] In a further embodiment H is provided at least one compound of any one of embodiments A to E, and/or at least one pharmaceutically acceptable salt thereof, wherein Y is -N(R^7)-.

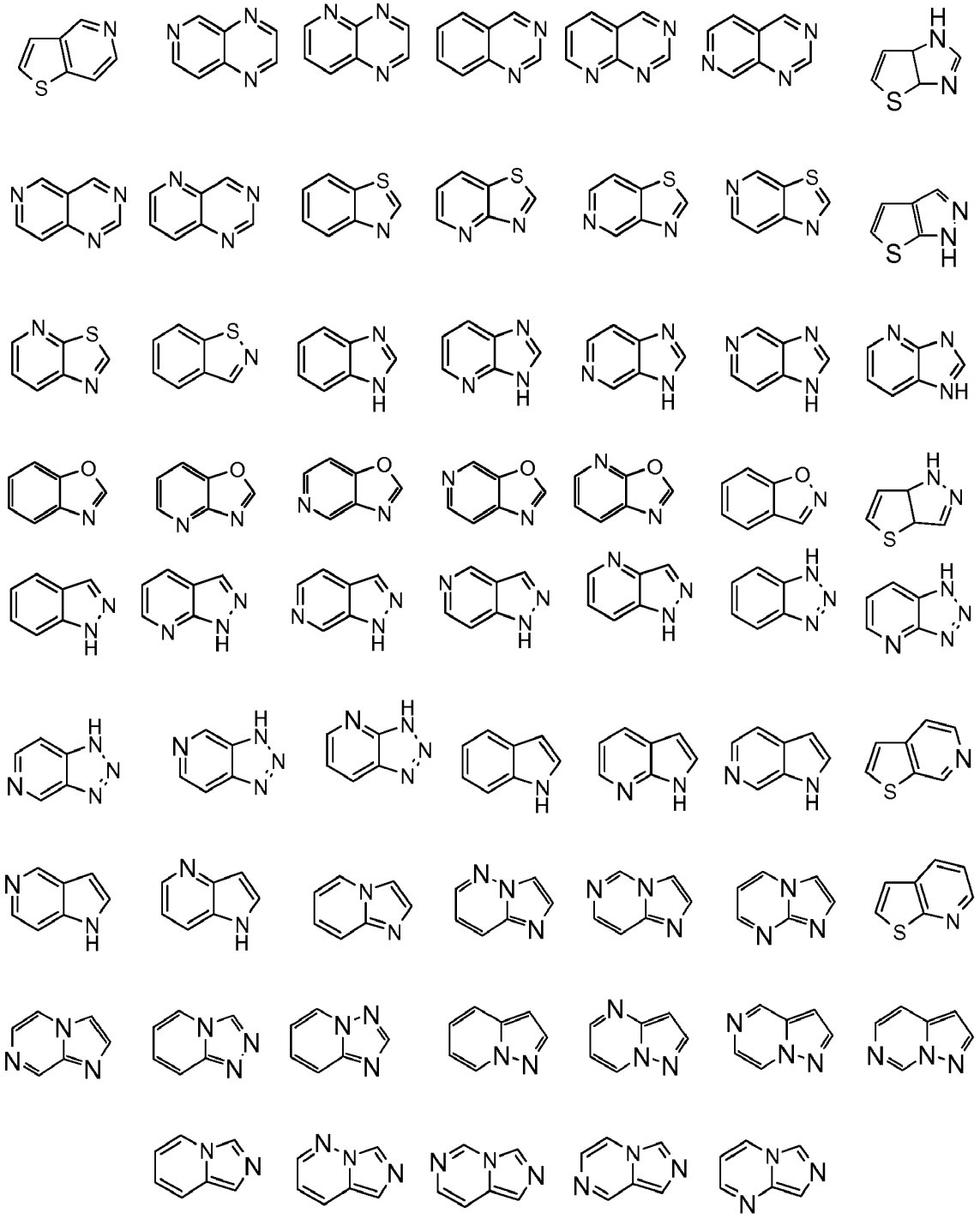
[0091] In a further embodiment I is provided at least one compound of embodiment H, and/or at least one pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen or methyl.

[0092] In a further embodiment J is provided at least one compound of any one of embodiments A to E, and/or at least one pharmaceutically acceptable salt thereof, wherein Y is absent.

[0093] In a further embodiment K is provided at least one compound of any one of embodiments A to J, and/or at least one pharmaceutically acceptable salt thereof, wherein R^1 is 8-10 membered heteroaryl optionally substituted with one or more groups selected from halo, -CF_3, -CF_2H, cycloalkyl, -C(O)R^{11}, -C(O)OR^{11}, -CN, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$,-NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -$NO_2$, -S(O)$_n$$R^{12}$, -S(O)$_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with -N$R^{13}R^{14}$, and lower alkyl substituted with heterocycle.

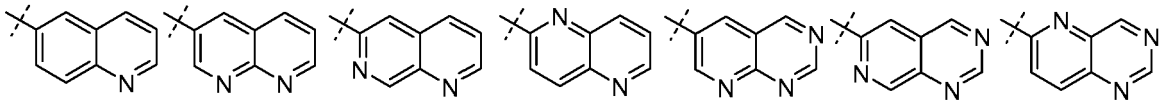
[0094] In a further embodiment L is provided at least one compound of any one of embodiments A to K, and/or at least one pharmaceutically acceptable salt thereof, wherein R^1 is a ring system selected from

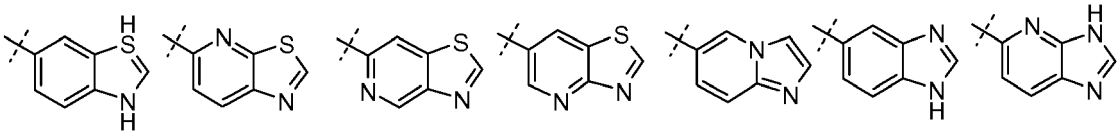


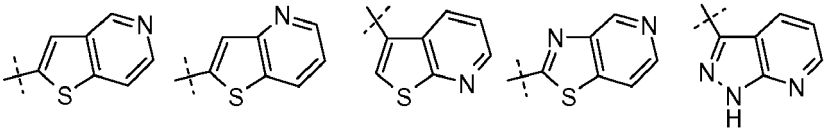


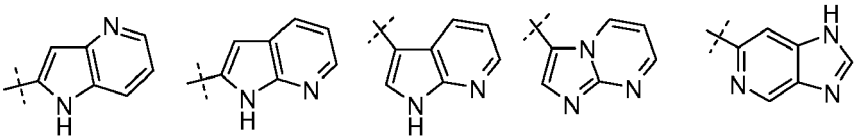
wherein each of said ring systems is optionally substituted with one or more groups selected from halo, CF_3, $-CF_2H$, cycloalkyl, $-C(O)R^{11}$, $C(O)OR^{11}$, -CN, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$,$-NR^{13}C(O)R^{11}$, $-NR^{13}S(O)_nR^{12}$, $-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-NO_2$, $-S(O)_nR^{12}$, $-S(O)_nNR^{13}R^{14}$, heterocycle, heteroaryl, aryl, alkenyl, alkynyl, lower alkyl, lower alkyl substituted with hydroxy, lower alkyl substituted with lower alkoxy, lower alkyl substituted with $-NR^{13}R^{14}$, and lower alkyl substituted with heterocycle.

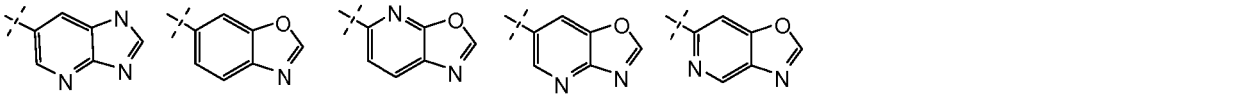
[0095] In a further embodiment M is provided at least one compound of any one of embodiments A to L, and/or at least one pharmaceutically acceptable salt thereof, wherein R^1 is a ring system selected from

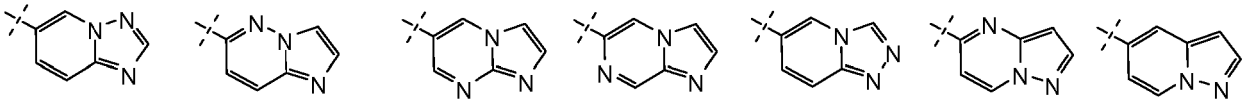


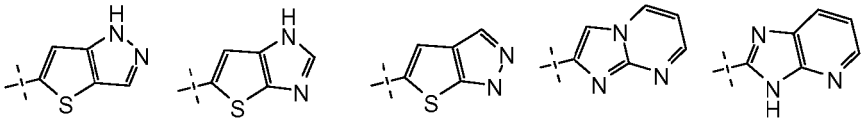


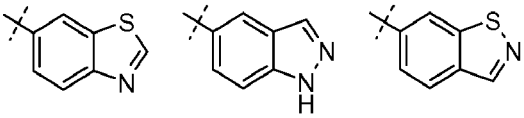


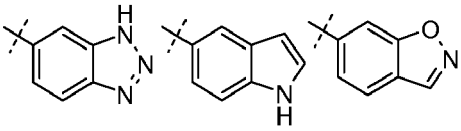


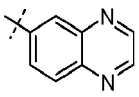










and  .

[0096] In a further embodiment N is provided at least one compound of any one of embodiments A to M, and/or at least one pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen and C_1-C_6 alkyl or R^2 and R^3, together with the carbon to which they are attached, form a 3-membered cycloalkyl.

[0097] In a further embodiment O is provided at least one compound of any one of embodiments A to N, and/or at least one pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen.

[0098] In a further embodiment P is provided at least one compound of any one of embodiments A to O, and/or at least one pharmaceutically acceptable salt thereof, wherein R^4 is aryl optionally substituted with one or more groups selected from lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, $-C(O)OR^{11}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, $-OC(O)R^{11}$, $-NR^{13}C(O)R^{11}$,$-NR^{13}S(O)_nR^{12}$, $-NR^{13}S(O)_nNR^{13}R^{14}$, $-NR^{13}C(O)OR^{12}$, and $-NR^{13}C(O)NR^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryloxy optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

aryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy,

heteroaryl optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$ -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$.

[0099] In a further embodiment Q is provided at least one compound of any one of embodiments A to O, and/or at least one pharmaceutically acceptable salt thereof, wherein R^4 is heterocycle optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$.

[0100] In a further embodiment R is provided at least one compound of embodiment Q, and/or at least one pharmaceutically acceptable salt thereof, wherein R^4 is selected from pyrrolidin-1-yl, piperidin-1-yl, tetrahydro-2H-pyran-4-yl, morpholin-4-yl, and 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl, each of which is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$.

[0101] In a further embodiment S is provided at least one compound of any one of embodiments A to O, and/or at least one pharmaceutically acceptable salt thereof, wherein R^4 is heteroaryl optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$.

[0102] In a further embodiment T is provided at least one compound of embodiment S, and/or at least one pharmaceutically acceptable salt thereof, wherein R^4 is selected from 1H-pyrazol-1-yl, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, 1H-imidazol-1-yl, 1H-imidazol-4-yl, oxazol-2-yl, thiazol-2-yl, isoxazol-3-yl, isoxazol-5-yl, 1H-pyrrol-2-yl, 1H-pyrrol-3-yl, thiophen-2-yl, thiophen-3-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl, each of which is optionally substituted with one or more groups selected from

lower alkyl optionally substituted with one or more groups selected from hydroxy, lower alkoxy, cyano, halo, -C(O)OR^{11}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, -OC(O)R^{11}, -NR^{13}C(O)R^{11},-NR^{13}S(O)$_n$$R^{12}$, -N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, and -N$R^{13}$C(O)N$R^{13}R^{14}$,

lower alkoxy optionally substituted with one or more groups selected from halo, hydroxy, and lower alkoxy,

heterocycle optionally substituted with one or more groups selected from lower alkyl, halo, hydroxy, and lower alkoxy, halo, cyano,-C(O)R^{11}, -C(O)OR^{11}, -N$R^{13}R^{14}$, -NR^{13}C(O)R^{11}, -NR^{13}S(O)$_n$$R^{12}$,-N$R^{13}$S(O)$_nNR^{13}R^{14}$, -N$R^{13}$C(O)O$R^{12}$, -N$R^{13}$C(O)N$R^{13}R^{14}$, -C(O)N$R^{13}R^{14}$, -S(O)$_n$$R^{12}$, and-S(O)$_nNR^{13}R^{14}$.

[0103] In a further embodiment U is provided at least one compound selected from compounds 1 to 332 and/or at least one pharmaceutically acceptable salt thereof.

[0104] In a further embodiment V is provided a composition comprising at least one compound of any one of embodiments A to U, and/or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

[0105] In a further embodiment W is provided a method of inhibiting the activity of c-Met comprising contacting the receptor with an effective amount of at least one compound of any one of embodiments A to U, and/or at least one pharmaceutically acceptable salt thereof.

[0106] In a further embodiment X is provided a method of treating cancer responsive to inhibition of c-Met comprising administering to a subject in recognized need thereof an effective amount of at least one compound of any one of embodiments A to U, and/or at least one pharmaceutically acceptable salt thereof.

[0107] In a further embodiment Y is provided a method for treating cancer responsive to inhibition of c-Met comprising:

administering to a subject in recognized need thereof an effective amount of at least one compound of any one of embodiments A to U, and/or at least one pharmaceutically acceptable salt thereof, and
administering to the subject an amount of an anti-neoplastic agent, wherein said anti-neoplastic agent is different from said at least one compound of any one of embodiments A to U, and/or at least one pharmaceutically acceptable salt thereof.

EXAMPLES

[0108] The examples below are intended to be purely exemplary and should not be considered to be limiting in any way. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric. All MS data were checked by agilent 6120 agilent 1100. All reagents, except intermediates, used in this invention are commercially available. All compound names except the reagents were generated by Chemdraw 8.0.

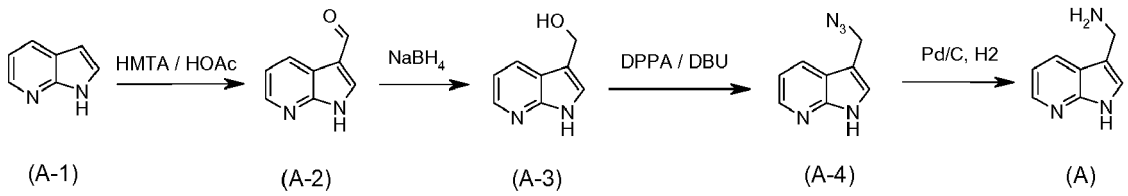
[0109] In the following examples, the abbreviations below are used:

AIBN	a,a'-azo-isobutyronnitrile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*t*-butyl-dicarbonate
i-$BuNO_2$	Isobutylnitrite
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMAP	4-Dimethylaminopyridine
DPPA	Diphenylphosphoryl azide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEA	*N,N*-diethylamine
ee	enantiomeric excess
Et_3N	triethylamine
h	hour
HATU	O-(7-Azabenzotriazol-1-yl)-*N,N,N,N*-tetra-methyluronium hexafluorophosphate
HMTA	Hexamethylenetetramine
HOAc	acetic acid
Lawesson's reagent	2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane
mL	milliliter(s)
min	minute(s)
MeOH	methanol
MsCl	methanesulfonyl chloride
NBS	*N*-Bromosuccinimide
$Pd(dppf)Cl_2$	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(PPh3)_4$	Tetrakis(triphenylphosphine)palladium(0)
PPh_3	Triphenylphosphine
THF	tetrahydrofuran
$Ti(i\text{-}OPr)_4$	Titanium(IV) isopropoxide
Xantphos	9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

Synthesis of amine ($NH_2CR^1R^2R^3$ in scheme I and II):

Intermediate A:

[0110]



1H-Prrolo[2,3-b]pyridine-3-carbaldehyde (A-2)

[0111] To a solution of 1H-pyrrolo[2,3-b]pyridine **(A-1)** (7.23 g, 61.2 mmol) in acetic acid (20 mL) and water (40 mL) was added HMTA (9.42 g, 67.3 mmol). The reaction mixture was stirred at 120 °C for 6 h. It was cooled with an ice bath, and the resulting precipitate was collected and dried to afford the title compound (7.90 g) MS (m/z): 147 $(M+1)^+$.

(1H-Prrolo[2,3-b]pyridin-3-yl)methanol (A-3)

[0112] To a solution of 1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde **(A-2)** (5.0 g, 34.21 mmol) in EtOH (150 mL) was added $NaBH_4$ (1.30 g, 34.21 mmol). The reaction mixture was stirred at room temperature for 0.5 h. It was concentrated and purified by chromatography on silica gel to afford the title compound (5.0 g). MS (m/z): 149 $(M+1)^+$.

3-(Aidomethyl)-1H-pyrrolo[2,3-b]pyridine (A-4)

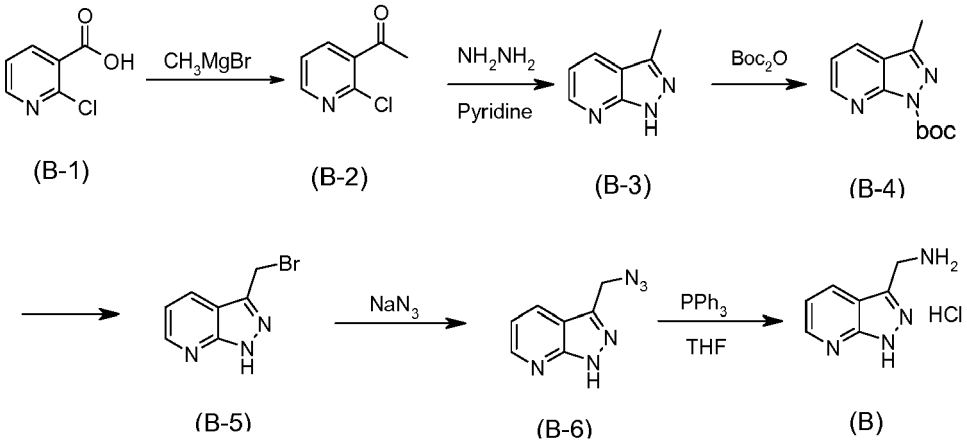
[0113] To a mixture of 1H-pyrrolo[2,3-b]pyridin-3-yl)methanol **(A-3)** (1.0 g, 6.75 mmol) in anhydrous THF (50 mL) were added DPPA (3.71 g, 13.5 mmol) and DBU (0.821 g, 5.4 mmol) respectively. It was refluxed under N_2 for 6 h, and then concentrated under vacuo. The resulting residue was dissolved in EtOAc (50 mL), washed with brine, dried over sodium sulfate and concentrated under vacuo, to obtain the crude product. The crude product was purified by chromatography on silica gel to afford the title compound (0.587 g). MS (m/z): 174 $(M+1)^+$.

(1 H-Prrolo[2,3-b]pyridin-3-yl)methanamine (A)

[0114] To a mixture of 3-(azidomethyl)-1H-pyrrolo[2,3-b]pyridine (**A-4**) (1.50 g, 8.63 mmol) in EtOAc (150 mL) was added 10% Pd/C (1.10 g). The resulting reaction mixture was stirred under one atmosphere of H_2 at room temperature for 3 h. The mixture was filtered, and the filtrate was concentrated to afford the title compound (1.15 g).

Intermediate B:

[0115]



1-(2-Cloropyridin-3-yl)ethanone (B-2)

[0116] To a solution of 2-chloronicotinic acid **(B-1)** (7.88 g, 50.0 mmol) in THF (**100 mL**) was added methyl magnesium bromide (42 mL, 3M ethyl ether solution) dropwise under 0°C. Upon completion of the addition, the reaction mixture was

stirred at 0 °C for 0.5 h and then at room temperature overnight. The reaction mixture was added into ice/water (150 mL), and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the title compound 1-(2-chloropyridin-3-yl)ethanone **(B-2).** MS (m/z): 156 $(M+1)^+$.

3-Mthyl-1H-pyrazolopyrrolo[3,4-b]pyridine (B-3)

[0117] A solution of 1-(2-chloropyridin-3-yl)ethanone **(B-2)** (6 g, 38.6 mmol) and hydrazine (85%, 9.1 g, 154.4 mmol) in pyridine (80 mL) was stirred under reflux overnight. The mixture was cooled to room temperature, concentrated, diluted with water (80 mL) and then extracted with ethyl acetate (100 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuo. The resulting residue was used for the next step without furtuer purification. MS (m/z): 134 $(M+1)^+$.

tert-Btyl 3-methyl-1H-pyrazolo[3,4-b]pyridine-1-carboxylate (B-4)

[0118] To a solution of 3-methyl-1H-pyrazolo[3,4-b]pyridine **(B-3)** in EtOAc (300 mL) were added $(Boc)_2O$ (16.4 g, 75 mmol), DMAP (610 mg, 5 mmol), and Et_3N (10 g, 100 mmol). The reaction mixture was stirred at room temperature overnight. Solvent was removed in vacuo, and the residue was purified by chromatography on silica gel to afford the title compound (5.3 g, 45.5% by two steps). MS (m/z): 134.

3-(Bomomethyl)-1H-pyrazolo[3,4-b]pyridine (B-5)

[0119] To a solution of tert-butyl 3-methyl-1H-pyrazolo[3,4-b]pyridine-1-carboxylate **(B-4)** (699 mg, 3 mmol) in CCl_4 (15 mL) were added NBS (641 mg, 3.6 mmol) and AIBN (70 mg, 0.3 mmol). The reaction mixture was stirred under reflux overnight and then filtered. The filtrate was washed with saturated aqueous Na_2CO_3 (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford the crude product. The crude product was used for next step without further purification. MS (m/z): 212 $(M+1)^+$.

3-(Aidomethyl)-1H-pyrazolo[3,4-b]pyridine (B-6)

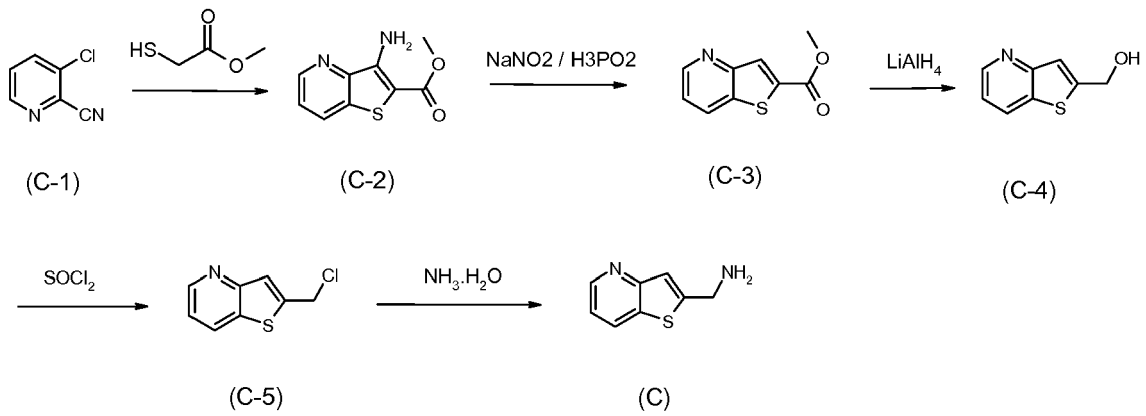
[0120] A mixture of 3-(bromomethyl)-1H-pyrazolo[3,4-b]pyridine **(B-5)** and NaN_3 (390 mg, 6 mmol) in DMF (6 mL) was stirred at 80°C for 1.5 h. After the mixture was cooled to room temperature, water (25 mL) was added. The resulting mixture was extracted with ethyl acetate (40 mLx3). The combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. Solvent was removed in vacuo, and the residue was purified by chromatography on silica gel. A solid was obtained (152 mg, 29.1% by two steps).

(1H-Pzolo[3,4-b]pyridin-3-yl)methanaminium chloride (B)

[0121] A mixture of 3-(azidomethyl)-1H-pyrazolo[3,4-b]pyridine **(B-6)** (152 mg, 0.87 mmol), PPh_3 (465 mg, 1.74 mmol) and 1 mL of NH_4OH in THF (20 mL) was stirred at room temperature overnight. The solution was concentrated, and the resulting residue was dissolved in ethyl acetate. The solution was treated with 2M HCl, which resulted in precipitates. The precipitates were collected by filtration to afford the title compound (121 mg). MS (m/z): 149 $(M+1)^+$.

Intermediate C:

[0122]



Methyl 3-aminothieno[3,2-b]pyridine-2-carboxylate (C-2)

[0123] To a mixture of 3-chloropyridine-2-carbonitrile **(C-1)** (1.01 g, 7.29 mmol) and K_2CO_3 (1.10 g, 7.96 mmol) in DMF (10 mL) and water (1 mL) was added methyl thioglycolate (0.709 mL, 7.93 mmol) dropwise. The reaction mixture was stirred at 40 °C for 3h. The mixture was quenched with cold water (70 mL) and placed on ice to enhance precipitation. The precipitate was collected by filtration to afford the title compound. MS (m/z): 209 $(M+1)^+$.

Methyl thieno[3,2-b]pyridine-2-carboxylate (C-3)

[0124] To a solution of methyl 3-aminothieno[3,2-b]pyridine-2-carboxylate **(C-2)** (930 mg, 4.47 mmol) in hypophosphorous acid (35 mL) chilled in an ice bath was added sodium nitrite (620 mg, 8.98 mmol) in a minimal amount of water. The reaction mixture was stirred for 3h in an ice bath, and then the pH was adjusted to about 7.0 with 30% aqueous sodium hydroxide solution. The resulting mixture was extracted with EtOAc. The combined organic layers were dried and concentrated to afford the title compound. MS (m/z): 194 $(M+1)^+$.

Thieno[3,2-b]pyridin-2-ylmethanol (C-4)

[0125] To a solution of methyl thieno[3,2-b]pyridine-2-carboxylate **(C-3)** (600 mg, 3.1 mmol) in 30 mL of anhydrous THF at 0 °C was added $LiAlH_4$ (472 mg, 12.4 mmol) in anhydrous THF (25 mL) dropwise over 20 mins. The reaction mixture was stirred at 0 °C for 30 mins. MeOH was added and the resulting mixture was purified by chromatography to afford the title compound. MS (m/z): 166 $(M+1)^+$.

2-(Cloromethyl)thieno[3,2-b]pyridine (C-5)

[0126] To a solution of thieno[3,2-b]pyridin-2-ylmethanol **(C-4)** (17 mg, 0.1 mmol) in anhydrous dichloromethane (10 mL) was added $SOCl_2$ (120 mg). After the mixture was stirred at room temperature for 2 hours, it was concentrated and used for the next step without further purification. MS (m/z): 184 $(M+1)^+$.

Thieno[3,2-b]pyridin-2-ylmethanamine (C)

[0127] 2-(Chloromethyl)thieno[3,2-b]pyridine **(C-5)** (183 mg, 1 mmol) was dissolved in NH_3/methanol (7 N, 10 mL). The resulting mixture was stirred at 50 °C for 16 hours and concentrated. The residue was purified by chromatography. MS (m/z): 165 $(M+1)^+$.

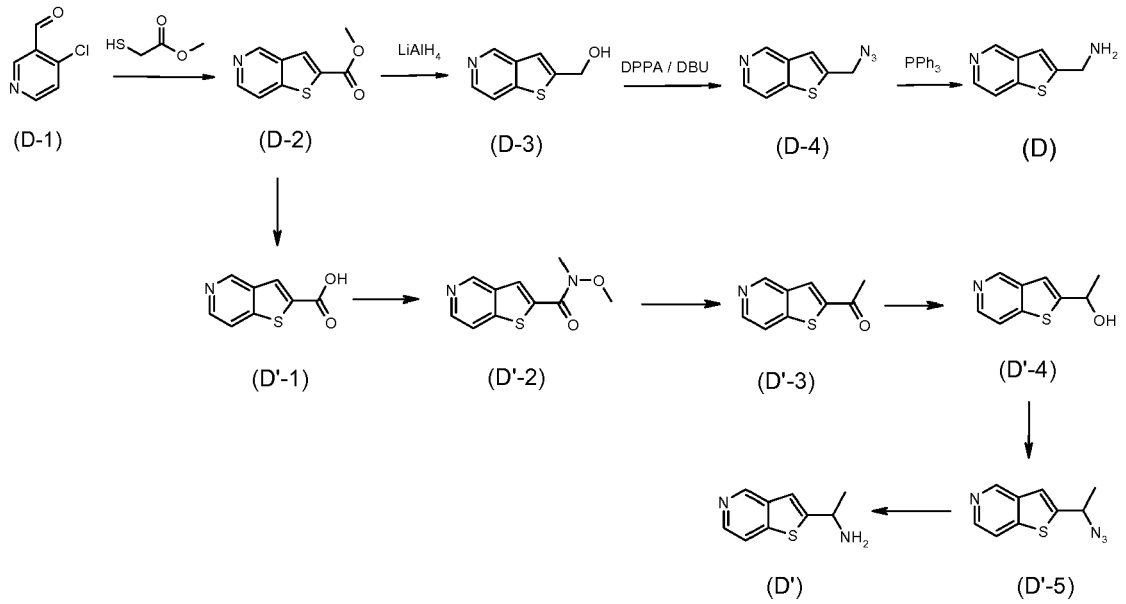
Intermediates D and D'

Methyl thieno[3,2-c]pyridine-2-carboxylate (D-2)

[0128] To a solution of 4-chloropyridine-3-carboxaldehyde **(D-1)** (1.4 g, 10 mmol) dissolved in DMF (10 mL) and water (1 mL) were added K_2CO_3 (1.66 g, 12 mmol) and methyl thioglycolate (1.07 mL, 12 mmol) portion-wise. The reaction mixture was stirred at 45°C overnight and then quenched with cold water. The flask was placed on ice to enhance precipitation. The precipitate was collected by filtration and air-dried to afford the title compound (1.23 g). MS (m/z): 194 $(M+1)^+$.

Thieno[3,2-c]pyridin-2-ylmethanol (D-3)

[0129] To a solution of methyl thieno[3,2-c]pyridine-2-carboxylate **(D-2)** (15 g, 77.6 mmol) in anhydrous THF (250 mL) was added $LiAlH_4$ (4.42 g, 116.4 mmol) in portions at 0°C. The suspension was stirred at 0°C for 1h and then quenched by adding saturated aqueous NH_4Cl and filtered. The filtrate was washed with brine and concentrated. The residue was used in the next step without any further purification (10.3 g).



2-(Azidomethyl)thieno[3,2-c]pyridine (D-4)

[0130] To a flame-dried round-bottomed flask containing thieno[3,2-c]pyridin-2-ylmethanol (D-3) (3.2 g, 19.4 mmol) was added DPPA (8 g, 6.26 mL, 29.1 mmol) in THF (50 mL). The reaction mixture was stirred for 5 mins and cooled to 0°C, followed by adding DBU (4.43 g, 4 mL, 29.1 mmol) via syringe. The mixture was allowed to stir at reflux overnight. The reaction was then partitioned between water and ethyl ether. The aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified by chromatography to afford the product (3.27 g). MS (m/z): 191 $(M+1)^+$.

Thieno[3,2-c]pyridin-2-ylmethanamine hydrochloride (D)

[0131] To a solution of 2-(azidomethyl)thieno[3,2-c]pyridine **(D-4)** (3 g, 15.8 mmol) in anhydrous THF (50 mL) was added Ph_3P (8.27 g, 31.5 mmol), followed by NH_4OH (2 mL). The solution was stirred at room temperature overnight. Solvent was removed, and the residue was purified by chromatography to afford the title compound (2.5 g).

Thieno[3,2-c]pyridine-2-carboxylic acid (D'-1)

[0132] To a solution of methyl thieno[3,2-c]pyridine-2-carboxylate **(D-2)** (12 g, 62.1 mmol) in MeOH (150 mL) and H_2O (15 mL) was added $LiOH.H_2O$ (5.2 g, 124.2 mmol). The solution was stirred at room temperature overnight, and then acidified with 1N aqueous HCl. The resulting white precipitate was collected by filtration and air-dried to afford the title compound. MS (m/z): 179 $(M)^+$.

***N*-Methoxy-*N*-methylthieno[3,2-c]pyridine-2-carboxamide (D'-2)**

[0133] To a solution of thieno[3,2-c]pyridine-2-carboxylic acid **(D'-1)** (11.5 g, 64.2 mmol) in DCM (200 mL) and DMF (50 mL) was added Et_3N (19.5 g, 26.6 mL, 192.6 mmol) followed by HATU (36.6 g, 96.3 mmol). The reaction solution was stirred at room temperature for 20 mins, and then treated with *N,O*-dimethylhydroxylamine hydrochloride (6.9 g, 70.6 mmol). Stirring continued overnight at room temperature. The solvent was removed.The residue was dissolved in EtOAc and washed with water and brine. The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel to give the title compound. MS (m/z): 223 $(M+1)^+$.

1-(Thieno[3,2-c]pyridin-2-yl)ethanone (D'-3)

[0134] To a solution of *N*-methoxy-*N*-methylthieno[3,2-c]pyridine-2-carboxamide **(D'-2)** (11.1 g, 50 mmol) in anhydrous THF (150 mL) was added MeMgBr (3M in ethyl ether, 25 mL, 75 mmol) at 0°C under N_2. The reaction mixture was allowed to warm to the ambient temperature and stirred overnight. Saturated aqueous NH_4Cl solution was added to quench the reaction. The resulting mixture was then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford the title compound. MS (m/z): 178 $(M+1)^+$.

1-(Thieno[3,2-c]pyridin-2-yl)ethanol (D'-4)

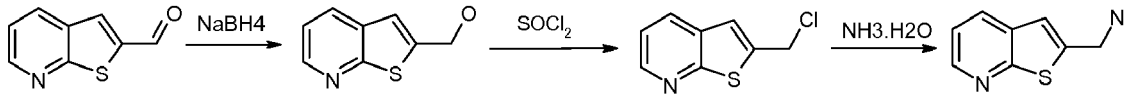
[0135] To a solution of 1-(thieno[3,2-c]pyridin-2-yl)ethanone **(D'-3)** (3.5 g, 1 mmol) in anhydrous THF (50 mL) was added $LiAlH_4$ (1.13 g, 1.5 mmol) in portions at 0°C. The suspension was stirred under this temperature for 1h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and filtered. The filtrate was washed with brine, concentrated, and then used for the next step without any further purification.

1-(Thieno[3,2-c]pyridin-2-yl)ethanamine (D')

[0136] **Intermediate D'** was prepared from 1-(thieno[3,2-c]pyridin-2-yl)ethanol **(D'-4)** following similar procedures for synthesizing **intermediate A** from **A-3,** as described above.

Intermediate E:

[0137]



Thieno[2,3-b]pyridin-2-ylmethanol (E-2)

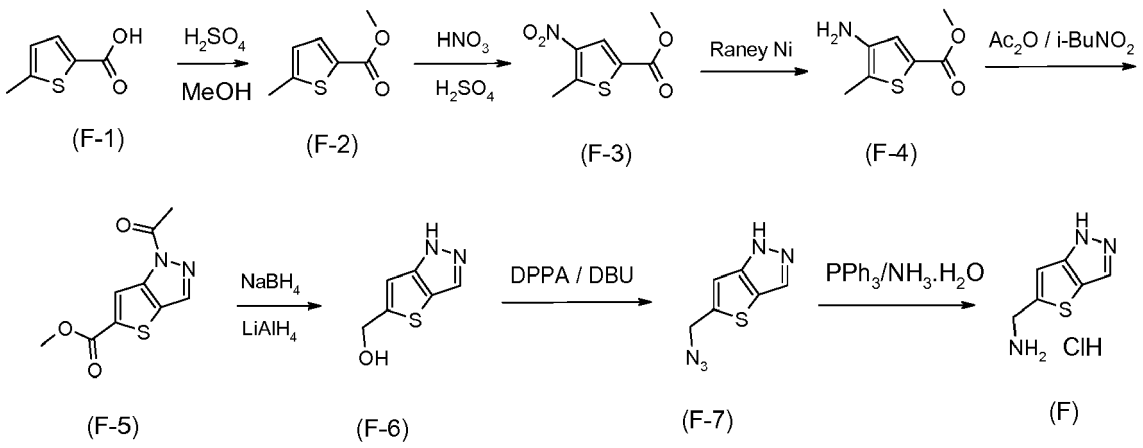
[0138] **E-2** was prepared from thieno[2,3-b]pyridine-2-carbaldehyde **(E-1)** following similar procedures for synthesizing **intermediate A-3** from **A-2,** as described above. MS (m/z): 166 $(M+1)^+$.

Thieno[2,3-b]pyridin-2-ylmethanamine(E)

[0139] **Intermediate E** was prepared from thieno[2,3-b]pyridine-2-ylmethanol **(E-2)** following similar procedures for synthesizing **intermediate C** from **C-4,** as described above. MS (m/z): 165 $(M+1)^+$.

Intermediate F:

[0140]



Methyl 5-methylthiophene-2-carboxylate (F-2)

[0141] To a solution of 5-methylthiophene-2-carboxylic acid **(F-1)** (14.0 g, 0.1 mol) in MeOH (250 mL) was added concentrated H_2SO_4 (2.0 mL). The reaction mixture was stirred under reflux for 60h. The solvent was removed in vacuo. Ethyl acetate was added to dilute the reaction mixture. Then the organic solution was washed with a saturated aqueous Na_2CO_3 solution, and dried over Na_2SO_4. The solvent was removed to afford the title compound (13.4 g).

Methyl 5-methyl-4-nitrothiophene-2-carboxylate (F-3)

[0142] A solution of concentrated HNO_3 (7.2 mL, 111.5 mmol) in concentrated H_2SO_4 (20 mL) was added dropwise to the solution of methyl 5-methylthiophene-2-carboxylate **(F-2)** (13.4 g, 86.0 mmol) in concentrated H_2SO_4 (30 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 mins and poured into ice-water. The precipitate was filtered and washed with water. A solid was collected as the product (14.8 g).

Methyl 4-amino-5-methylthiophene-2-carboxylate (F-4)

[0143] To a solution of methyl 5-methyl-4-nitrothiophene-2-carboxylate **(F-3)** (14.8 g, 73.6 mmol) in MeOH/THF (1:1, 300 mL) was added Raney Ni. The reaction mixture was degassed and charged with hydrogen 3 times, and then stirred at room temperature for 36 h under 1 atmosphere of hydrogen. Raney Ni was filtered, and the filtrate was concentrated. The residue was treated with aqueous HCl (1 N, 150 mL) and filtered. The filtrate was treated with aqueous NaOH (1 N) to bring pH to about 8 to 9. Then the mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, and the solvent was removed to give the title compound (8.1 g).

Methyl 1-acetyl-1H-thieno[3,2-c]pyrazole-5-carboxylate (F-5)

[0144] To a solution of methyl 4-amino-5-methylthiophene-2-carboxylate **(F-4)** (5.1 g, 30 mmol) in toluene (120 mL) were added acetic anhydride (16.0 g, 0.12 mol) and potassium acetate (1.5 g, 15.1 mmol). The reaction mixture was stirred at 100 °C for 3h. After cooled to room temperature, the reaction mixture was treated with isobutyl nitrite (10.5 g, 90.0 mmol), and then stirred at 100°C overnight. Wate was added, and then the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography eluting with Pet/EtOAc=10/1 to afford the title compound (5.3 g) as the product.

(1H-Thieno[3,2-c]pyrazol-5-yl)methanol (F-6)

[0145] To a solution of methyl 1-acetyl-1H-thieno[3,2-c]pyrazole-5-carboxylate **(F-5)** (4.5 g, 20.0 mmol) in MeOH (30 mL) was slowly added $NaBH_4$ (836 mg, 22.0 mmol). The mixture was stirred at room temperature for 30 mins, and then concentrated. The residue was dissolved in anhydrous THF (80 mL) and then $LiAlH_4$ (1.5 g, 40.0 mmol) was slowly added at 0°C. The reaction mixture was stirred at 0°C for 30 min. Aqueous NH_4Cl solution was added dropwise to quench the reaction. The resulting mixture was filtered, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (2.9 g).

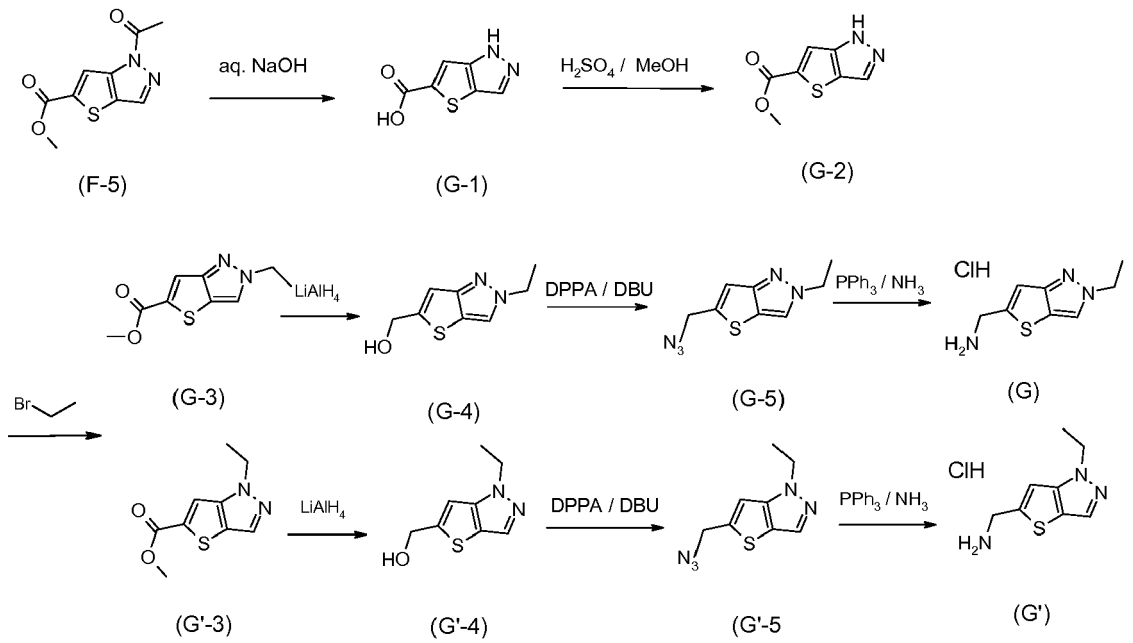
(1H-Thieno[3,2-c]pyrazol-5-yl)methanaminium chloride (F)

[0146] **Intermediate F** was prepared from (1H-thieno[3,2-c]pyrazol-5-yl)methanol **(F-6)** following similar procedures for synthesizing **intermediate D** from **D-3,** as described above.

Intermediate G and G':

1H-Thieno[3,2-c]pyrazole-5-carboxylic acid (G-1)

[0147] To a solution of methyl 1-acetyl-1H-thieno[3,2-c]pyrazole-5-carboxylate **(F-5)** (4.9 g, 21.8 mmol) in MeOH (15 mL) was added an aqueous KOH solution (6 N, 10 mL). The reaction mixture was stirred at room temperature for 2h, and then concentrated in vacuo. Aqueous HCl (6 N) was added to adjust pH to 5-6. The precipitates were collected by filtration to afford the title compound (3.0 g).



Methyl 1H-thieno[3,2-c]pyrazole-5-carboxylate (G-2)

[0148] To a solution of 1H-thieno[3,2-c]pyrazole-5-carboxylic acid **(G-1)** (3.0 g, 17.9 mmol) in MeOH (50 mL) was added concentrated H_2SO_4 (0.3 mL). The reaction mixture was stirred at reflux for 60 h. Solvent was removed in vacuo. Ethyl acetate was added to dilute the mixture. The mixture was washed with aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated in vacuo to afford the title compound (2.4 g).

Methyl 2-ethyl-2H-thieno[3,2-c]pyrazole-5-carboxylate (G-3) and Methyl 1-ethyl-1H-thieno[3,2-c]pyrazole-5-carboxylate (G'-3)

[0149] To a solution of methyl 1H-thieno[3,2-c]pyrazole-5-carboxylate **(G-2)** (760 mg, 4.2 mmol) in DMF (4 mL) were added bromoethane (915 mg, 8.3 mmol) and K_2CO_3 (1.7 g, 12.6 mmol). The reaction mixture was stirred at 110 °C for 3 h in a sealed tube. After cooled to room temperature, the mixture was concentrated and purified by chromatography to afford two products:

[0150] Methyl 2-ethyl-2H-thieno[3,2-c]pyrazole-5-carboxylate (351 mg) **(G-3).** MS (m/z): 211 $(M+1)^+$.

[0151] Methyl 1-ethyl-1H-thieno[3,2-c]pyrazole-5-carboxylate (272 mg) **(G'-3).** MS (m/z): 211 $(M+1)^+$.

(2-Ethyl-2H-thieno[3,2-c]pyrazol-5-yl)methanaminium chloride (G)

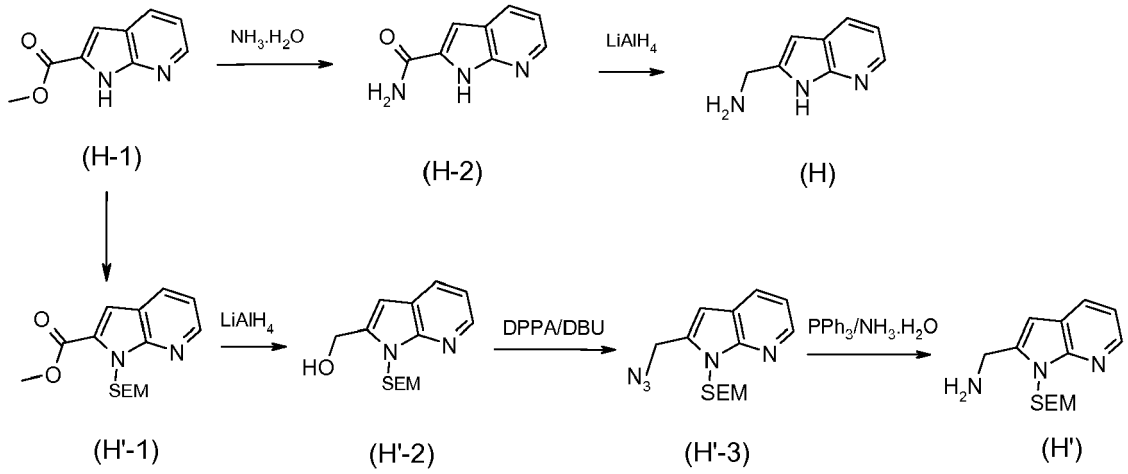
[0152] **Intermediate G** was prepared from methyl 2-ethyl-2H-thieno[3,2-c]pyrazole-5-carboxylate **(G-3)** following similar procedures for synthesizing **intermediate D** from **D-2,** as described above. MS (m/z): 182 $(M+1)^+$.

(1-Ethyl-1H-thieno[3,2-c]pyrazol-5-yl)methanamine chloride (G')

[0153] **Intermediate G'** was prepared from methyl 1-ethyl-1H-thieno[3,2-c]pyrazole-5-carboxylate **(G'-3)** following similar procedures for synthesizing **intermediate D** from **D-2,** as described above. MS (m/z): 182 $(M+1)^+$.

Intermediate H and H':

[0154]



1H-Pyrrolo[2,3-b]pyridine-2-carboxamide (H-2)

[0155] To a solution of methyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate **(H-1)** (880 mg, 5.0 mmol) in MeOH (2 mL) was added $NH_3.H_2O$ (6 mL). The reaction was heated at 80°C overnight. After being cooled to room temparature, the mixture was concentrated in vacuo to afford the title compound (805 mg) as a yellow solid, which was used for the next step without further purification. MS (m/z): 162 $(M+1)^+$.

(1 H-Pyrrolo[2,3-b]pyridin-2-yl)methanamine (H)

[0156] To a solution of 1H-pyrrolo[2,3-b]pyridine-2-carboxamide **(H-2)** (805 mg, 5.0 mmol) in dried THF (10 mL) at 0°C under 1 atm of N_2 was slowly added $LiAlH_4$ (570 mg, 15 mmol). The mixture was stirred at 80°C overnight. The mixture was then cooled to 0°C concentrated, and then purified by chromatography on silica gel to afford the title compound (720 mg). MS (m/z): 148 $(M+1)^+$.

Methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-^{1}H-pyrrolo[2,3-b]pyridine-2-carboxylate (H'-1)

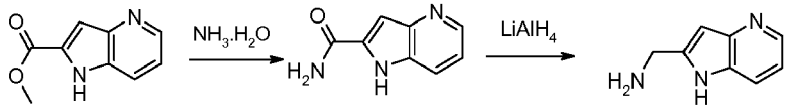
[0157] To a solution of methyl 1H-pyrrolo[2,3-b]pyrid1ine-2-carboxylate **(H-1)** (528 mg, 3 mmol) in dried THF (5 mL) at 0°C was added NaH (240 mg, 6 mmol). The reaction was stirred for 0.5 h under N_2, and then SEMCl (526 mg, 3 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. H_2O was added to quench the reaction. The resulting mixture was extracted with EtOAc. The oragnic layer was dried over Na_2SO_4, and concentrated to afford the title compound (750 mg), which was used for the next step without purification. MS (m/z): 307 $(M+1)^+$.

(1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)methanamine (H')

[0158] **Intermediate H'** was prepared from methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-^{1}H-pyrrolo[2,3-b]pyridine-2-carboxylate **(H'-1)** following similar procedures for synthesizing **intermediate D** from **D-2,** as described above. MS (m/z): 278 $(M+1)^+$.

Intermediate I:

[0159]



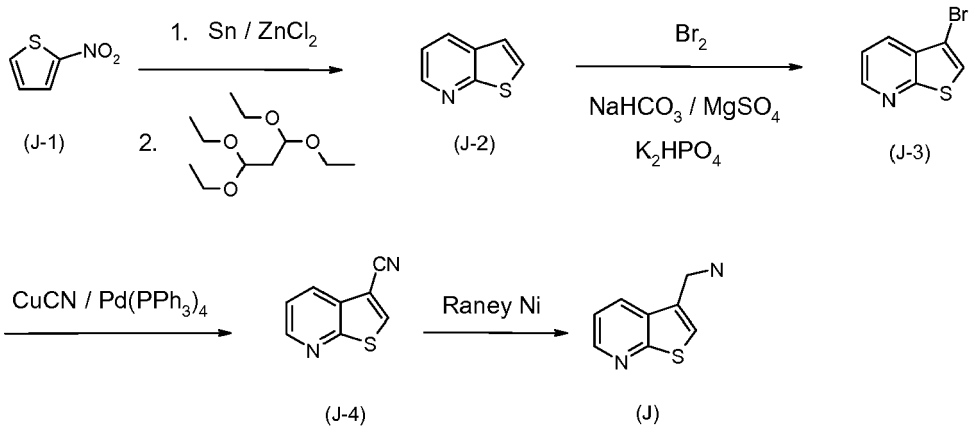
(I-1) (I-2) (I)

(1H-Pyrrolo[3,2-b]pyridin-2-yl)methanamine (I)

[0160] **Intermediate** I was prepared from methyl 1H-pyrrolo[3,2-b]pyridine-2-carboxylate **(1-1)** following similar procedures for synthesizing **intermediate** H, as described above. MS (m/z): 148 $(M+1)^+$.

Intermediate J:

[0161]



(J-1) (J-2) (J-3) (J-4) (J)

Thieno[2,3-b]pyridine (J-2)

[0162] To a vigorously stirred mixture of of 2-nitrothiophene **(J-1)** (13 g , 0.1 mol) and concentrated hydrochloric acid (195 mL) was added tin (25 g) at 0°C. After most of the tin was dissolved, EtOH (70 mL) and anhydrous $ZnCl_2$ (6 g) were added. The mixture was heated to 85°C, and then treated with malonaldehyde bis(diethyl acetal) (17.2 g , 0.078 mol) in EtOH (30 mL). The resulting reaction was maintained at 85 °C for 1 h, then poured onto ice (100 g), basified with $NH_3.H_2O$, and extracted with DCM (75 mLx3). The combined organic layers were concentrated and purified by chromatography on silica gel to give the title compound. MS (m/z): 135 $(M)^+$.

3-Bromothieno[2,3-b]pyridine (J-3)

[0163] Bromine (2.08 g ,13 mmol) was dropwise added to a mixture of thieno[2,3-b]pyridine (J-2) (1.35 g , 10 mmol), dipotassium monohydrogen orthophosphate (940 mg, 5.4 mmol), sodium bicarbonate (840 mg 10 mmol), and magnesium sulfate (2.0 g, 16.7mmol) in chloroform (40 mL) which has been stirred at reflux for 16 h, the resulting mixture was stirred under reflux for 24 h, then filtered and washed with DCM. The filtrate was concentrated, and purified by chromatography. MS (m/z): 214 $(M+1)^+$.

Thieno[2,3-b]pyridine-3-carbonitrile (J-4)

[0164] To a stirred solution of 3-bromothieno[2,3-b]pyridine **(J-3)** (107 mg, 0.5 mmol) and CuCN (60 mg , 0.67 mmol) in anhydrous DMF(4 mL) was added $Pd(PPh_3)_4$ (57 mg, 0.05 mmol). The reaction was degassed with nitrogen and stirred at 120 °C for 5 h. Then the cooled mixture was concentrated and purified by chromatography to afford the title compound. MS (m/z): 161 $(M+1)^+$.

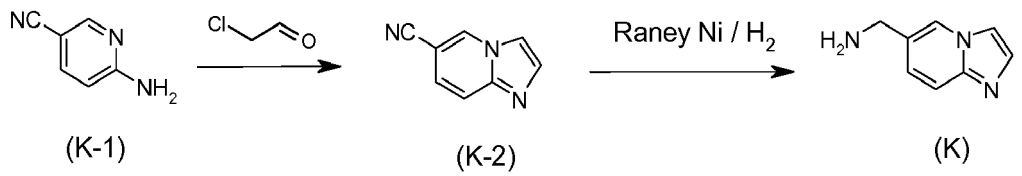
Thieno[2,3-b]pyridin-3-ylmethanamine (J)

[0165] To a solution of thieno[2,3-b]pyridine-3-carbonitrile **(J-4)** (320 mg, 2 mmol) in NH_3.EtOH (25 mL) was added

Ranye/Ni (about 300 mg). The reaction was degassed with hydrogen and stirred at room temperature for 2 h. Then the mixture was filtered, and the filtrate was concentrated to give the title compound, which was used for next step without purification. MS (m/z): 165 $(M+1)^+$.

Intermediate K:

[0166]



H-Imidazo[1,2-a]pyridine-6-carbonitrile (K-2)

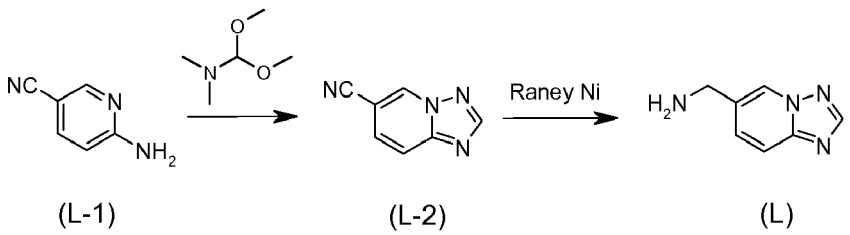
[0167] To a solution of 6-aminonicotinonitrile **(K-1)** (4.0 g, 33.6 mmol) in anhydrous EtOH (160 mL) was added 2-chloroacetaldehyde (40% in H_2O, 27.5 mL, 168 mmol). The reaction was refluxed for 4h, and then concentrated. The resulting residue was dissolved in water and adjusted to pH > 7 with a saturated $NaHCO_3$ solution. The precipitate was collected and dried to afford the title compound (4.80 g).

(H-Imidazo[1,2-a]pyridin-6-yl)methanamine (K)

[0168] **Intermediate K** was prepared from H-imidazo[1,2-a]pyridine-6-carbonitrile **(K-2)** following similar procedures for synthesizing **intermediate J** from **J-4,** as described above.

Intermediate L:

[0169]



[1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile (L-2)

[0170] To a stirred solution of 6-aminonicotinonitrile **(L-1)** (8.7 g, 73 mmol) in DMF (35 mL) was added *N,N*-dimethylformamide dimethyl acetal (35 mL, 294 mmol). The reaction mixture was heated to 130°C overnight. After cooled to room temperature, the volatiles were removed under reduced pressure to afford the desired intermediate *N'*-(5-cyanopyridin-2-yl)-*N,N*-dimethylformamidine.

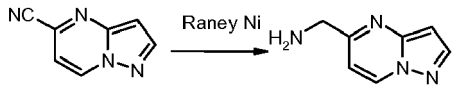
[0171] To an ice-cooled, stirred solution of the above product in methanol (200 mL) and pyridine (11.5 mL, 143 mmol) was added hydroxylamine-O-sulfonic acid (11.3 g, 100 mmol). The reaction mixture was allowed to warm to room temperature and was stirred overnight. Then the volatiles were removed under reduced pressure, and the residue was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by chromatography on silica gel to give the title compound (5.5 g). MS (m/z): 145 $(M+1)^+$.

[1,2,4]Triazolo[1,5-a]pyridin-6-ylmethanamine (L)

[0172] **Intermediate L** was prepared from [1,2,4]triazolo[1,5-a]pyridine-6-carbonitrile **(L-2)** following similar procedures for synthesizing **intermediate J** from **J-4,** as described above .

Inermediate M:

[0173]



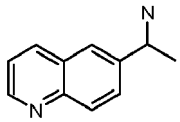
(M-1) (M)

Pyrazolo[1,5-a]pyrimidin-5-ylmethanamine (M)

[0174] **Intermediate M** was prepared from pyrazolo[1,5-a]pyrimidine-5-carbonitrile **(M-1)** following similar procedures for synthesizing **intermediate J** from **J-4,** as described above . MS (m/z): 149 $(M+1)^+$.

Intermediate N:

[0175]

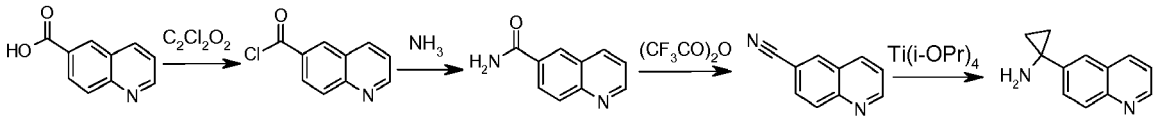


(N)

[0176] **Intermediate N** was prepared from quinoline-6-carboxylic acid as described in US2007/ 0265272.

Intermediate O:

[0177]



(O-1) (O-2) (O-3) (O-4) (O)

Quinoline-6-carbonyl chloride (O-2)

[0178] To a mixture of quinoline-6-carboxylic acid **(O-1)** (2.0 g, 11.5 mmol) in CH_2Cl_2 (250 mL) was added 3 drops of DMF at 0°C, followed by oxalyl chloride (7.3 g, 57.5 mmol) dropwise. The resulting reaction was stirred at room temperature overnight, and then concentrated to afford the title compound (2.2 g).

Quinoline-6-carboxamide (O-3)

[0179] To a solution of quinoline-6-carbonyl chloride **(O-2)** (2.2 g, 10.5 mmol) in THF (100 mL) was added ammonia (5 mL) at 0°C. The mixture was stirred at room temperature for 1 h, then concentrated and washed with water (15 mL) to afford the title compound (1.5 g). MS (m/z): 173 $(M+1)^+$.

Quinoline-6-carbonitrile (O-4)

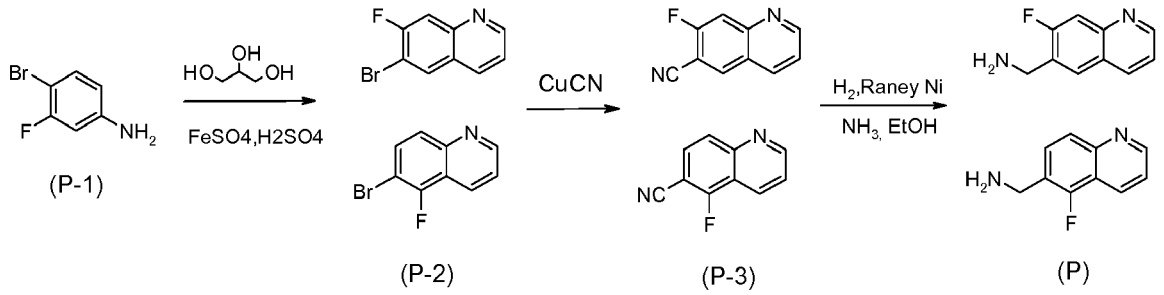
[0180] To a mixture of quinoline-6-carboxamide **(O-3)** (1.2 g, 7.2 mmol) and triethylamine (2.2 g, 21.8 mmol) in DCM (50 mL) at 0°C was added trifluoroacetic acid anhydride (1.9 g, 8.9 mmol). The reaction was stirred for 10 mins at 0°C, then quenched with water. The resulting mixture was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to afford the desired title compound (1.0 g). MS (m/z): 154 $(M)^+$.

1-(Quinolin-6-yl)cyclopropanamine (O)

[0181] Ethylmagnesium bromide (7.7 mmol, 3 M in ethyl ether) was added to a solution of quinoline-6-carbonitrile **(O-4)** (540 mg, 3.5 mmol) and $Ti(Oi\text{-}Pr)_4$ (3.9 mmol, 1.16 mL) in Et_2O (15 mL) at -70°C. The resulting yellow solution was stirred for 10 mins, warmed to room temperature over 1.5h, and then was treated with $BF_3.OEt_2$ (7 mmol, 0.88 mL). The resulting mixture was stirred for 1h. Then 1N aqueous HCl (11 mL) and ethyl ether (40 mL) were added, followed by NaOH (10% aq, 30 mL). The mixture was extracted with ethyl ether. The combined ethyl ether layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the crude title compound, which was used for the next step without further purification. MS (m/z): 185 $(M+1)^+$.

Intermediate P

[0182]



6-Bromo-7-fluoroquinoline and 6-bromo-5-fluoroquinoline (P-2)

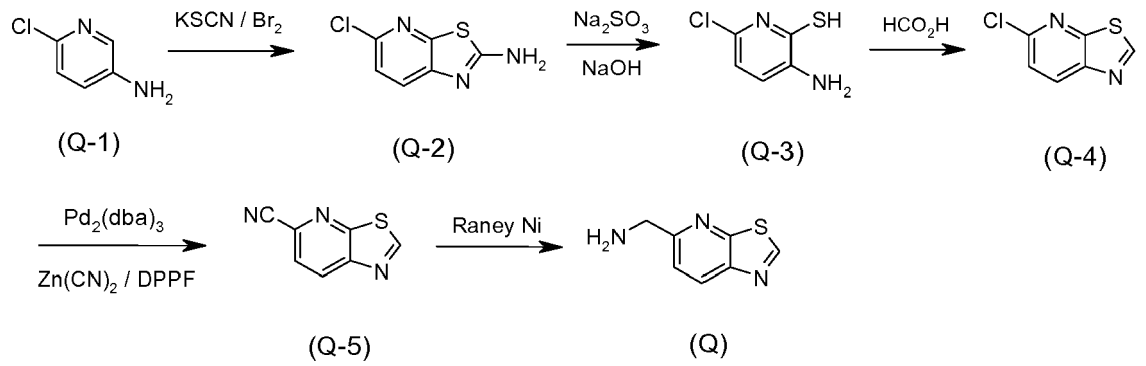
[0183] A mixture of 4-bromo-3-fluoroaniline **(P-1)** (5.7 g, 30 mmol), propane-1,2,3-triol (11.04 g, 120 mmol), $FeSO_4.7H_2O$ (1.92 g, 6.9 mmol), and nitrobenzene (2.22 g, 18 mmol) was stirred at room temperature for 10 mins, then concentrated H_2SO_4 (9.7 g, 9.9 mmol) was added. The resulting mixture was stirred at reflux for 7h. After cooling to room temperature, the reaction was poured into water, basified with $NH_3.H_2O$ to pH about 8, and extracted with DCM. The concentrated organic layer was purified by chromatography on silica gel (eluted with Pet/EtOAc=15/1) to afford the title compound mixture. 6.78 g. MS (m/z): 226 $(M+1)^+$.

(7-Fluoroquinolin-6-yl)methanamine and (5-fluoroquinolin-6-yl)methanamine (P)

[0184] These compounds were prepared from 6-bromo-7-fluoroquinoline and 6-bromo-5-fluoroquinoline **(P-2)** following similar procedures for synthesizing **Intermediate J** from **J-3,** as described above. MS (m/z): 177 $(M+1)^+$.

Intermediate Q:

[0185]



5-Chlorothiazolo[5,4-b]pyridin-2-amine (Q-2)

[0186] To glacial acetic acid (125 mL) pre-cooled to 5°C were added potassium thiocyanate (93 g, 961 mmol) and 6-chloropyridin-3-amine **(Q-1)** (15 g, 117 mmol). The mixture was placed in a freezing mixture of ice and salt and stirred, while 10 mL of bromine in glacial acetic acid (30 mL) was added from an addition funnel at such a rate that the temperature never rose beyond 0°C. After all the bromine had been added, the solution was stirred for an additional 2h at 0°C and at room temperature overnight. Water (60 mL) was added quickly, and the slurry maintained at 90°C was filtered hot. The orange filter cake was placed in the reaction flask. Glacial acetic acid (60 mL) was added to the flask. The mixture in the flask was maintained at 85°C was filtered hot once again. The combined filtrates were cooled and neutralized with concentrated ammonia solution to pH 6. A precipitate was collected as the title compound (19 g). MS (m/z): 186 $(M+1)^+$.

3-Amino-6-chloropyridine-2-thiol (Q-3)

[0187] 5-Chlorothiazolo[5,4-b]pyridin-2-amine **(Q-2)** (19 g,103 mmol) containing sodium sulfite (2 g) was refluxed in 20% aqueous sodium hydroxide solution (150 mL) overnight. The solids were completely dissolved after 1h, then cooled to room temperature. The solution was neutralized with formic acid. A precipitate was collected by filtration as the title compound (16.4 g).

5-Chlorothiazolo[5,4-b]pyridine (Q-4)

[0188] 3-Amino-6-chloropyridine-2-thiol **(Q-3)** (16.4 g, 103 mmol) in formic acid (80 mL) was refluxed at 110°C for 2h. The reaction mixture was cooled and neutralized with concentrated ammonia to pH 7. A precipitate was collected by filtration as the title compound (14.5 g). MS (m/z): 171 $(M+1)^+$.

Thiazolo[5,4-b]pyridine-5-carbonitrile (Q-5)

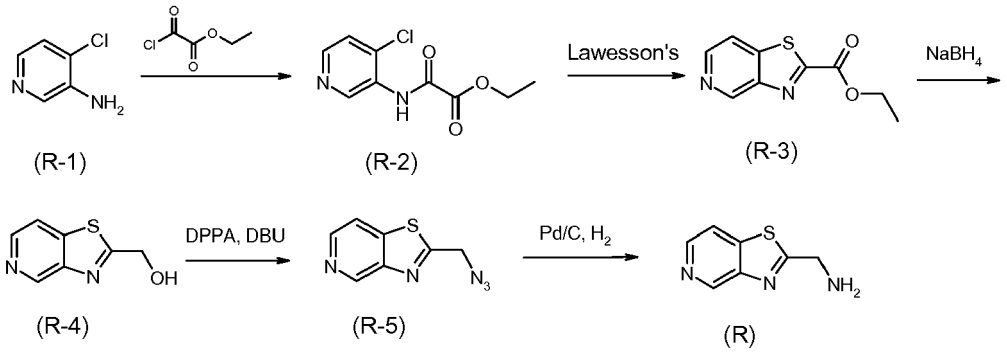
[0189] To an 8 mL screw cap vial equipped with a magnetic stirring bar were added 5-chlorothiazolo[5,4-b]pyridine **(Q-4)** (460 mg, 2.7 mmol), $Zn(CN)_2$ (316 mg, 2.7 mmol), $Pd_2(dba)_3$ (123 mg, 0.13 mmol), DPPF (150 mg, 0.27 mmol) and DMF (5 mL, wet, containing 1% of H_20). The vial was flushed with nitrogen, then sealed with the screw cap. The mixture was stirred at 120°C for overnight, and then concentrated in vacuo. The resulting residue was purified by chromatography on silica gel to give the title compound (151 mg).

Thiazolo[5,4-b]pyridin-5-ylmethanamine (Q)

[0190] **Intermediate Q** was prepared from thiazolo[5,4-b]pyridine-5-carbonitrile **(Q-5)** following similar procedures for synthesizing **intermediate J** from **J-4,** as described above . MS (m/z): 166 $(M+1)^+$.

Intermediate R:

[0191]



Ethyl 2-(4-chloropyridin-3-ylamino)-2-oxoacetate (R-2)

[0192] To a solution of 4-chloropyridin-3-amine **(R-1)** (5 g, 38.9 mmol) in THF (100 mL) was added Et_3N (4.72 g, 6.5 mL, 46.7 mmol), followed by ethyl 2-chloro-2-oxoacetate (5.84 g, 4.78 mL, 42.8 mmol) in THF (5 mL) dropwise at 0°C.

The resulting mixture was stirred at room temperature for 1 h, and then concentrated in vacuo. The resulting residue was dissolved in EtOAc, and washed with aqueous saturated $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, and concentrated to give the title compound, which was used for the next step without further purification. MS (m/z): 229 $(M+1)^+$.

Ethyl thiazolo[4,5-c]pyridine-2-carboxylate (R-3)

[0193] A solution of ethyl 2-(4-chloropyridin-3-ylamino)-2-oxoacetate **(R-2)** (8 g, 35 mmol) and Lawesson's reagent (8.5 g, 21 mmol) in toluene (100 mL) was refluxed for 2h, and then concentrated in vacuo. The residue was purified by chromatography on silica gel to give the title compound. MS (m/z): 209 $(M+1)^+$.

Thiazolo[4,5-c]pyridin-2-ylmethanol (R-4)

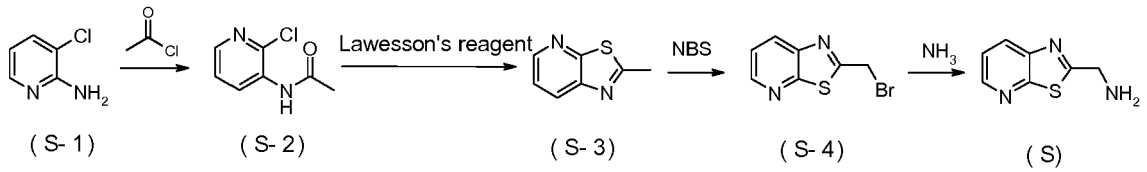
[0194] To a solution of ethyl thiazolo[4,5-c]pyridine-2-carboxylate **(R-3)** (5 g, 24 mmol) in ethanol (100 mL) was added $NaBH_4$ (0.9 g, 24 mmol) in portions at 0°C. The suspension was stirred at room temperature for 1h, and then concentrated. The resulting residue was dissolved in EtOAc, washed with water. The organic layer was separated, dried over Na_2SO_4, concentrated in vacuo and purified by chromatography on silica gel to give the title compound. MS (m/z): 167 $(M+1)^+$.

Thiazolo[4,5-c]pyridin-2-ylmethanamine (R)

[0195] **Intermediate R** was prepared from thiazolo[4,5-c]pyridin-2-ylmethanol **(R-4)** following similar procedures for synthesizing intermediate **A** from **A-3,** as described above . MS (m/z): 165 $(M)^+$.

Intermediate S:

[0196]



***N*-(2-Chloropyridin-3-yl)acetamide (S-2)**

[0197] To a mixture of 3-chloropyridin-2-amine **(S-1)** (12.8 g, 100 mmol) and Et_3N (3 mL) in dried DCM (50 mL) was added acetyl chloride (8 mL) dropwise. The reaction was stirred at room temperature overnight, then adjusted to pH about 7 with an aqueous $NaHCO_3$ solution, and extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to afford the title compound (17.1 g). MS (m/z): 171.6 $(M+1)^+$.

2-Methylthiazolo[5,4-b]pyridine (S-3)

[0198] **Intermediate S-3** was prepared from *N*-(2-chloropyridin-3-yl)acetamide **(S-2)** following similar procedures for synthesizing **intermediate R-3** from **R-2,** as described above . MS (m/z): 151.6 $(M+1)^+$.

2-(Bromomethyl)thiazolo[5,4-b]pyridine (S-4)

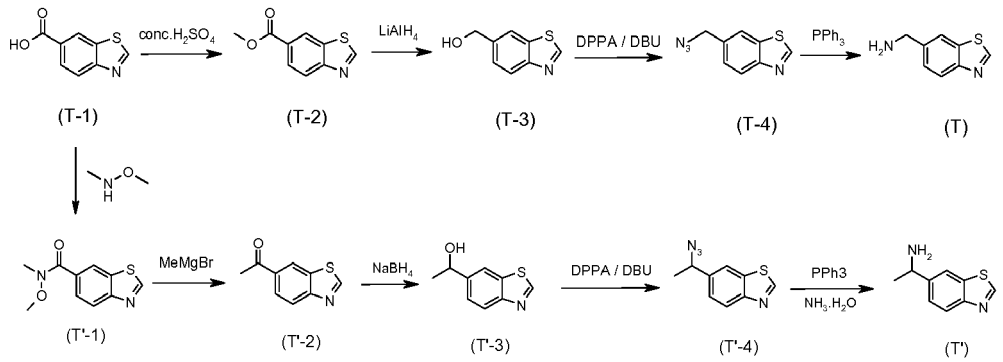
[0199] **Intermediate S-4** was prepared from 2-methylthiazolo[5,4-b]pyridine **(S-3)** following similar procedures for synthesizing **intermediate B-5** from **B-4**, as described above .

Thiazolo[5,4-b]pyridin-2-ylmethanamine(S)

[0200] **Intermediate S** was prepared from 2-(bromomethyl)thiazolo[5,4-b]pyridine **(S-4)** following similar procedured for synthesizing **intermediate C** from **C-5,** as described above. MS (m/z): 166 $(M+1)^+$.

Intermediate T and T'

[0201]



Methyl benzo[d]thiazole-6-carboxylate (T-2)

[0202] **Intermediate T2** was prepared from benzo[d]thiazole-6-carboxylic acid **(T-1)** following similar procedures for synthesizing intermediate **F-2** from **F-1,** as described above.

Benzo[d]thiazol-6-ylmethanamine (T)

[0203] **Intermediate T** was prepared from methyl benzo[d]thiazole-6-carboxylate **(T-2)** following similar procedures for synthesizing **intermediate D** from **D-2,** as described above. MS (m/z): 165 $(M+1)^+$.

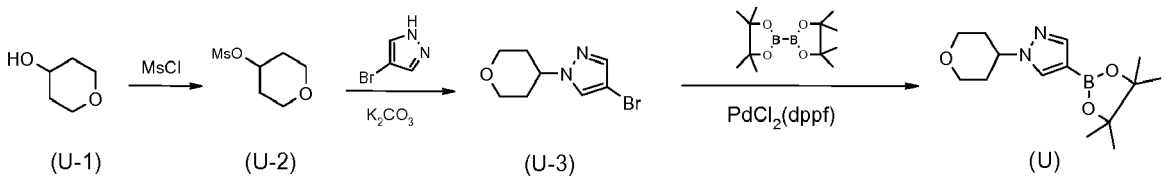
1-(Benzo[d]thiazol-6-yl)ethanamine (T')

[0204] **Intermediate T'** was prepared from benzo[d]thiazole-6-carboxylic acid **(T-1)** following similar procedures for synthesizing intermediate **D'-5 from D'-1,** as described above, and intermediate **D** from **D-4** as described above.. MS (m/z): 179$(M+1)^+$.

Synthesis of boric acid or ester intermediates:

Intermediate U

[0205]



Tetrahydro-2H-pyran-4-yl methanesulfonate (U-2)

[0206] To a mixture of tetrahydro-2H-pyran-4-ol **(U-1)** (1.02 g, 10 mmol) and Et_3N (1 mL) in dried DCM (20 mL) was added MsCl (2 mL) dropwise. The reaction was stirred at room temperature for 1 h, then washed with water. The organic layer was separated, dried over Na_2SO_4, and concentrated to afford the title compound (1.8 g).

4-Bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole (U-3)

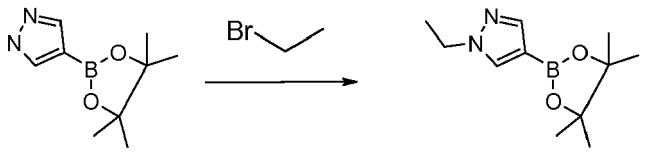
[0207] The mixture of tetrahydro-2H-pyran-4-yl methanesulfonate **(U-2)** (1.8 g, 10 mmol), 4-bromo-1H-pyrazole (1.46 g, 10 mmol) and K_2CO_3 (1.4 g, 10 mmol) in DMF (10 mmol) was stirred at 80°C overnight, then purified by chromatography to afford the title compound (861 mg). MS (m/z): 231 $(M+1)^+$.

1-(Tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (U)

[0208] To a mixture of 4-bromo-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole **(U-3)** (1.13 g, 4.48 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (861 mg, 3.73 mmol) and KOAc(12.43 g, 12.68 mmol) in DMSO (5 mL) was added Pd (dppf)Cl_2 (172 mg, 0.21 mmol) under N_2. The mixture was stirred overnight at 80°C under N_2. After cooling to room temperature, the reaction mixture was poured into water, and extracted with EtOAc. The organic phase was separated, concentrated in vacuo and then purified by chromatography to afford the title compound (170 mg). MS (m/z): 279 $(M+1)^+$.

Intermediate V

[0209]



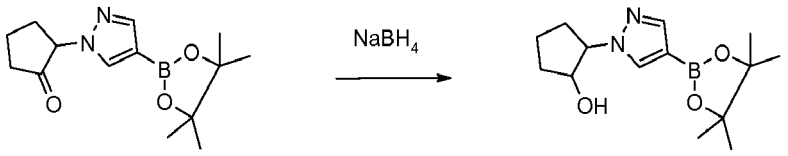
(V-1) (V)

1-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (V)

[0210] To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole **(V-1)** (3 g, 15 mmol) in DMF (6 mL) were added bromoethane (3.24 g, 30 mmol) and K_2CO_3 (4.26 g, 30 mmol). The reaction mixture was stirred at 60°C overnight, then diluted with EtOAc, washed with water and then brine. The organic layer was separated, then dried over Na_2SO_4, and concentrated to afford the title compound (3.40 g). MS (m/z): 223 $(M+1)^+$.

Intermediate W

[0211]



(W-1) (W)

2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)cyclopentanone (W-1)

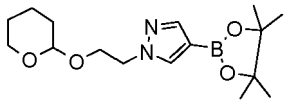
[0212] **Intermediate W-1** was prepared from 2-chlorocyclopentanone (1.06 g, 9 mmol) following the similar procedures of synthesizing **intermediate (V),** as described above. MS (m/z): 277 $(M+1)^+$.

2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)cyclopentanol (W)

[0213] To a solution of 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1 - yl)cyclopentanone **(W-1)** (550 mg, 2 mmol) in methanol (5 mL) was added $NaBH_4$ (150 mg, 4 mmol). The reaction was stirred at room temperature for 1h. The solvent was removed in vacuo, and the residue was extracted with EtOAc, washed with water, and purified by chromatography on silica gel to afford the title compound (200 mg). MS (m/z): 279 $(M+1)^+$.

Intermediate X

[0214]



(X)

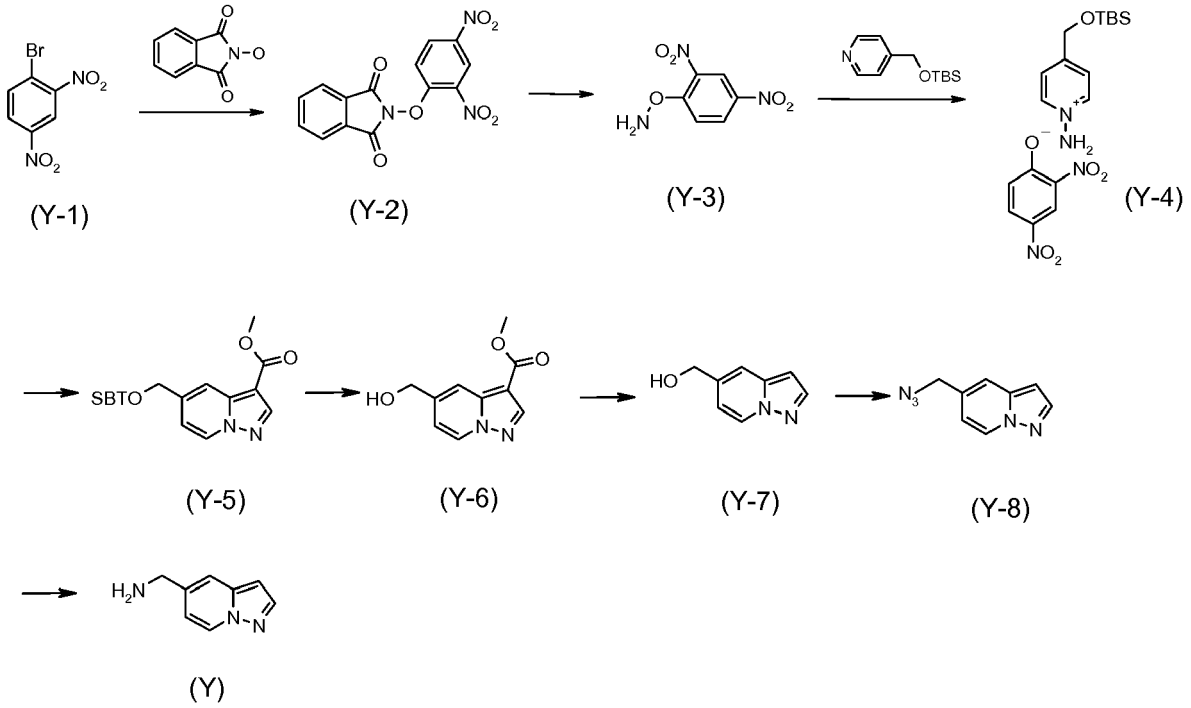
[0215] This intermediate was prepared from 4-bromo-1 H-pyrazole as described in US2007/ 0265272.

Other pyrazole boric acids or esters were prepared according to the procedures of intermediates (U-X)

Intermediate Y:

2-(2,4-Dinitrophenoxy)isoindoline-1,3-dione (Y-2)

[0216] To a suspension of 2-hydroxyisoindoline-1,3-dione (20.0 g, 0.12 mol) in acetone (400 mL) was added Et_3N (14.9 g, 0.15 mol), the mixture was stirred at room temperature until it became a homogeneous solution, then 1-bromo-2,4-dinitrobenzene **Y-1** (30.2 g, 0.12 mol) was added. The reaction was stirred at room temperature for 3 h, then poured into ice-water, the resulting precipitate was filtered and washed three times with cold MeOH, dried in vacuum to afford the title compound (38.1 g).



2-(2,4-Dinitrophenyl)hydroxylamine (Y-3)

[0217] To a solution of 2-(2,4-dinitrophenoxy)isoindoline-1,3-dione **Y-2** (20.0 g, 60.7 mmol) in CH_2Cl_2 (400 ml) was added a solution of hydrazine hydrate (10.0 mL, 85%, 177 mmol) in MeOH (60 ml) at 0°C. The reaction mixture was stirred at 0°C for 6h, then treated with cold aqueous HCl (1N, 400 ml). The resulting mixture was rapidly filtered and washed with MeCN. The filtrate was transfered into a funnel. The organic phase was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, then concentrated to afford the title compound (7.9 g). MS (m/z): $183(M-16)^-$.

1-Amino-4-((*tert*-butyldimethylsilyloxy)methyl)pyridinium 2,4-dinitrophenolate (Y-4)

[0218] To a solution of pyridin-4-ylmethanol (21.8 g, 0.20 mol) in CH_2Cl_2 (200 mL) were added Et_3N (30.0 g, 0.30 mmol) and TBSCl (45.0 g, 0.30 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 h, then quenched with water. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic

layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford 4-((*tert*-butyldimethylsilyloxy)methyl)-pyridine.

[0219] A mixture of 4-((tert-butyldimethylsilyloxy)methyl)pyridine (8.9 g, 39.7 mmol) and O-(2,4-dinitrophenyl)hydroxylamine **Y-3** (7.9 g, 39.7 mmol) in MeCN (27 ml) was stirred at 40°C for 24 h, then concentrated to afford the title compound (17.1g), used in next step without further purification. MS (m/z): $239(M-183)^+$.

Methyl 5-((tert-butyldimethylsilyloxy)methyl)pyrazolo[1,5-a]pyridine-3-carboxylate (Y-5)

[0220] To a solution of 1-amino-4-((tert-butyldimethylsilyloxy)methyl)pyridinium 2,4-dinitrophenolate **Y-4** (13.4 g, 31.6 mmol) in DMF (60 mL) were added methyl propiolate (2.7 g, 31.6 mmol) and K_2CO_3 (6.5 g, 47.4 mmol). The reaction was stirred at room temperature for 24 h, then treated with water. The resulting mixture was extracted with ethyl acetate (100 ml x 3), the combined organic layers were washed with water, brine and dried over Na_2SO_4, then concentrated in vacuo, the residue was purified by silica gel chromatography to afford the title compound (2.9 g). MS (m/z): $321(M+1)^+$.

Methyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-3-carboxylate (Y-6)

[0221] To a solution of methyl 5-((tert-butyldimethylsilyloxy)methyl)pyrazolo[1,5-a]pyridine-3-carboxylate **Y-5** (2.9 g, 9.1 mmol) in dry THF (20 mL) was added TBAF (3.5 g, 13.7 mmol). The reaction mixture was stirred at room temperature for 10 mins, then treated with ethyl acetate. The resulting mixture was washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound (1.9 g).

Pyrazolo[1,5-a]pyridin-5-ylmethanol (Y-7)

[0222] A suspension of methyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-3-carboxylate **Y-6** (1.9 g, 9.1 mmol) in 40% H_2SO_4 was stirred at 80°C for 24 h, then neutralized with 3N NaOH to pH=7-8. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford the title compound (1.1g). MS (m/z): $149(M+1)^+$.

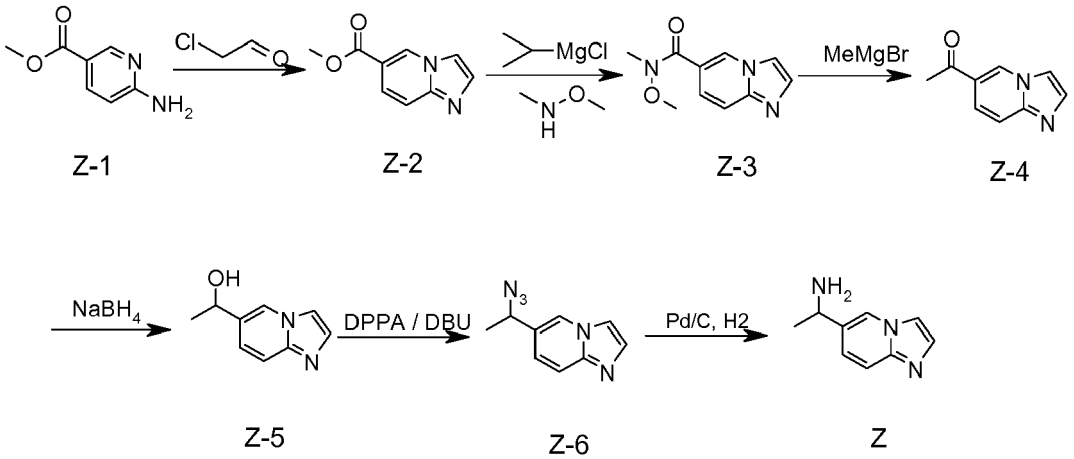
Intermediate (Y)

[0223] **Intermediate** Y was prepared from pyrazolo[1,5-a]pyridin-5-ylmethanol **(Y-7)** following similar procedures for synthesizing intermediate **D** from **D-3.**

Intermediate Z

Methyl H-imidazo[1,2-a]pyridine-6-carboxylate (Z-2)

[0224]



[0225] To a solution of **Z-1** (9.0 g, 59.21 mmol) in anhydrous EtOH (160 ml) was added chloroacetaldehyde (40% in H_2O, 48.6 mL, 296 mmol). The reaction mixture was refluxed for 4h, then concentrated. The residue was dissolved in water and adjusted to pH>7 with a saturated NaHCO3 solution, extracted with EtOAc and purified by silica gel chroma-

tography to afford the title compound (6.60 g). MS (m/z): 177 $(M+1)^+$.

***N*-Methoxy-*N*-methylH-imidazo[1,2-a]pyridine-6-carboxamide (Z-3)**

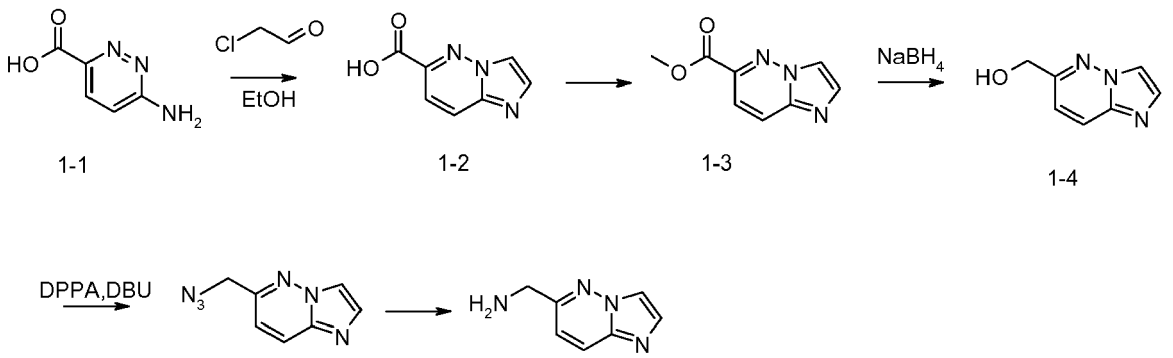
[0226] To a mixture of Z-2 (5.0 g, 28.4 mmol) and N-methoxymethanamine (5.54 g, 56.8 mmol) in dry THF (50 ml) at -20°C under N_2 was added isopropylmagnesium chloride (56.8 mL, 113.6 mmol) over 30 mins. The resulting mixture was stirred at -20°C for 30 mins, then quenched with 20% NH_4Cl solution, and extracted with EtOAc (50 mL x3). The combined organic layers were dried over Na_2SO_4, concentrated and purified by silicon gel chromatography to afford the title compound (3.0 g). MS (m/z): 206 $(M+1)^+$.

1-(H-imidazo[1,2-a]pyridin-6-yl)ethanamine (Z)

[0227] It was prepared from compound **Z-3** following similar procedures for synthesizing intermediate **D'** from **D'-2.**

Intermediate 1

[0228]



intermediate 1

Imidazo[1,2-b]pyridazine-6-carboxylic acid (1-2)

[0229] To a mixture of 6-aminopyridazine-3-carboxylic acid **(1-1)** (1.39 g, 10 mmol) in ethanol in a sealed flask was added 2-chloroacetaldehyde(4 mL, 40% aqueous). The reaction mixture was stirred at room temperature for 5 min, then heated at 100°C overnight. After cooled to room temperature, the mixture was concentrated to afford the title compound (1.63 g). MS (m/z): 164 $(M+1)^+$

Methyl imidazo[1,2-b]pyridazine-6-carboxylate (1-3)

[0230] To a mixture of imidazo[1,2-b]pyridazine-6-carboxylic acid **(1-2)** (1.63 g, 10 mmol) in $SOCl_2$ (15 mL) was added 10 drops of DMF at room temperature. The resulting solution was heated at reflux for 3 h. After cooled to room temperature, the reaction was concentrated, and the resulting solid was dissolved in methanol, and stirred for a while, then treated with an aqueous saturated $NaHCO_3$ solution to pH7. The mixture was purified by silica gel chromatography to afford the title compound (891 mg). MS (m/z): 178 $(M+1)^+$

Imidazo[1,2-b]pyridazin-6-ylmethanol (1-4)

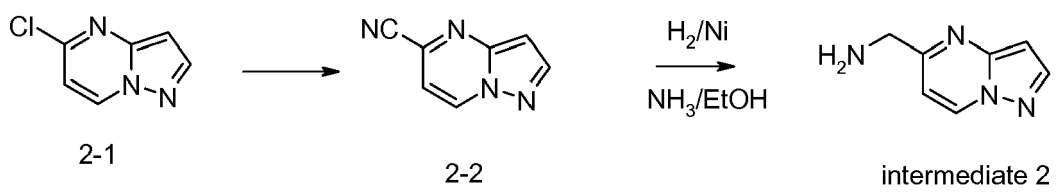
[0231] To a solution of methyl imidazo[1,2-b]pyridazine-6-carboxylate **(1-3)** (891 mg, 5.03 mmol) in ethanol (25 mL) was added $NaBH_4$ (420 mg, 11.1 mmol) at room temperature. The suspension was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuum. The residue was purified by chromatography on silica gel to afford the title compound (630 mg). MS (m/z): 150 $(M+1)^+$

Imidazo[1,2-b]pyridazin-6-ylmethanamine (Intermediate 1)

[0232] **Intermediate 1** was prepared from imidazo[1,2-b]pyridazin-6-ylmethanol **(1-4)** following the procedures similar to procedure of **intermediate D** from **D-3.** MS (m/z): 149 $(M+1)^+$

Intermediate 2

[0233]



Pyrazolo[1,5-a]pyrimidine-5-carbonitrile (2-2)

[0234] To a mixture of 5-chloropyrazolo[1,5-a]pyrimidine **(2-1)** (1.0 g, 6.45 mmol) and $Zn(CN)_2$ (770 mg, 6.58 mmol) in dried DMF (20 mL) exchanged by N_2 was added $Pd(PPh_3)_4$ (400 mg, 3.46 mmol). The reaction mixture was stirred at 110°C overnight. After cooled to the room temperature, the solution was concentrated and purified by chromatography on silica gel to afford the title compound (620 mg)

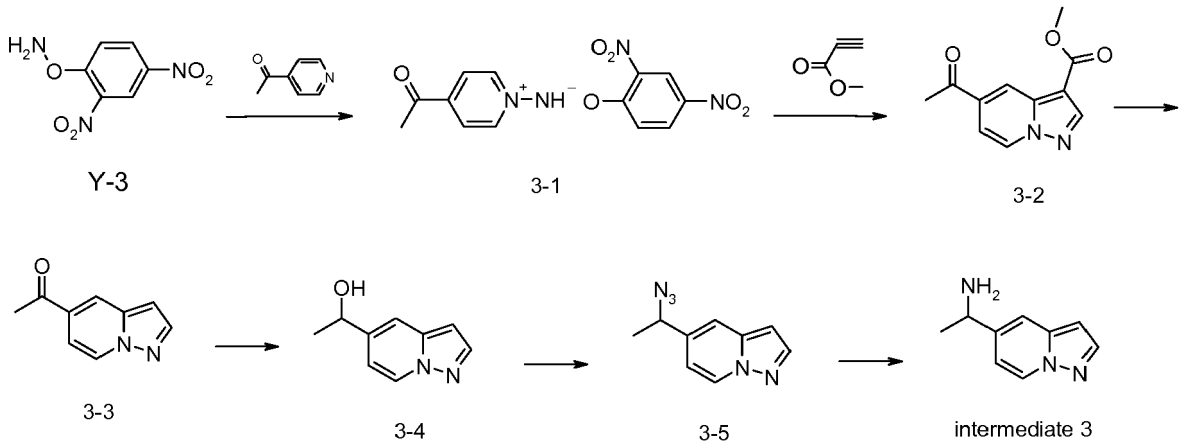
Pyrazolo[1,5-a]pyrimidin-5-ylmethanamine(Intermediate 2)

[0235] To a solution of pyrazolo[1,5-a]pyrimidine-5-carbonitrile **(2-2)** (620 mg, 4.31 mmol) in NH_3 in MeOH (5 mL) was added Raney Ni (100 mg). The reaction mixture was stirred at room temperature for 3 h under H_2. The mixture was filtered, and the filtrate was concentrated to afford the title compound (600 mg). MS (m/z): $149(M+1)^+$.

Intermediate 3

(3-1)

[0236] To a solution of 1-(pyridin-4-yl)ethanone (100 mg, 0.82 mmol) dissolved in CH_3CN (3 mL) was added **Y-3** (180 mg, 0.9 mmol). The reaction mixture was heated to 40°C and stirred at 40°C for 24 h. Solvent was removed in vacuum. The residue was used in next step without further purification (225 mg).



Methyl 5-acetylpyrazolo[1,5-a]pyridine-3-carboxylate (3-2)

[0237] To a mixture of **(3-1)** (100 mg, 0.31 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in DMF (1 mL) was added methyl propiolate (29 mg, 0.34 mmol) dropwise. The reaction mixture was stirred vigorously at room temperature for 24 h. The suspension was filtered. The filtrate was concentrated. The resulting residue was dissolved in Et_2O and washed with water. The organic layer was separated, concentrated and purified by chromatography on silica gel to afford the title compound (20 mg). MS (m/z): $219(M+1)^+$.

1-(Pyrazolo[1,5-a]pyridin-5-yl)ethanone (3-3)

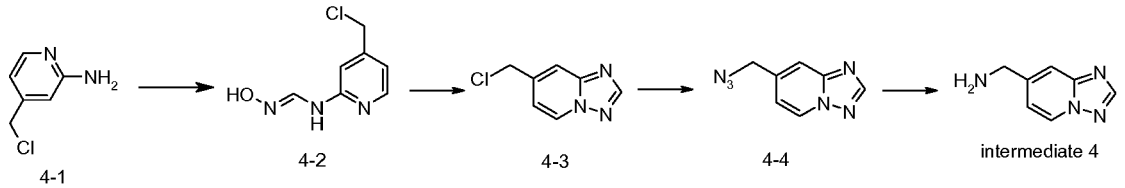
[0238] A suspension of methyl 5-acetylpyrazolo[1,5-a]pyridine-3-carboxylate **(3-2)** (90 mg, 0.41 mmol) dissolved in 50% H_2SO_4 (2 mL) was stirred at 80°C for 3 h. After cooled to 0°C, the solution was treated with 5N NaOH solution, and then extracted with Et_2O. The organic layer was separated, dried, concentrated and purified by flash chromatography to afford the title compound (25 mg).

1-(Pyrazolo[1,5-a]pyridin-5-yl)ethanamine (Intermediate 3)

[0239] **Intermediate 3** was prepared from 1-(pyrazolo[1,5-a]pyridin-5-yl)ethanone **(3-3)** following the procedures similar to the procedures of **intermediate D'** from **D'-3.** MS (m/z): 162 $(M+1)^+$.

Intermediate 4

[0240]



***N*-(4-(Chloromethyl)pyridin-2-yl)-*N*-hydroxyformimidamide(4-2)**

[0241] To a solution of 4-(chloromethyl)pyridin-2-amine **(4-1)** (1.56 g, 8.7 mmol) in propan-2-ol (15 mL) was added DMF-DMA (1.56 mL, 11.3 mmol) at room temperature under N_2. The reaction mixture was heated to 90°C for 3 h. After cooled to 50°C, the mixture was treated with $NH_2OH.HCl$ (0.781 g, 11.3 mmol), then stirred at 50°C overnight. After cooled to room temperature, the mixture was concentrated and purified by chromatography on silica gel to afford the title compound (820 mg) .MS (m/z): 186 $(M+1)^+$.

7-(Chloromethyl)-[1,2,4]triazolo[1,5-a]pyridine(4-3)

[0242] To a solution of *N*-(4-(chloromethyl)pyridin-2-yl)-*N'*-hydroxyformimidamide **(4-2)** (820 mg, 4.4 mmol) in anhydrous THF (5 mL) cooled to 0°C was added TFAA (1.1 g, 5.28 mmol) dropwise under N_2. The reaction mixture was stirred at room temperature for 3 h. Then the mixture was treated with aqueous $NaHCO_3$ to pH 8, concentrated and purified by chromatography on silica gel to afford the title compound (400 mg). MS (m/z): 168 $(M+1)^+$.

7-(Azidomethyl)-[1,2,4]triazolo[1,5-a]pyridine(4-4)

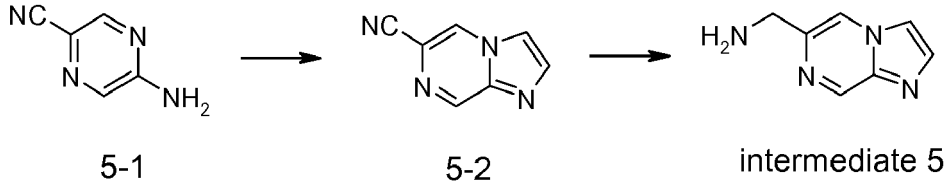
[0243] To a solution of 7-(chloromethyl)-[1,2,4]triazolo[1,5-a]pyridine **(4-3)** (400 mg, 2.4 mmol) in dried DMF (5 mL) was added NaN_3 (250 mg, 3.6 mmol) under N_2. The reaction mixture was stirred at 80°C for 2 h, then quenched with aqueous $Na_2S_2O_3$. The resulting mixture was extracted with EtOAc, dried on Na_2SO_4, and concentrated to afford the title compound (340 mg), which was used in next step without further purification. MS (m/z): 175 $(M+1)^+$.

[1,2,4]Triazolo[1,5-a]pyridin-7-ylmethanamine(Intermediate 4)

[0244] To a solution of 7-(azidomethyl)-[1,2,4]triazolo[1,5-a]pyridine **(4-4)** (340 mg, 1.9 mmol) in methanol (20 mL) was added Pd/C (30 mg). The reaction mixture was stirred at room temperature under H_2 (1 atm) for 2 h. The mixture was filtered to remove Pd/C. The filtrate was concentrated to afford the title compound (300 mg) MS (m/z): 149$(M+1)^+$.

Intermediate 5

[0245]



Imidazo[1,2-a]pyrazine-6-carbonitrile (5-2)

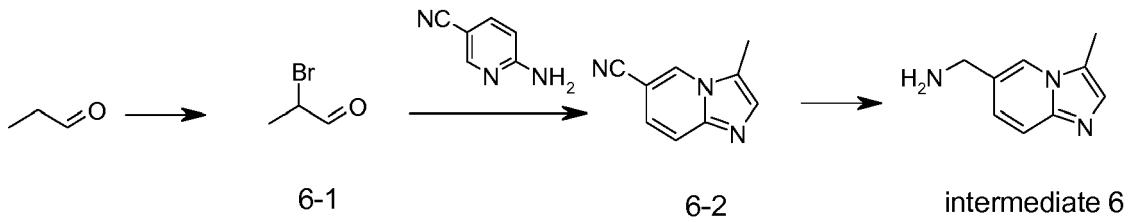
[0246] To a solution of 5-aminopyrazine-2-carbonitrile **(5-1)** (350 mg, 2.92 mmol) in ethanol (15 mL) was added 2-chloroacetaldehyde (4 mL, 40% in water). The mixture was stirred at 110°C overnight. The solution was concentrated, then purified by chromatography on silica gel to afford the title compound (280 mg). MS (m/z): 145.1 $(M+H)^+$.

Imidazo[1,2-a]pyrazin-6-ylmethanamine (Intermediate 5)

[0247] To a solution of imidazo[1,2-a]pyrazine-6-carbonitrile **(5-1)** (180 mg, 1.25 mmol) in methanol (15 mL) were added Raney nickel (slurry in water, 150 mg) and 1 N ammonia. The reaction mixture was stirred under H_2 (1 atm) for 2 h. The mixture was filtered, and the filtrate was concentrated to afford the title compound (160 mg). MS (m/z): 149.1 $(M+H)^+$

Intermediate 6

[0248]



2-Bromopropanal (6-1)

[0249] To a solution of propionaldehyde (20mL, 265 mmol) in 25 mL of dioxane at 0°C was added bromine (13.5 mL, 265 mmol) within 1 h. The reaction mixture was allowed to continue stirring for an additional 10 min untill the reaction became colorless. The mixture was diluted with 200 mL of ether, and washed with aqueous $NaHSO_4$, $NaHCO_3$ and brine. The aqueous layer was extracted with ether. The combined organic layer was dried over Na_2SO_4 and concentrated. The resulting oil was further purified by distillation under vacuum to afford the title compound (8.5 g).

3-Methylimidazo[1,2-a]pyridine-6-carbonitrile (6-2)

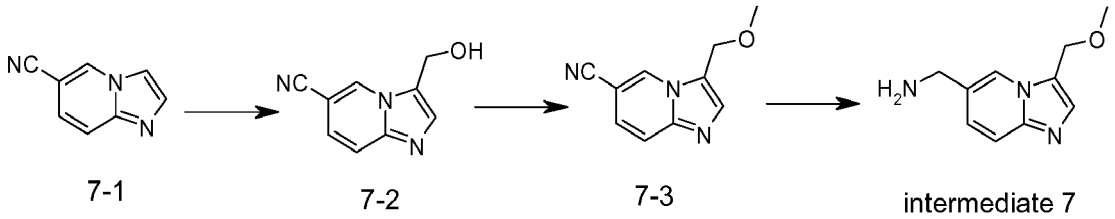
[0250] To a solution of 6-aminonicotinonitrile (1.2 g, 10.1 mmol) in ethanol (80 mL) was added 2-bromopropanal **(6-1)** (6.9 g, 50.5 mmol). The reaction mixture was stirred at 80 °C overnight. The solution was concentrated, diluted with water (20 mL) and adjusted to PH>7 with saturated aqueous $NaHCO_3$ solution. The precipitate was collected to afford the title compound (430 mg). MS (m/z): 158 $(M+H)^+$.

(3-Methylimidazo[1,2-a]pyridin-6-yl)methanamine (Intermediate 6)

[0251] To a solution of 3-methylimidazo[1,2-a]pyridine-6-carbonitrile **(6-2)** (200 mg, 1.27 mmol) in methanol (30 mL) were added Raney nickel (slurry in water, 100 mg) and 1N mmonia. The reaction mixture was stirred under H_2 for 2 h, then filtered and concentrated to afford the title compound (200 mg). MS (m/z): 162 $(M+H)^+$

Intermediate 7

[0252]



3-(Hydroxymethyl)imidazo[1,2-a]pyridine-6-carbonitrile (7-2)

[0253] To a solution of imidazo[1,2-a]pyridine-6-carbonitrile **(7-1)** (1.43 g, 10 mmol) in 3 mL of acetic acid were added sodium acetate (3.03 g, 37 mmol) and then formaldehyde (6mL, 37% in water). The reaction mixture was stirred at 100 °C overnight. After cooled to room temperature, the mixture was adjusted to pH>7 with aqueous Na_2CO_3. The precipitate was collected to afford the title compound (1.4 g). MS (m/z): 174.0 $(M+H)^+$

3-(Methoxymethyl)imidazo[1,2-a]pyridine-6-carbonitrile (7-3)

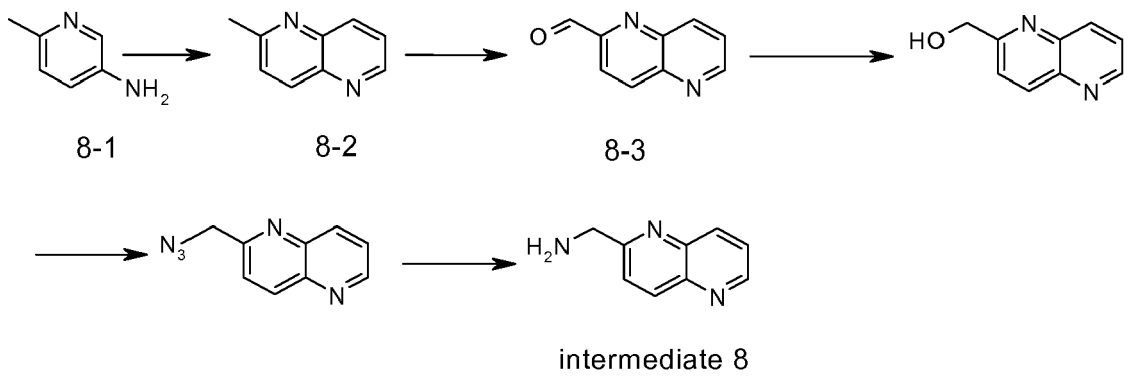
[0254] To a solution of 3-(hydroxymethyl)-imidazo[1,2-a]pyridine-6-carbonitrile **(7-2)** (346 mg, 2 mmol) in 20 mL of THF was added sodium hydride (240 mg, 60% in oil) at 0°C. The reaction mixture was stirred at 0 °C for 1 h, then methyl iodide (615 mg, 4.3 mmol) was added. The reaction was stirred at room temperature overnight. The mixture was treated with aqueous Na_2CO_3, then concentrated. The residue was diluted with water and extracted with EtOAc. The combined organics were dried over Na_2SO_4 and concentrated to afford the title compound (300 mg). MS (m/z): 188.0 $(M+H)^+$

(3-(Methoxymethyl)imidazo[1,2-a]pyridin-6-yl)methanamine (Intermediate 7)

[0255] To a solution of 3-(methoxymethyl)imidazo[1,2-a]pyridine-6-carbonitrile **(7-3)** (300 mg, 1.6 mmol) in methanol (30 mL) were added Raney nickel (slurry in water, 150mg) and 1N ammonia. The reaction mixture was stirred under H_2 for 2 h. The mixture was filtered. The filtrate was concentrated to afford the title compound (300 mg). MS (m/z): 192.0 $(M+H)^+$

Intermediate 8

[0256]



2-Methyl-1,5-naphthyridine (8-2)

[0257] A mixture of 6-methylpyridin-3-amine **(8-1)** (4.8 g, 44.4 mmol) and propane-1,2,3-triol (20 g, 222 mmol) in 5 mL of H_2O was stirred at room temperature for 5 min, then concentrated H_2SO_4 (47 g, 488 mmol) was added dropwise within 20 min at room temperature. After addition, the reaction mixture was stirred at 150 °C for 30 min. After cooled to room temperature, the mixture was poured into water, adjusted with 6 N NaOH to pH 13, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography on silica gel to afford the title compound (2.9 g). MS: 145$(M+1)^+$.

1,5-Naphthyridine-2-carbaldehyde (8-3)

[0258] A mixture of 2-methyl-1,5-naphthyridine **(8-2)** (2.9 g, 20.1 mmol) and SeO_2(2.2 g, 20.1 mmol) in 40 mL of dioxane was refluxed for 3 h. After cooled to room temperature, the reaction mixture was concentrated. The residue was treated with brine and extracted with DCM/i-PrOH=4/1. The organic layer was washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography on silica gel to afford the title compound (1.81 g).

(1,5-Naphthyridin-2-yl)methanol (8-4)

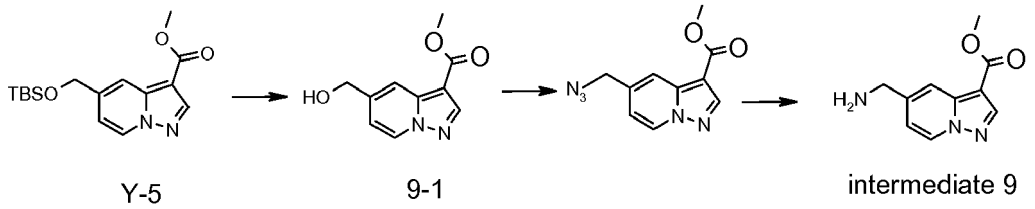
[0259] To a solution of 1,5-naphthyridine-2-carbaldehyde **(8-3)** (1.0 g, 6.32 mmol) in MeOH (15 mL) and THF (15 mL) was added $NaBH_4$ (84 mg, 2.21 mmol). The reaction mixture was stirred at 0 °C for 0.5 h. The mixture was concentrated and purified by chromatography on silica gel to afford the title compound (790 mg).

(1,5-Naphthyridin-2-yl)methanamine (Intermediate 8)

[0260] **Intermediate** 8 was prepared from (1,5-naphthyridin-2-yl)methanol **(8-4)** following the procedures similar to the procedure for synthesizing **intermediate** D from **D-3.** MS (m/z): 160 $(M+1)^+$.

Intermediate 9

[0261]



Methyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-3-carboxylate (9-1)

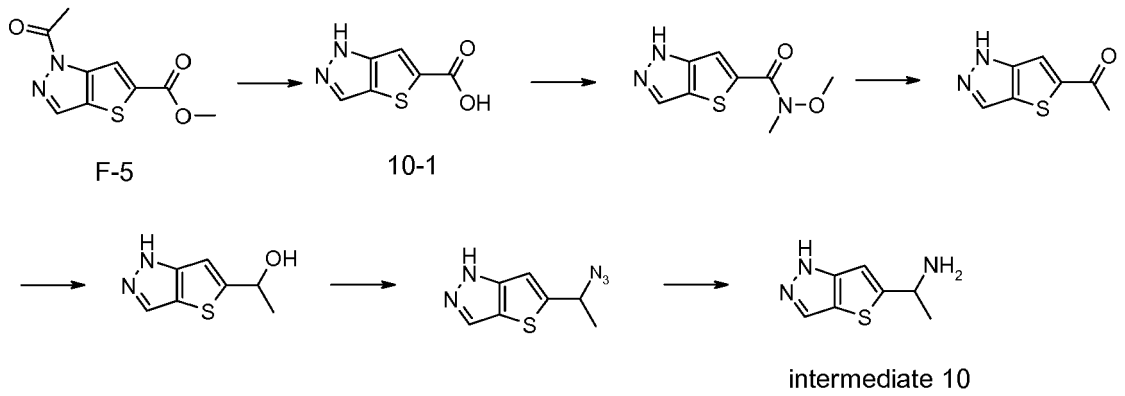
[0262] To a solution of methyl 5-((tert-butyldimethylsilyloxy)methyl)pyrazolo[1,5-a]pyridine-3-carboxylate **(Y-5)** (2.9 g, 9.1 mmol) in anhydrous THF (20 mL) was added TBAF (3.5 g, 13.7 mmol). The reaction mixture was stirred at room temperature for 10 min, then treated with ethyl acetate (50 mL). The resulting mixture was washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound (1.9 g).

Methyl 5-(aminomethyl)pyrazolo[1,5-a]pyridine-3-carboxylate (intermediate 9)

[0263] **Intermediate 9** was prepared from methyl 5-(hydroxymethyl)pyrazolo[1,5-a]pyridine-3-carboxylate **(9-1)** following the procedures similar to the procedure of synthesizing intermediate **D** from **D-3.** MS (m/z): 148 $(M+1)^+$.

Intermediate 10

[0264]



1H-Thieno[3,2-c]pyrazole-5-carboxylic acid (10-1)

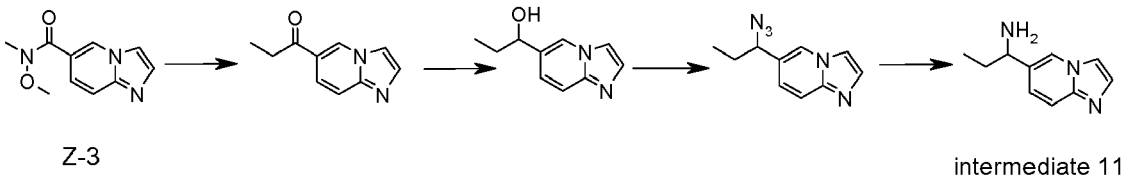
[0265] To a solution of methyl 1H-thieno[3,2-c]pyrazole-5-carboxylate **(F-5)** (4.2 g, 18.7 mmol) in MeOH (50 mL) was added a solution of $LiOH.H_2O$ (3.1 g, 74.8 mmol) in water (5 mL). The reaction mixture was stirred at room temperature overnight. Then 1N HCl was added to adjust to pH to ~ 5, the resulting precipitate was collected and dried to afford the title compound.

1-(1H-thieno[3,2-c]pyrazol-5-yl)ethanamine (intermediate 10)

[0266] **Intermediate 10** was prepared from 1H-thieno[3,2-c]pyrazole-5-carboxylic acid **(10-1)** following similar procedures for synthesizing intermediate **T'** from **T-1.** MS (m/z): 168 $(M+1)^+$.

Intermediate 11

[0267]



1-(imidazo[1,2-a]pyridin-6-yl)propan-1-amine

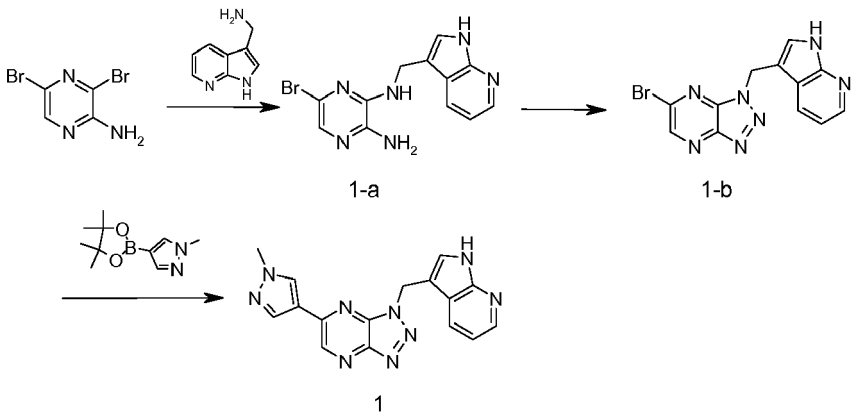
[0268] **Intermediate 11** was prepared from **Z-3** following similar procedures for synthesizing intermediate **Z** from **Z-3.**

Example 1. Preparation of Compounds 1-332

[0269] Compounds of the present invention can be made according to the following examples. It will be understood by those skilled in the art that the following examples do not limit the invention. For example, it may be possible to alter exact solvents, conditions, quantities, or utilize the equivalent reagents and intermediates with appropriate protecting groups.

Compound 1,1-((1H-Pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]-triazolo[4,5-b] pyrazine

[0270]



1-a 1-b 1

***N*^{2}-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-bromopyrazine-2,3-diamine**

[0271] A mixture of (1H-pyrrolo[2,3-b]pyridin-3-yl)methanamine **(intermediate A)** (442 mg, 3.0 mmol), 3,5-di-bromopyrazin-2-amine (758 mg, 3.0 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1160 mg, 9.0 mmol) in EtOH (70 mL) was stirred at 150 °C overnight. After being cooled to room temperature, it was concentrated and purified by chromatography to afford the title compound (70 mg) MS (m/z): 319 $(M+1)^+$.

1-((1 H-Pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-bromo-1 H-[1,2,3] triazolo[4,5-b]pyrazine

[0272] To the ice-cooled mixture of N^2-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-bromopyrazine-2,3-diamine (48 mg, 0.15 mmol) in HOAc/H_2O (1.5 mL/1.5 mL) was added $NaNO_2$ (31 mg, 0.45 mmol) in water (0.2 mL). The reaction was stirred for 1.5 h in an ice bath, then aqueous H_2SO_4 (49%, 0.1 mL) was added. The resulting mixture was allowed to warm to room temperature and stir overnight, then was adjusted to pH>8 with 3 N aqueous NaOH solution, and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered and concentrated to give the title compound (46 mg) MS (m/z): 332 $(M+1)^+$.

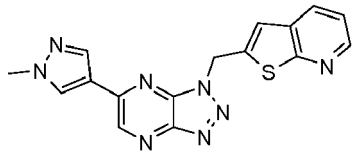
1-((1H-Pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]-triazolo[4,5-b]pyrazine

[0273] The mixture of 1-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-6-bromo-1H-[1,2,3] triazolo-[4,5-b]pyrazine (46 mg, 0.14 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (77 mg, 0.35 mmol), $PdCl_2$(dppf) (12 mg, 0.014 mmol) and Cs_2CO_3 (137 mg, 0.42 mmol) in dioxane/H_2O (10:1, 8 mL) was stirred at 80°C overnight. After being cooled to room temperature, the mixture was concentrated and purified by chromatography to afford the title compound (18 mg) MS (m/z): 332 (M+H).

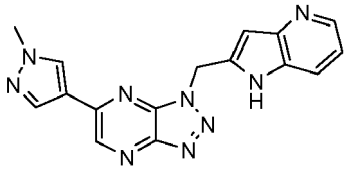
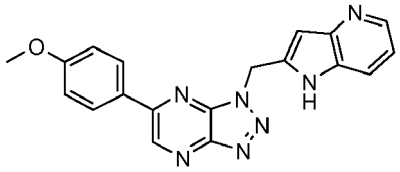
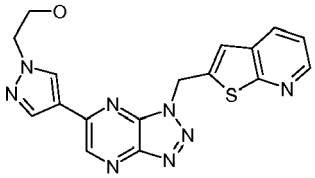
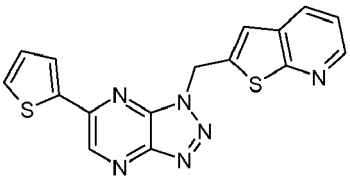
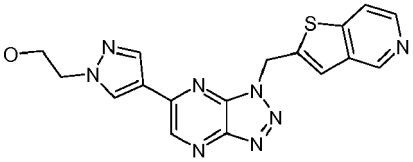
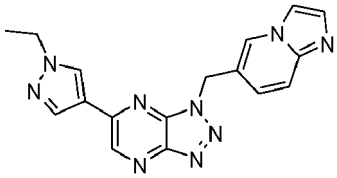
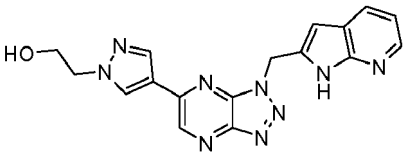
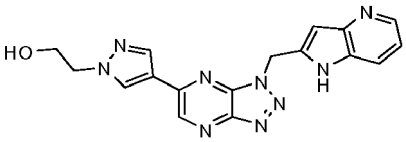
Compounds 2-59, 265-269, 272, 274-277,279-290, 293-296, 298-299, 301-305, 308-310,316-317, 326, 328-329, 331

[0274] The following compounds 2-59, 265-269, 272, 274-277,279-290, 293-296, 298-299, 301-305, 308-310,316-317, 326, 328-329, 331 were prepared according to the procedures of Compound **1** using the corresponding intermediates and boronic acid or ester under appropriate conditions that will be recognized by one skilled in the art:

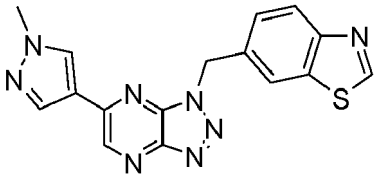
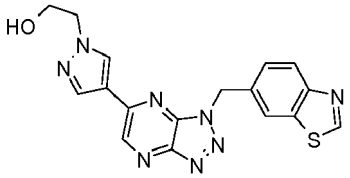
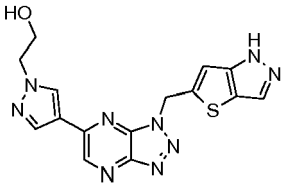
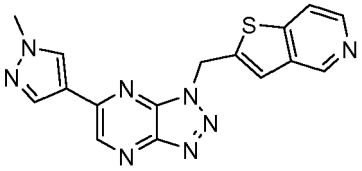
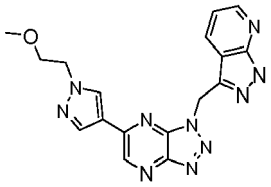
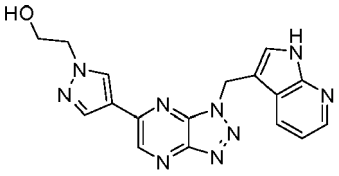
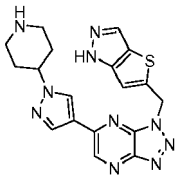
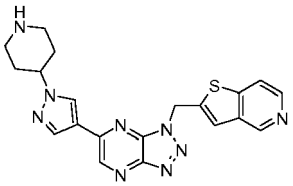
Table 1

Compound	Structure	LC/MS data
2		349 $(M+1)^+$

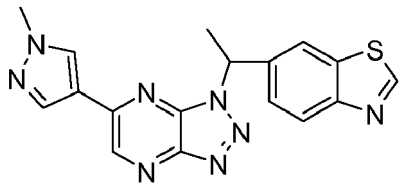
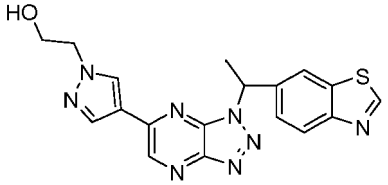
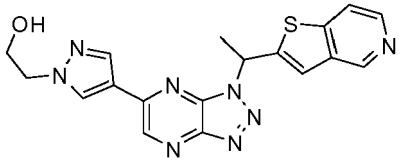
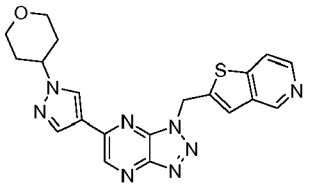
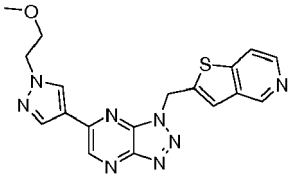
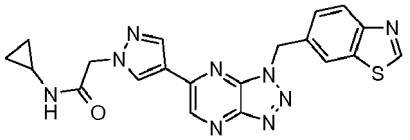
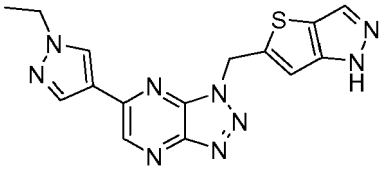
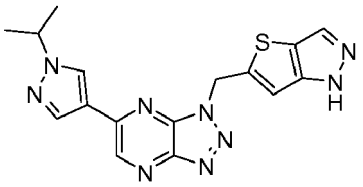
(continued)

Compound	Structure	LC/MS data
3		332 $(M+1)^+$
4		358 $(M+1)^+$
5		379 $(M+1)^+$
6		351 $(M+1)^+$
7		379 $(M+1)^+$
8		346 $(M+1)^+$
9		362 $(M+1)^+$
10		362 $(M+1)^+$

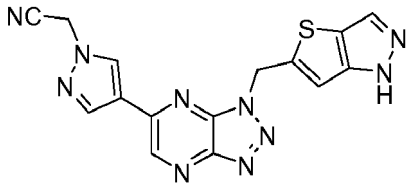
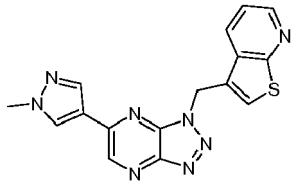
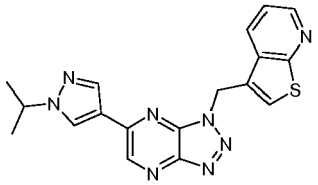
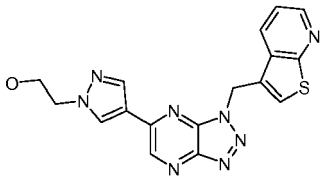
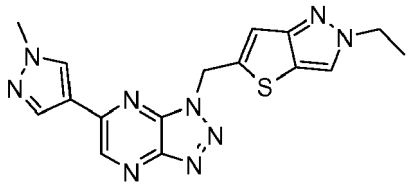
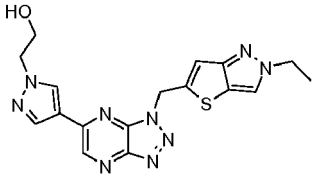
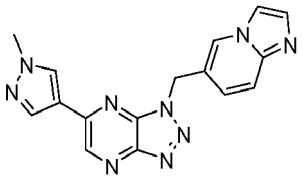
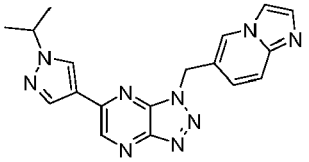
(continued)

Compound	Structure	LC/MS data
11		349 $(M+1)^+$
12		379 $(M+1)^+$
13		367.4 $(M)^+$
14		348 $(M)^+$
15		377 $(M+1)^+$
16		362 $(M+1)^+$
17		407 $(M+1)^+$
18		418 $(M+1)^+$

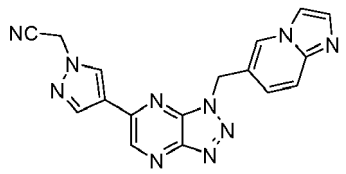
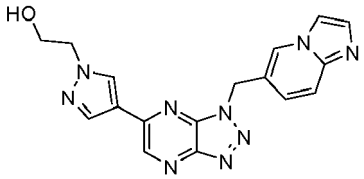
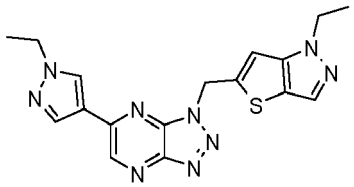
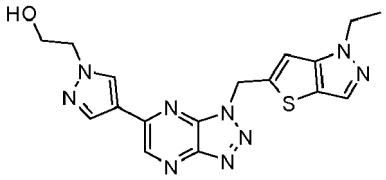
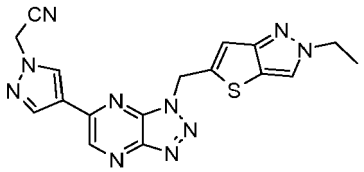
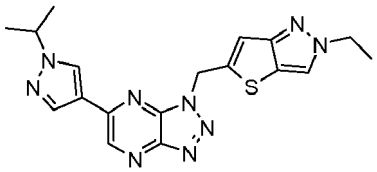
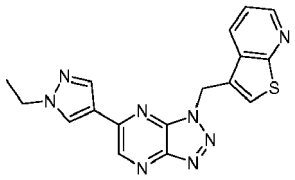
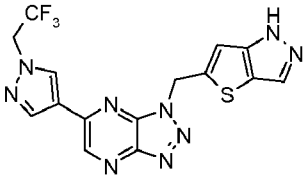
(continued)

Compound	Structure	LC/MS data
19		363 $(M+1)^+$
20		393 $(M+1)^+$
21		393 $(M+1)^+$
22		419 $(M+1)^+$
23		393 $(M+1)^+$
24		432 $(M+1)^+$
25		352 $(M+1)^+$
26		366 $(M+1)^+$

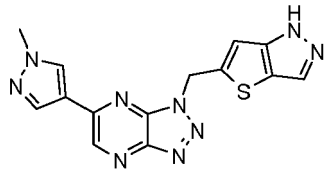
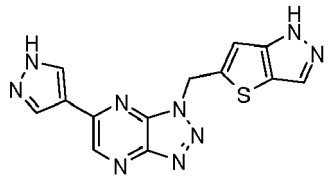
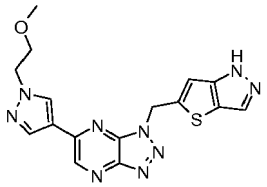
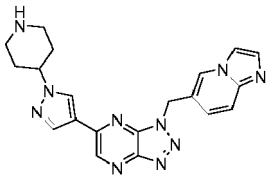
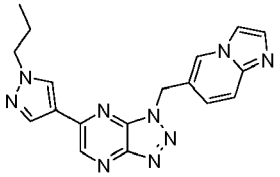
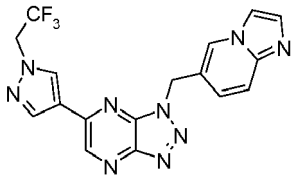
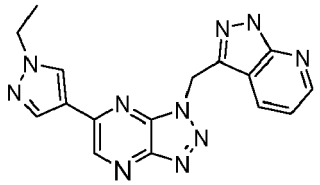
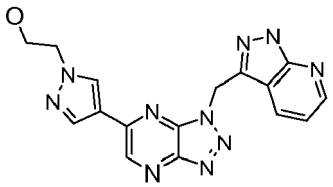
(continued)

Compound	Structure	LC/MS data
27		363 $(M+1)^+$
28		349 $(M+1)^+$
29		377 $(M+1)^+$
30		379 $(M+1)^+$
31		366 $(M+1)^+$
32		396.7 $(M+1)^+$
33		332 $(M+1)^+$
34		360 $(M+1)^+$

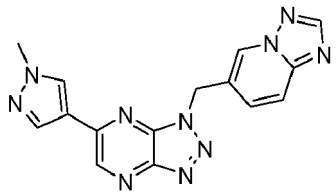
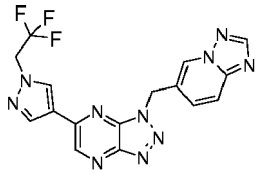
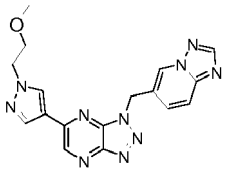
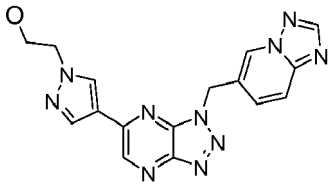
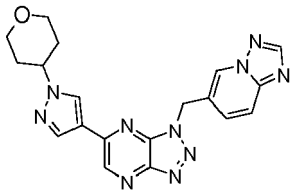
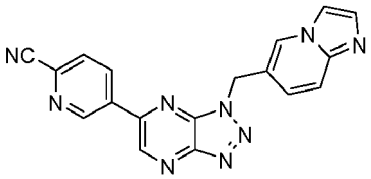
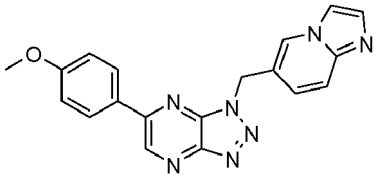
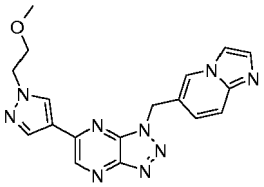
(continued)

Compound	Structure	LC/MS data
35		357 $(M+1)^+$
36		362 $(M+1)^+$
37		380 $(M+1)^+$
38		396 $(M+1)^+$
39		391.7 $(M+1)^+$
40		394.5 $(M+1)^+$
41		363 $(M+1)^+$
42		406.9 $(M+1)^+$

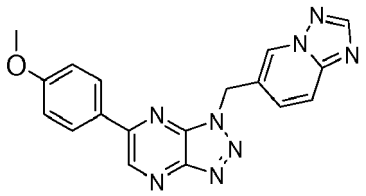
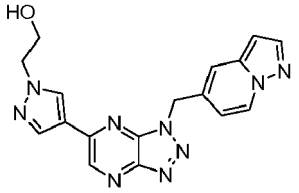
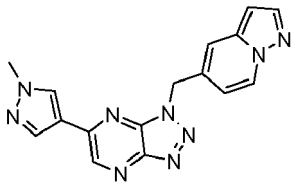
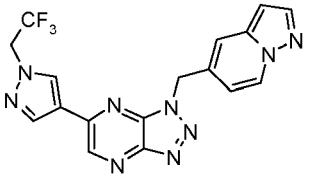
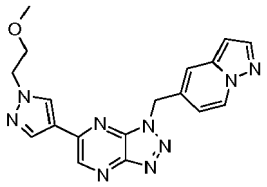
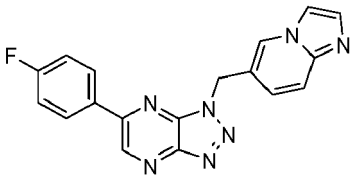
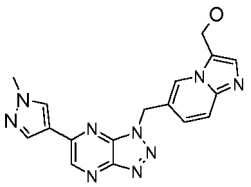
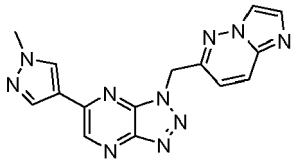
(continued)

Compound	Structure	LC/MS data
43		338 (M+1)+
44		324 (M+1)+
45		382 (M+1)+
46		401 (M+1)+
47		360 (M+1)+
48		400 (M+1)+
49		347 (M+1)+
50		363 (M+1)+

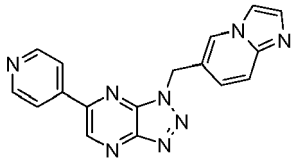
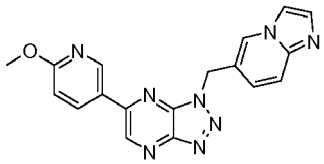
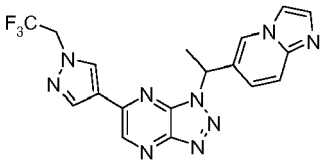
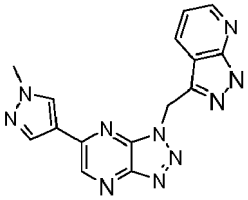
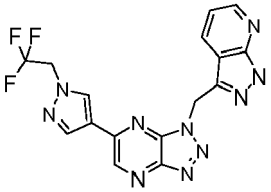
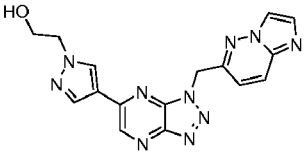
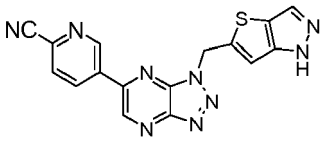
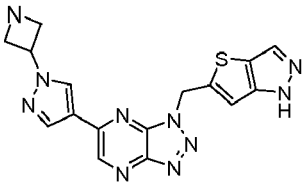
(continued)

Compound	Structure	LC/MS data
51		333 $(M+1)^+$
52		401 $(M+1)^+$
53		377 $(M+1)^+$
54		363 $(M+1)^+$
55		403 $(M+1)^+$
56		354 $(M+1)^+$
57		358 $(M+1)^+$
58		376 $(M+1)^+$

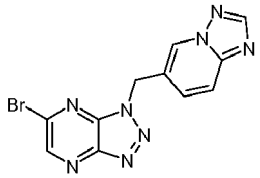
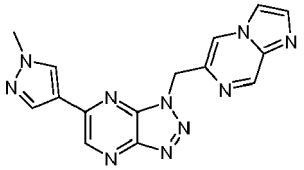
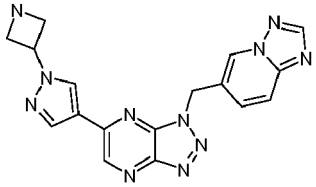
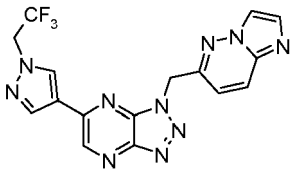
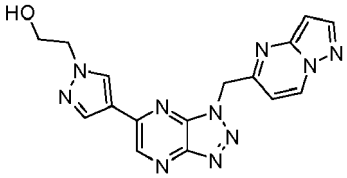
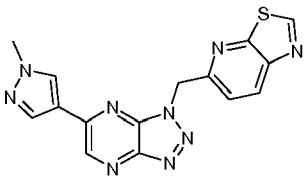
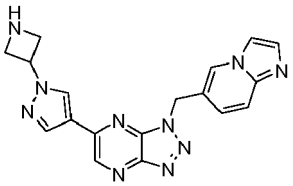
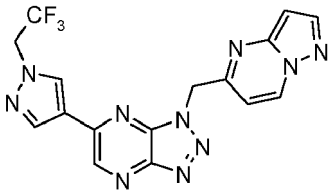
(continued)

Compound	Structure	LC/MS data
59		359 (M+1)+
265		362 (M+1)+
266		332 (M+1)+
267		400 (M+1)+
268		376 (M+1)+
269		346 (M+1)+
272*		362 (M+1)+
274		333.1 (M+1)+

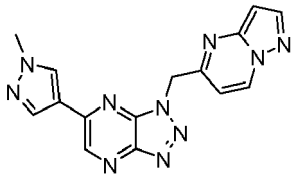
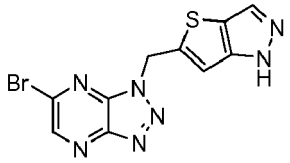
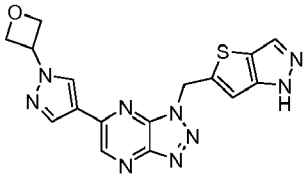
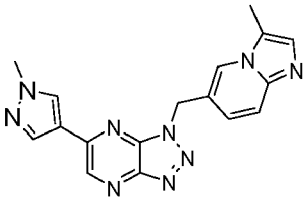
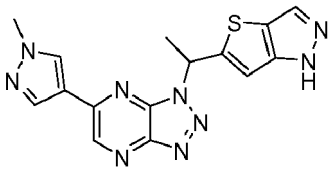
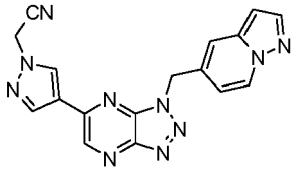
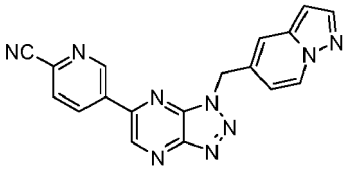
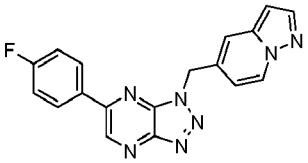
(continued)

Compound	Structure	LC/MS data
275		329.1 (M+1)$^+$
276		359 (M+1)$^+$
277		413.9 (M+1)$^+$
279		333 (M+1)$^+$
280		401 (M+1)$^+$
281		363.1 (M+1)$^+$
282		360.1 (M+1)$^+$
283		379.0 (M+1)$^+$

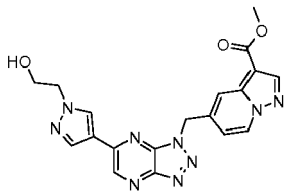
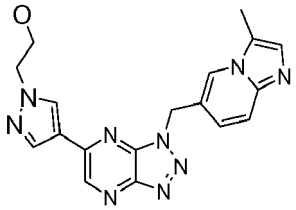
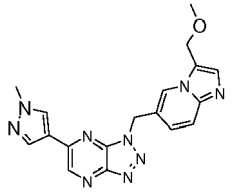
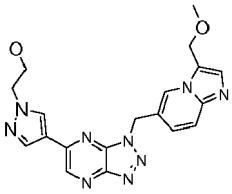
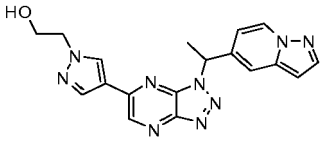
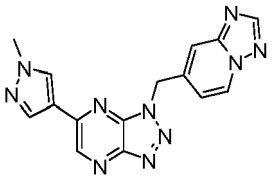
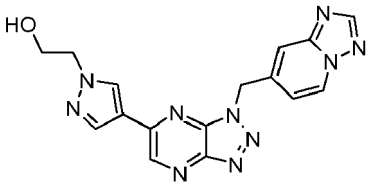
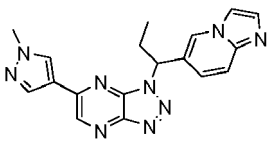
(continued)

Compound	Structure	LC/MS data
284		332.9 (M+1)$^+$
285		333 (M+1)$^+$
286		374.1 (M+1)$^+$
287		400.9 (M+1)$^+$
288		363.0 (M+1)'
289		350 (M+1)$^+$
290		373 (M+1)$^+$
293		401 (M+1)$^+$

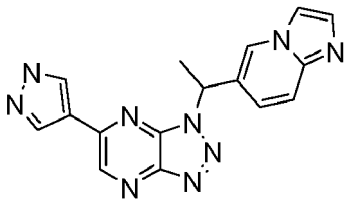
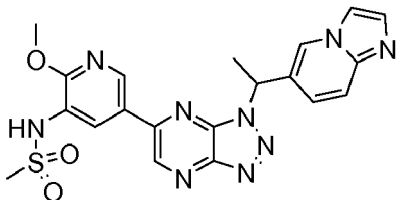
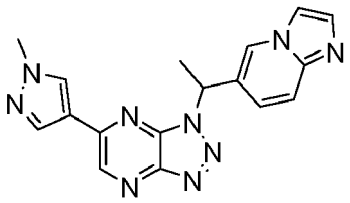
(continued)

Compound	Structure	LC/MS data
294		333 (M+1)$^+$
295		335.9 (M+1)$^+$
296		380.0 (M+1)$^+$
298		346 (M+1)$^+$
299		351.9 (M+1)$^+$
301		357.0 (M+1)$^+$
302		354.1 (M+1)$^+$
303		346.1 (M+1)$^+$

(continued)

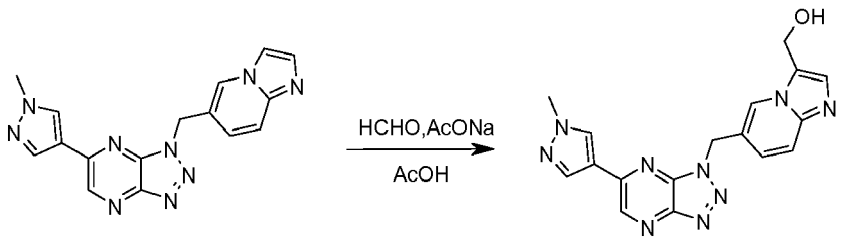
Compound	Structure	LC/MS data
304		420.0 $(M+1)^+$
305		376.0 $(M+1)^+$
308		376.0 $(M+1)^+$
309		405.9 $(M+1)^+$
310		375.9 $(M+1)^+$
316		333.0 $(M+1)^+$
317		362.9 $(M+1)^+$
326		360.1 $(M+1)^+$

(continued)

Compound	Structure	LC/MS data
328		332.1 $(M+1)^+$
329		466.1 $(M+1)^+$
331		346 $(M+1)^+$

***Compound 272** was prepared from **Compound 33** by the following procedure:

[0275]

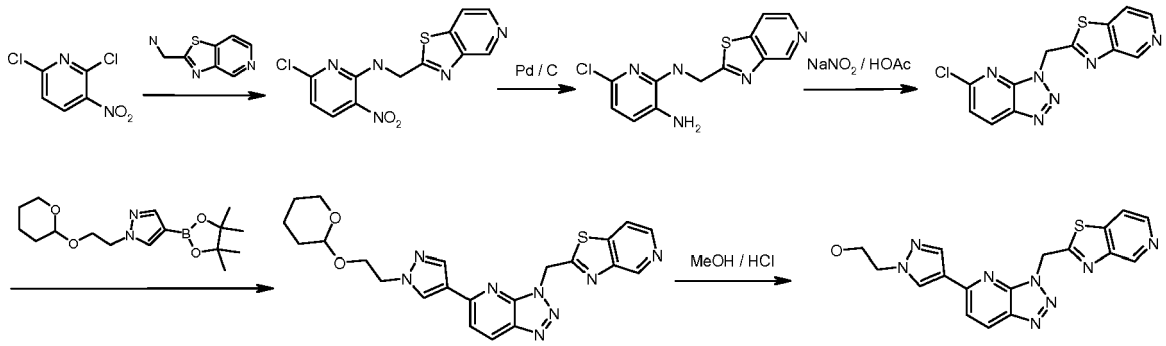


33 272

[0276] To a solution of compound 33 (66 mg, 0.2 mmol) in 0.1 mL of acetic acid were added sodium acetate (60 mg, 0.73 mmol) and an aqueous solution of formaldehyde (37%, 0.2 mL, 2.8 mmol). The reaction mixture was stirred at 100°C overnight. After cooled to room temperature, the reaction mixture was diluted with water and basified with a saturated sodium carbonate aqueous solution. The resulting precipitate was filtered. The filtrate was purified by chromatography to afford **compound 272** (30 mg).

Compound 60:

[0277]



3-Nitro-6-chloro-*N*-(thiazolo[4,5-c]pyridin-2-ylmethyl)pyridin-2-amine

[0278] To a solution of 3-nitro-2,6-dichloropyridine (106 mg, 0.55 mmol) in isopropanol (3 mL)was sequentially added Na_2CO_3 (116 mg, 1.1 mmol) and **intermediate R** (100 mg, 0.61 mmol). The reaction mixture was stirred at room temperature overnight, and then concentrated. The residue was extracted with EtOAc. The organic layer was separated, concentrated, and purified by chromatography on silica gel to afford the title compound. MS (m/z): 322 $(M)^+$.

6-Chloro-N^2-(thiazolo[4,5-c]pyridin-2-ylmethyl)pyridine-2,3-diamine

[0279] 10% Pd/C (20 mg) was added to a solution of 3-nitro-6-chloro-*N*-(thiazolo[4,5-c]pyridin-2-ylmethyl)pyridin-2-amine (100 mg, 0.31 mmol) in MeOH (2 mL) and THF (10 mL). The mixture was stirred at room temperature under 1 atm of H_2 for 1h, and then filtered. The filtrate was concentrated and purified by chromatography on silica gel to afford the title compound. MS (m/z): 292 $(M+1)^+$.

5-Chloro-3-(thiazolo[4,5-c]pyridin-2-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[0280] A solution of $NaNO_2$ (42.5 mg, 0.62 mmol) in H_2O (0.5 mL) was added dropwise to a solution of 6-chloro-N^2-(thiazolo[4,5-c]pyridin-2-ylmethyl)pyridine-2,3-diamine (90 mg, 0.31 mmol) in AcOH (1 mL) and H_2O (1 mL) at 0°C. The reaction solution was stirred at 0°C for 1h, then basified with 30% aqueous NaOH to pH ~ 9. The resulting precipitate was collected by filtration to afford the title compound. MS (m/z): 303 $(M+1)^+$.

5-(1-(2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-3-(thiazolo[4,5-c]pyridin-2-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[0281] To a solution of **intermediate X** (75 mg, 0.23 mmol), 5-chloro-3-(thiazolo[4,5-c]pyridin-2-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridine (64 mg, 0.21 mmol) in dioxane (1.5 mL) and H_2O (0.15 mL) were added $Pd(dppf)Cl_2$ (32.7 mg, 0.04 mmol) and Cs_2CO_3 (98 mg, 0.3 mmol) under N_2. The resulting mixture was stirred at 120°C overnight under N_2, and then concentrated. The residue was purified by chromatography to afford the title compound. MS (m/z): 463 $(M+1)^+$.

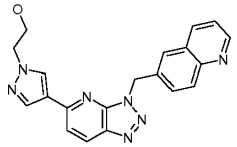
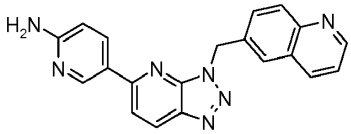
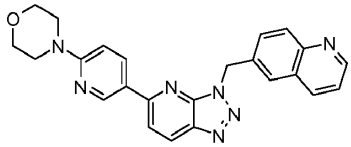
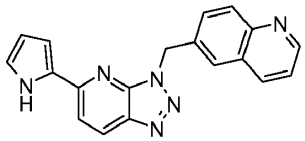
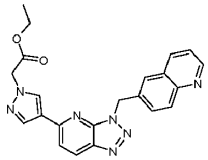
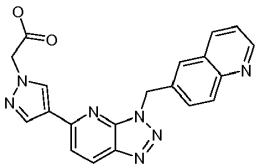
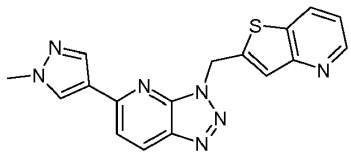
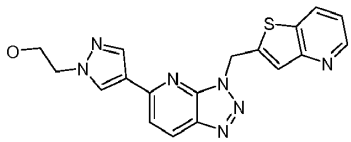
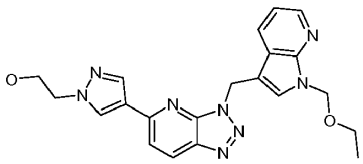
2-(4-(3-(Thiazolo[4,5-c]pyridin-2-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-5-yl)-1H-pyrazol-1-yl)ethanol

[0282] 5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-3-(thiazolo[4,5-c]pyridin-2-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridine (20 mg, 0.04 mmol) was dissolved in MeOH/HCl (2 mL). The reaction mixture was stirred at room temperature for 1h, and then concentrated. The residue was purified by chromatography to afford the title compound. MS (m/z): 379 $(M+1)^+$.

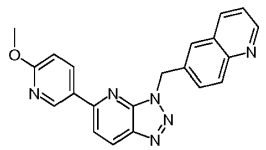
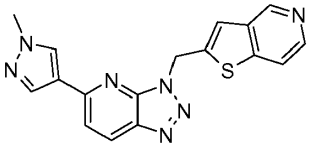
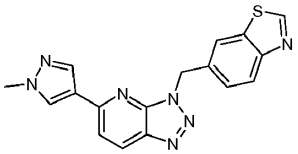
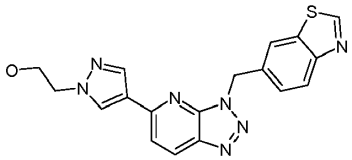
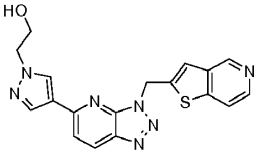
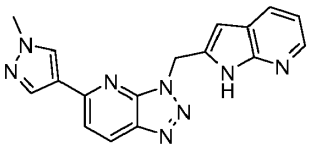
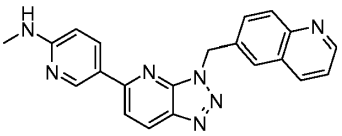
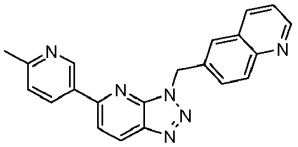
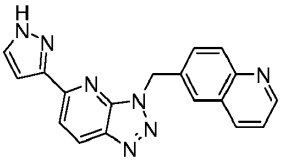
Compounds 61-76, 79, 81-151, 273, 291, 292, 297, 332

[0283] The following compounds **61-76, 79, 81--151, 273, 291, 292, 297, 332** were prepared according to the procedures of Compound **60** using the corresponding intermediates and boronic acid or ester under appropriate conditions that will be recognized by one skilled in the art:

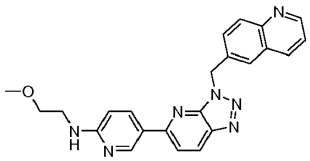
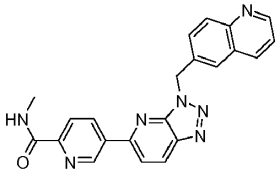
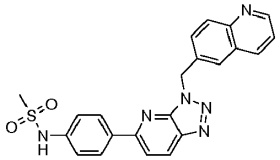
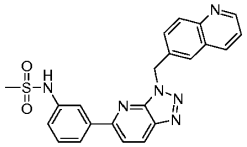
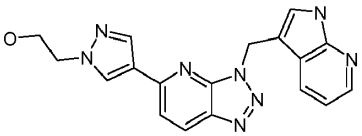
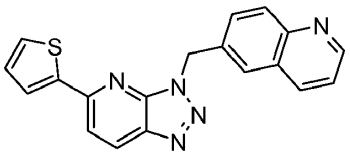
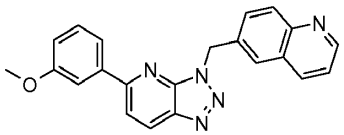
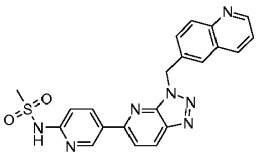
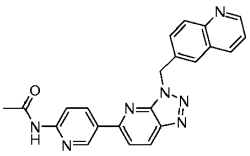
Table 2

Compound	Structure	LC/MS data
61		372 $(M+1)^+$
62		354 $(M+1)^+$
63		424 $(M+1)^+$
64		327 $(M+1)^+$
65		414 $(M+1)^+$
66		386 $(M+1)^+$
67		348 $(M+1)^+$
68		378 $(M+1)^+$
69		419 $(M+1)^+$

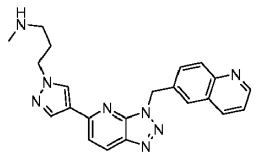
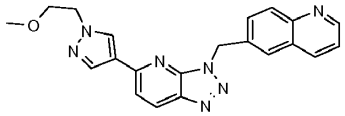
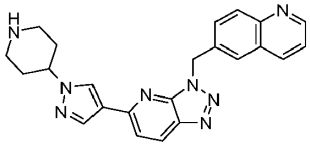
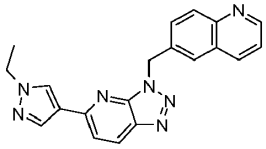
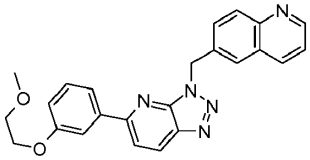
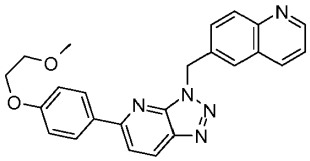
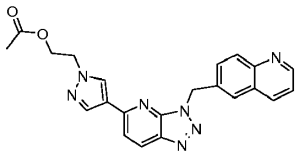
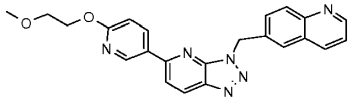
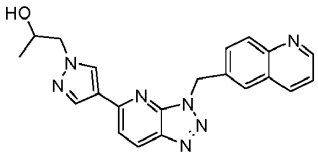
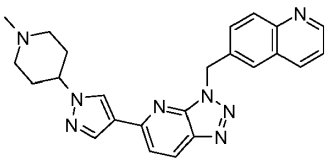
(continued)

Compound	Structure	LC/MS data
70		369 $(M+1)^+$
71		348 $(M+1)^+$
72		348 $(M+1)^+$
73		378 $(M+1)^+$
74		378 $(M+1)^+$
75		331 $(M+1)^+$
76		368 $(M+1)^+$
79		353 $(M+1)^+$
81		328 $(M+1)^+$

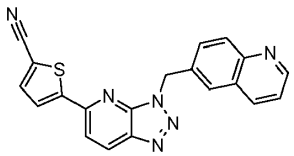
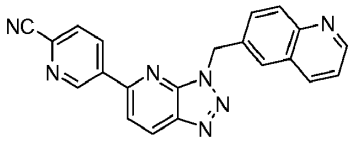
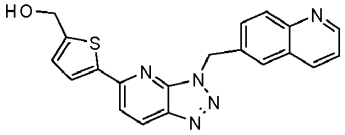
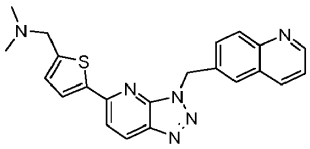
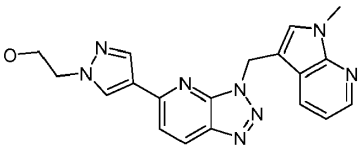
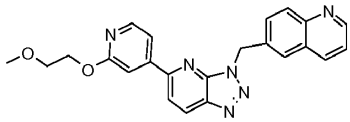
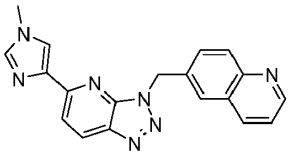
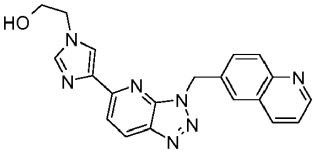
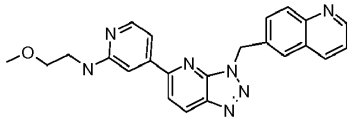
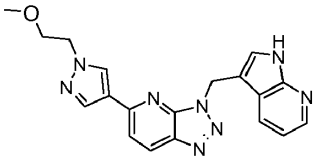
(continued)

Compound	Structure	LC/MS data
82		412 $(M+1)^+$
83		396 $(M+1)^+$
84		431 $(M+1)^+$
85		431 $(M+1)^+$
86		361 $(M+1)^+$
87		344 $(M+1)^+$
88		368 $(M+1)^+$
90		432 $(M+1)^+$
91		396 $(M+1)^+$

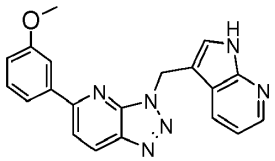
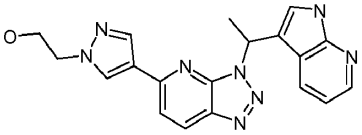
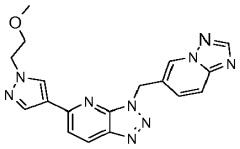
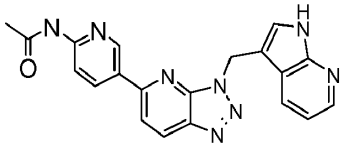
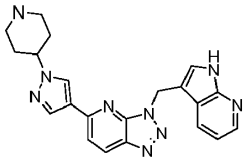
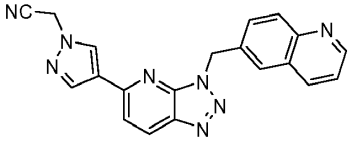
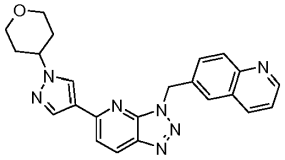
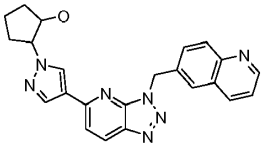
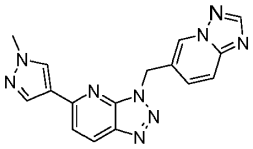
(continued)

Compound	Structure	LC/MS data
92		399 $(M+1)^+$
93		386 $(M+1)^+$
94[1]		411 $(M+1)^+$
95		356 $(M+1)^+$
96		412 $(M+1)^+$
97		412 $(M+1)^+$
98[2]		414 $(M+1)^+$
99		413 $(M+1)^+$
100		386 $(M+1)^+$
101[3]		425 $(M+1)^+$

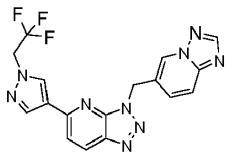
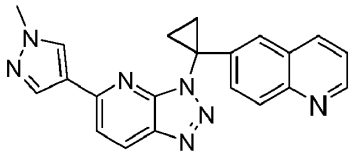
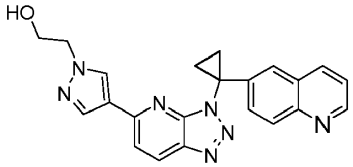
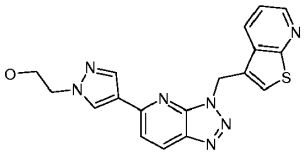
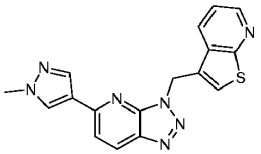
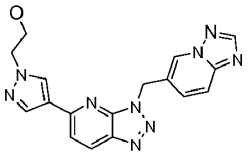
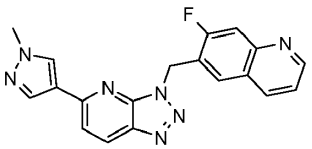
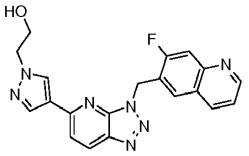
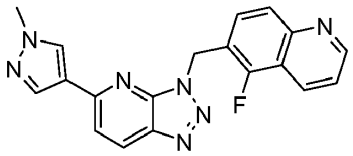
(continued)

Compound	Structure	LC/MS data
102		369 $(M+1)^+$
103		364 $(M+1)^+$
104[4]		374 $(M+1)^+$
105[5]		401 $(M+1)^+$
106		375 $(M+1)^+$
107		413 $(M+1)^+$
108[6]		342 $(M+1)^+$
109[6]		372 $(M+1)^+$
110		412 $(M+1)^+$
111		375 $(M+1)^+$

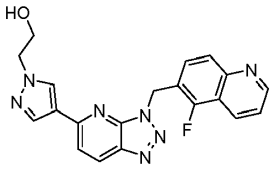
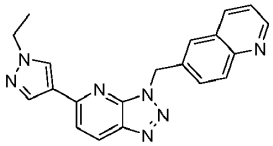
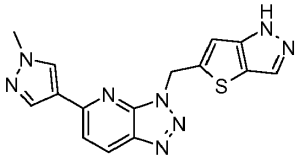
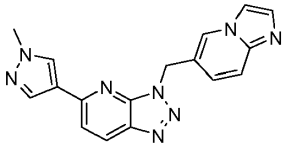
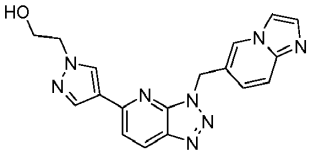
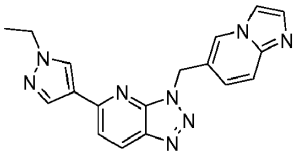
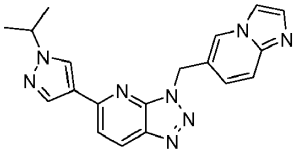
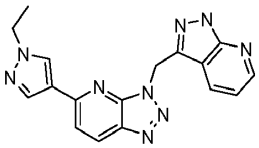
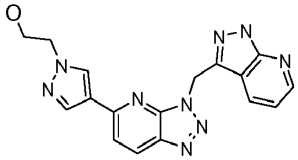
(continued)

Compound	Structure	LC/MS data
112		357 $(M+1)^+$
113		375 $(M+1)^+$
114		376 $(M+1)^+$
115		385 $(M+1)^+$
116[7]		400 $(M+1)^+$
117		367 $(M+1)^+$
118		412 $(M+1)^+$
119		412 $(M+1)^+$
120		332 $(M+1)^+$

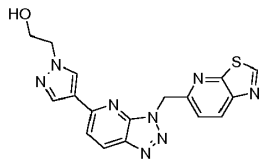
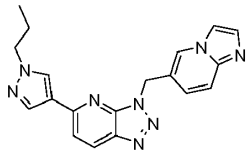
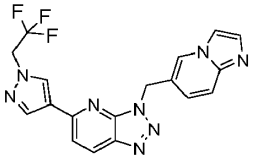
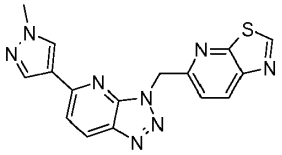
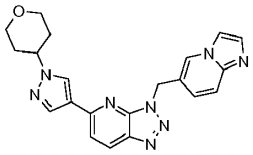
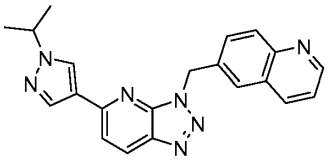
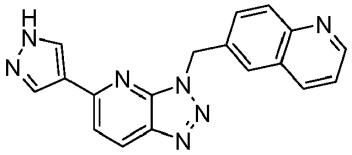
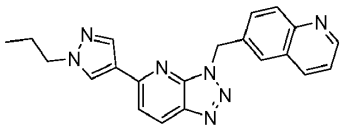
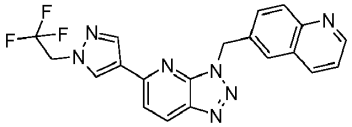
(continued)

Compound	Structure	LC/MS data
121		400 $(M+1)^+$
122		368 $(M+1)^+$
123		398 $(M+1)^+$
124		378 $(M+1)^+$
125		348 $(M+1)^+$
126		362 $(M+1)^+$
127		360 $(M+1)^+$
128		390 $(M+1)^+$
129		360 $(M+1)^+$

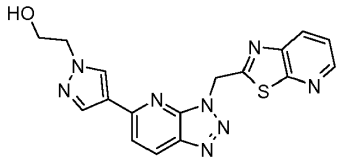
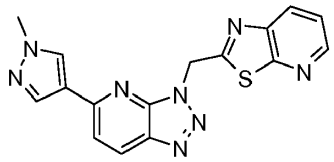
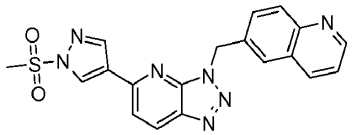
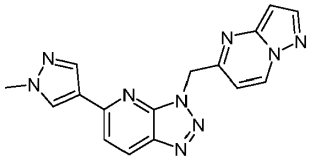
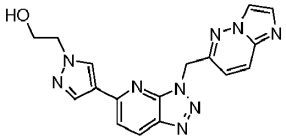
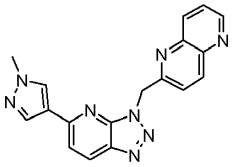
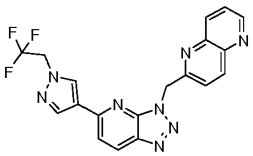
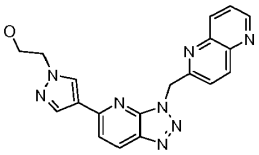
(continued)

Compound	Structure	LC/MS data
130		390 $(M+1)^+$
131		356 $(M+1)^+$
132		337 $(M+1)^+$
133		331 $(M+1)^+$
134		361 $(M+1)^+$
135		345 $(M+1)^+$
136		359 $(M+1)^+$
137		346 $(M+1)^+$
138[8]		362 $(M+1)^+$

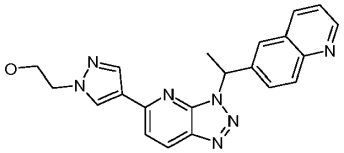
(continued)

Compound	Structure	LC/MS data
139		379 $(M+1)^+$
140		359 $(M+1)^+$
141		399 $(M+1)^+$
142		349 $(M+1)^+$
143		401 $(M+1)^+$
144		370 $(M+1)^+$
145		328 $(M+1)^+$
146		370 $(M+1)^+$
147		410 $(M+1)^+$

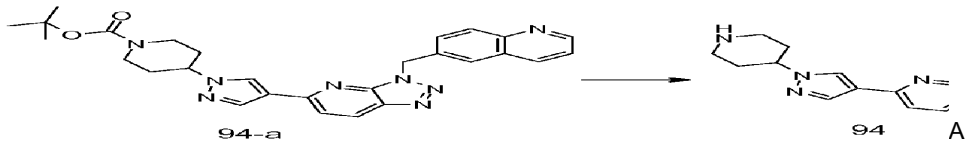
(continued)

Compound	Structure	LC/MS data
148[9]		379 $(M+1)^+$
149[9]		349 $(M+1)^+$
150		406 $(M+1)^+$
151		332 $(M+1)^+$
273		362.1 $(M+1)^+$
291		343.1 $(M+1)^+$
292		411 $(M+1)^+$
297		373.1 $(M+1)^+$

(continued)

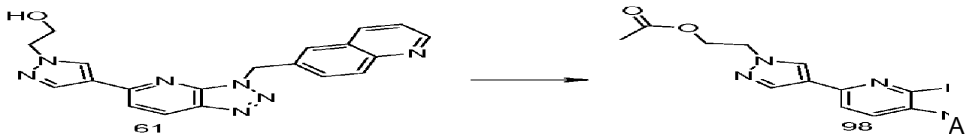
Compound	Structure	LC/MS data
332		386 $(M+1)^+$

[1] Using the following procedure, Compound **94** was synthesized from intermediate **94-a** that was prepared according to the procedures of Compound **60** using the corresponding intermediates and boronic acid or ester under appropriate conditions that will be recognized by one skilled in the art. :



A solution of **94-a** (30 mg, 0.06 mmol) in TFA (2 mL) and DCM (2 mL) was stirred at room tempature overnight, then concentrated. The residue was dissolved in aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was concentrated and purified on silica gel to afford Compound **94.**

[2]Compound **98** was prepared from Compound **61** using the following procedure:

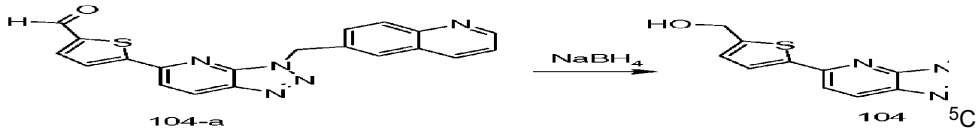


A solution of Compound **61** in DCM was treated with Et_3N and acetyl chloride at room temparature for 3 h. It was then treated with water and extracted with DCM (15 mL x 2). The combined organic extracts were dried, concentrated and the residue was purified on silica to afford Compound **98.**

[3]Compound **101** was prepared from Compound **94** using the following procedure:

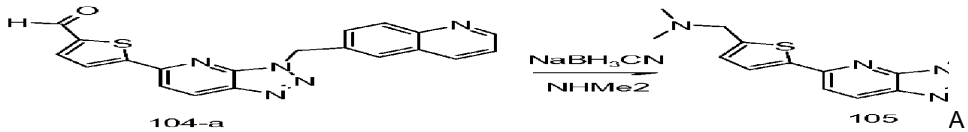
To a solutoin of Compound **94** (18 mg, 0.044 mmol) in anhydrous DCM (2 mL) was added Et_3N (12.2 uL, 0.088 mmol), followed by CH_3I (2.4 uL, 0.048 mmol) at 0 °C. The reaction mixture was warmed to room tempature, and stirred for over 1 h. A saturated sodium bicarbonate aqueous solution was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated. The resulting residue was purified on silica to afford Compound **101.**

[4] Compound **104** was prepared according to the procedure of Intermediates **W-1** to **W** using Intermediate **104-a** that was prepared according to the procedures of Compound **60.**



[5]C

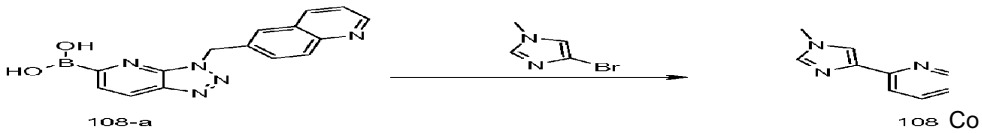
ompound **105** was prepared from intermediate **104-a** by the following procedure



A

mixture of intermediate **104-a** (37 mg, 0.1 mmol) and exessive amount of dimethylamine in methanol (5 mL) was stirred at room temperature for 1 h. Sodium cyano borohydride (12 mg) was added. The resulting mixture was stirred at room temperature for 16 h, then concentrated. The residue was treated with saturated aqueous sodium bicarbonate and DCM. The organic layer was separated, concentrated. The residue was purified on silica to afford Compound **105** (8 mg).

[6] Under similar conditions of Compound **60,** Compound **108** was prepared by using Intermediate **108-a** that was prepared according to the procedure of intermediates **U-3** to **U**



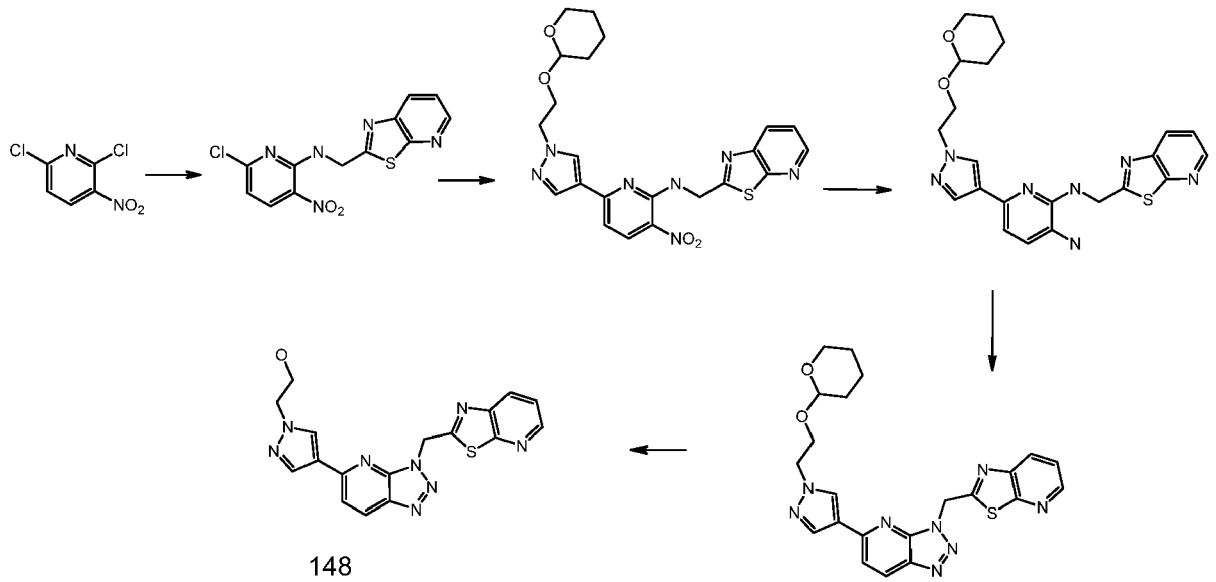
Co

mpound **109** was prepared similar to Compound **108**

[7] Compound **116** was prepared according to the procedures of Compound **94.**

[8] $P(t\text{-}Bu)_3HBF_4$ and $Pd_2(dba)_3$ were used instead of $Pd(dppf)Cl_2$ in the procedure of Compound **138.**

[9] Compounds **148** was prepared by the following route using similar conditions described for Compound **60.**

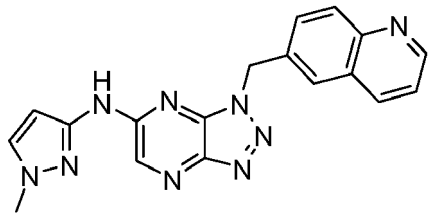


148

[0284] According to the procedure of Compound **148,** Compound **149** was prepared using the corresponding intermediates and reagents under appropriate conditions that will be recognized by one skilled in the art:

Compound 152: *N*-(1-methyl-1H-pyrazol-3-yl)-1-(quinolin-6-ylmethyl)-1H-[1,2,3]triazolo-[4,5-b]pyrazin-6-amine

[0285]

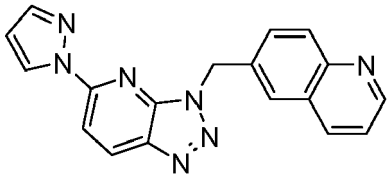


[0286] To a suspension of 6-((6-bromo-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)quinoline (68 mg, 0.2 mmol) (prepared from quinolin-6-ylmethanamine following the procedures of **Compound 1**) and 1-methyl-1H-pyrazol-3-amine (20 mg, 0.22 mmol) in dioxane (5mL) were added Cs_2CO_3 (72 mg, 0.22 mmol) and H_2O (0.5 mL). The mixture was degassed and charged with N_2 three times, then $Pd_2(dba)_3$ (0.02 mmol, 18 mg) and xantphos (0.04 mmol, 23 mg) were added. The resulting mixture was stirred at 120°C under one atmosphere of N_2 overnight, then concentrated. The resulting residue was purified by chromatography to afford the title compound (10 mg). MS (m/z): 358 $(M+1)^+$.

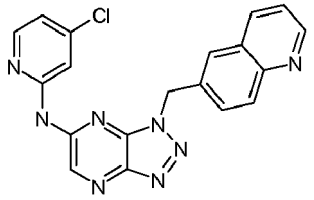
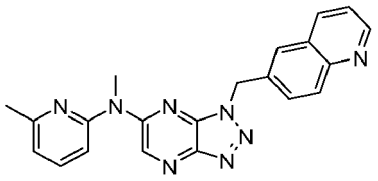
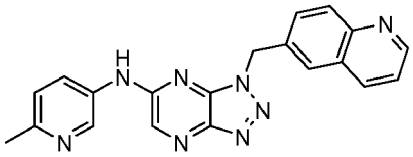
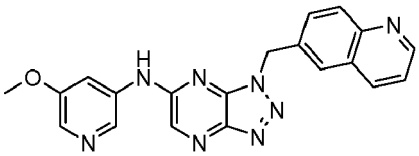
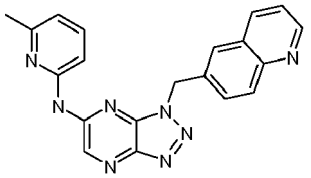
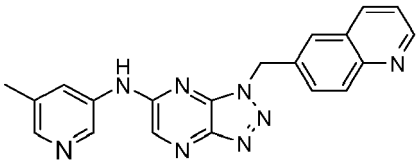
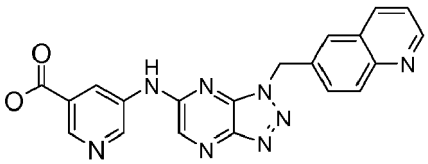
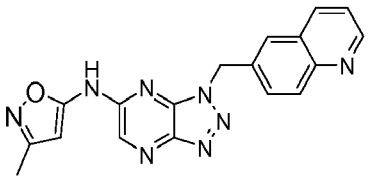
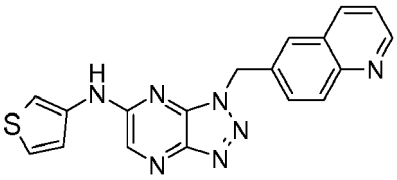
Compounds 80, 153-240

[0287] The following compounds **80, 153-240** were prepared according to the procedure of Compound **152** using the corresponding intermediates and amines under appropriate conditions that will be recognized by one skilled in the art:

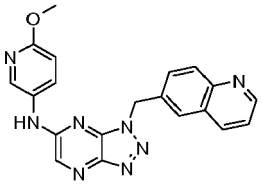
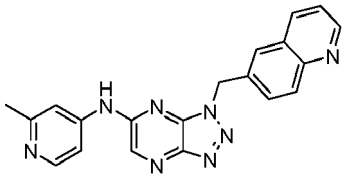
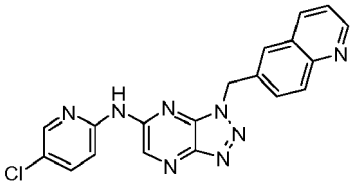
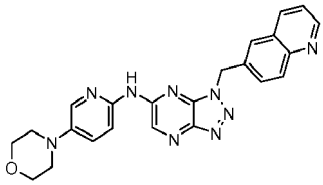
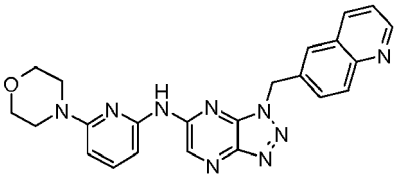
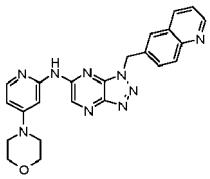
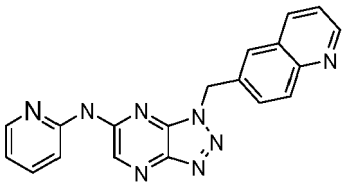
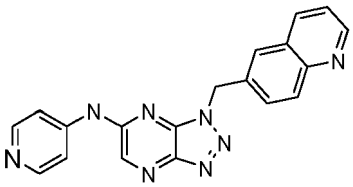
Table 3

Compound	Structure	LC/MS data
80		328 $(M+1)^+$

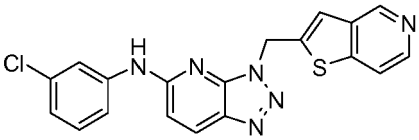
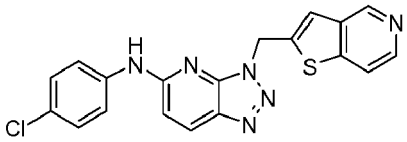
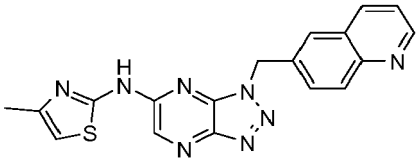
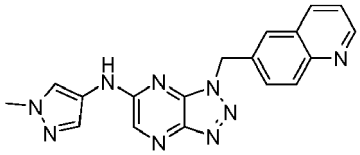
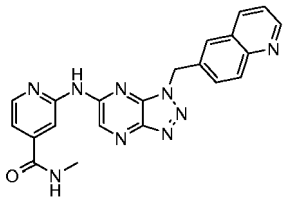
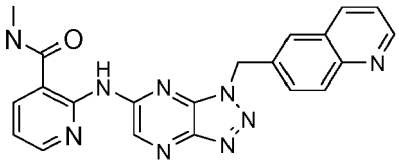
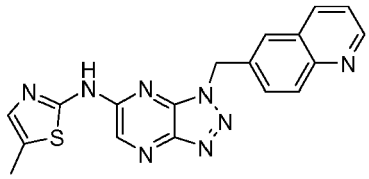
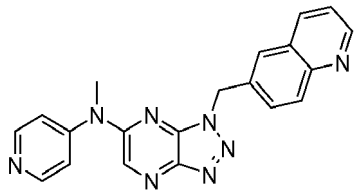
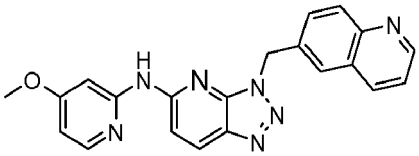
(continued)

Compound	Structure	LC/MS data
153		389 $(M+1)^+$
154[10]		383 $(M+1)^+$
155		369 $(M+1)^+$
156		385 $(M+1)^+$
157		369 $(M+1)^+$
158		369 $(M+1)^+$
159		399 $(M+1)^+$
160		359 $(M+1)^+$
161		360 $(M+1)^+$

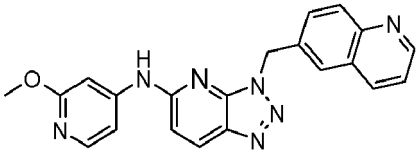
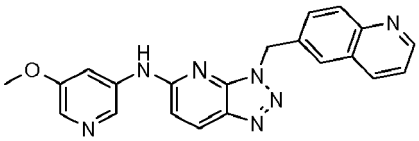
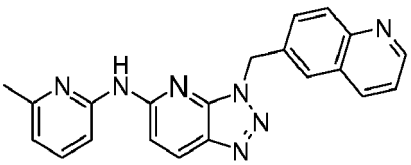
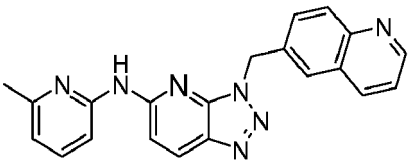
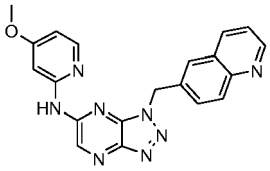
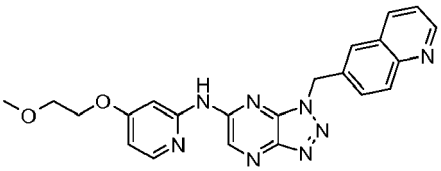
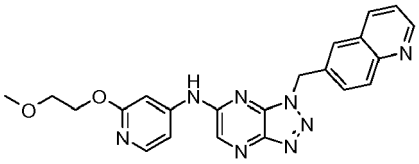
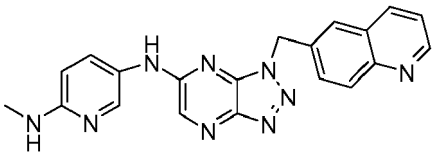
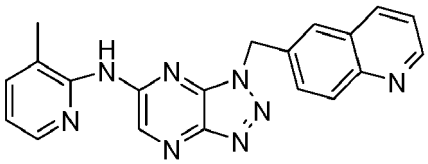
(continued)

Compound	Structure	LC/MS data
162		385 $(M+1)^+$
163		369 $(M+1)^+$
164		389 $(M+1)^+$
165		440 $(M+1)^+$
166		440 $(M+1)^+$
167		440 $(M+1)^+$
168		355 $(M+1)^+$
169		355(M+1)+

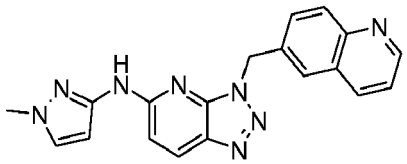
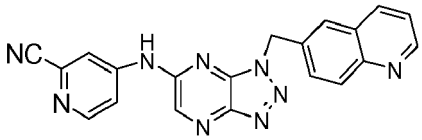
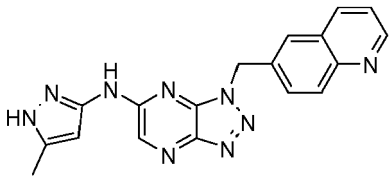
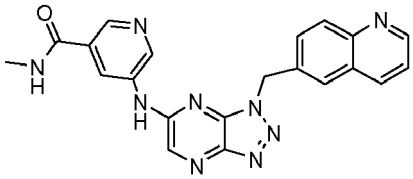
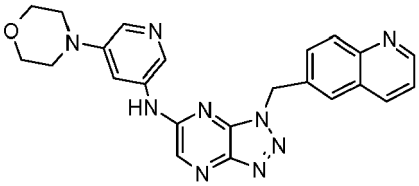
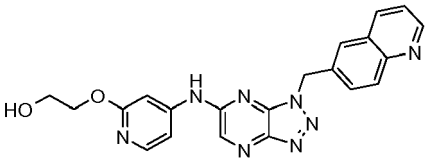
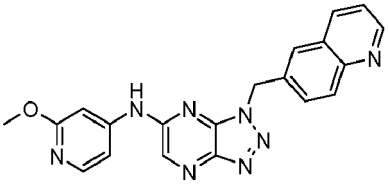
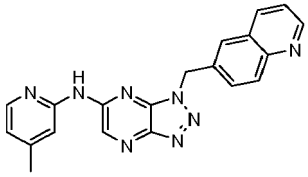
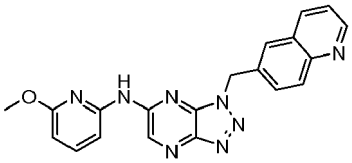
(continued)

Compound	Structure	LC/MS data
170		393 $(M+1)^+$
171		393 $(M+1)^+$
172		375 $(M+1)^+$
173		358 $(M+1)^+$
174		412 $(M+1)^+$
175		412 $(M+1)^+$
176		375 $(M+1)^+$
177[10]		369 $(M+1)^+$
178		384 $(M+1)^+$

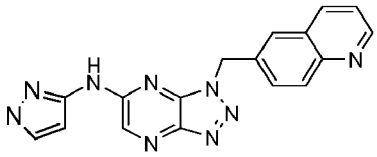
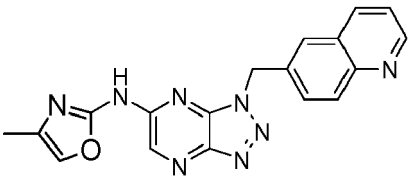
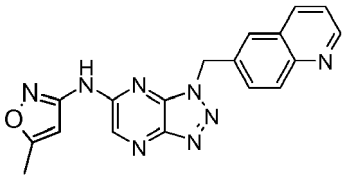
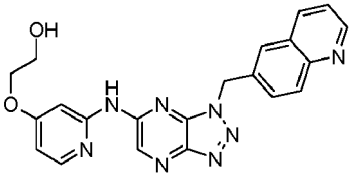
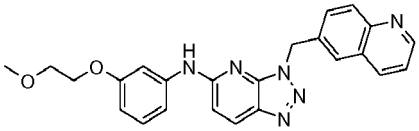
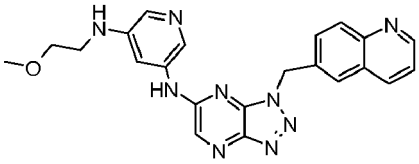
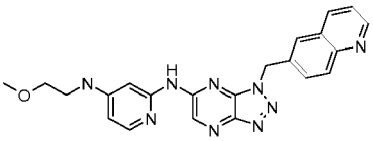
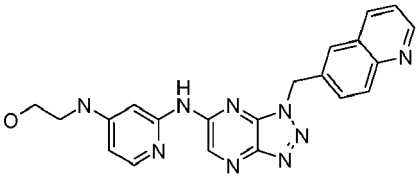
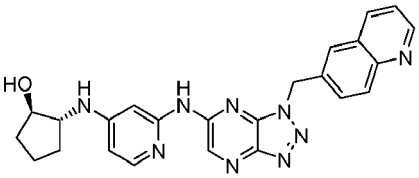
(continued)

Compound	Structure	LC/MS data
179		384 $(M+1)^+$
180		384 $(M+1)^+$
181		368(M+1)+
182		368 $(M+1)^+$
183		385 $(M+1)^+$
185		429 $(M+1)^+$
186		429 $(M+1)^+$
187		384 $(M+1)^+$
188		369 $(M+1)^+$

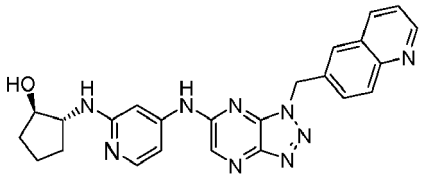
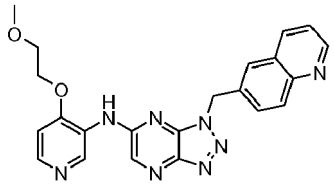
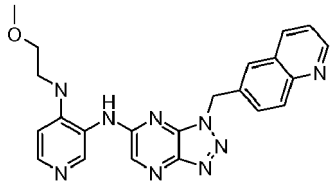
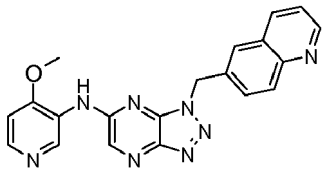
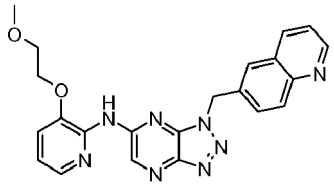
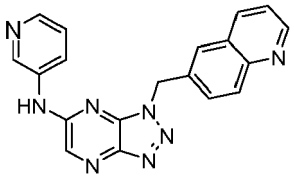
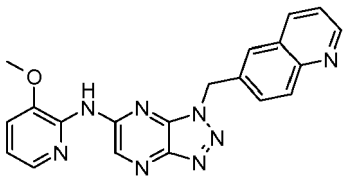
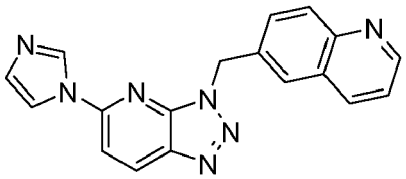
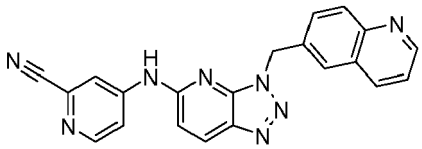
(continued)

Compound	Structure	LC/MS data
189		357(M+1)+
190		380 $(M+1)^+$
191		358 $(M+1)^+$
192		412 $(M+1)^+$
193		440 $(M+1)^+$
194		415 $(M+1)^+$
195		385 $(M+1)^+$
196		369 $(M+1)^+$
197		385 $(M+1)^+$

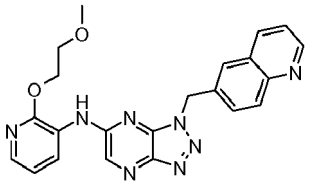
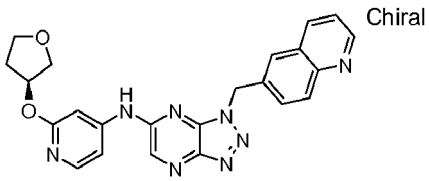
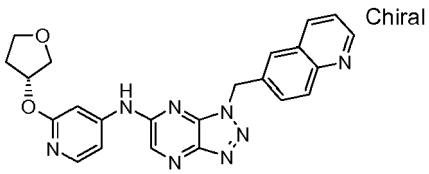
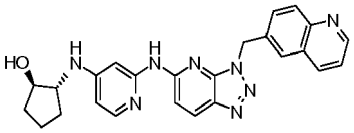
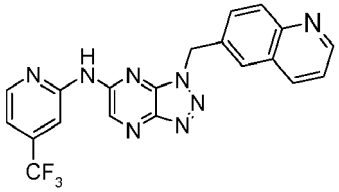
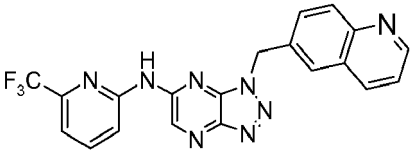
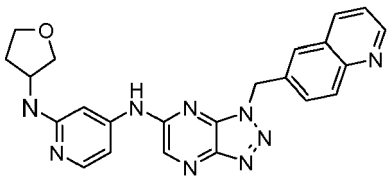
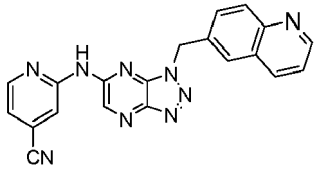
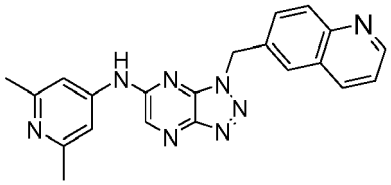
(continued)

Compound	Structure	LC/MS data
198		344 $(M+1)^+$
199		359 $(M+1)^+$
200		359 $(M+1)^+$
201		415 $(M+1)^+$
202		427 $(M+1)^+$
203		428 $(M+1)^+$
204		428 $(M+1)^+$
205		414 $(M+1)^+$
206		454 $(M+1)^+$

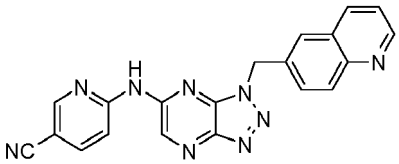
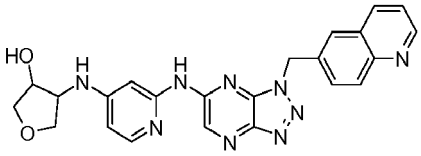
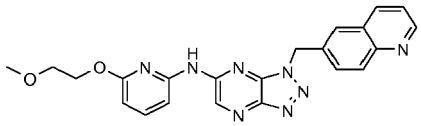
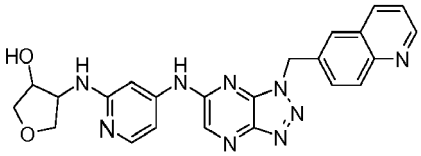
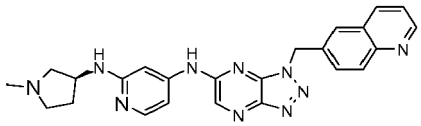
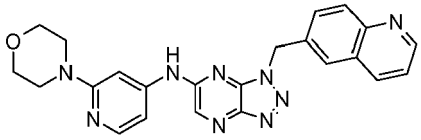
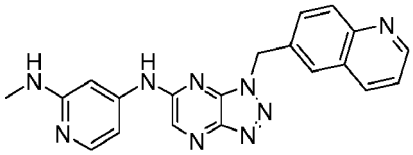
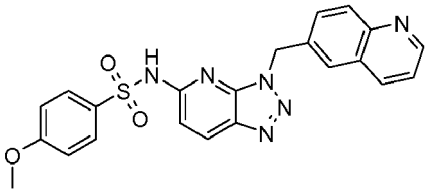
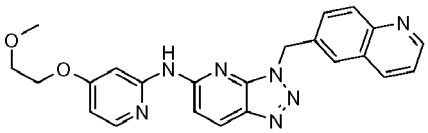
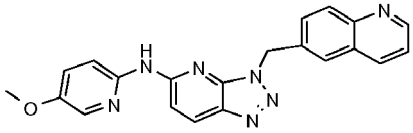
(continued)

Compound	Structure	LC/MS data
207		454 $(M+1)^+$
208		429 $(M+1)^+$
209		428(M+1)+
210		385 $(M+1)^+$
211		429 $(M+1)^+$
212		355 $(M+1)^+$
213		385 $(M+1)^+$
214		328 $(M+1)^+$
215		379 $(M+1)^+$

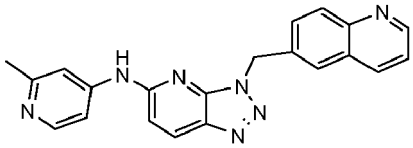
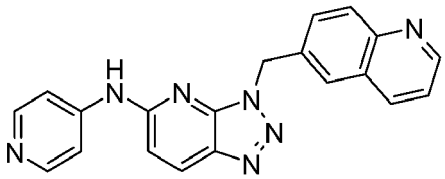
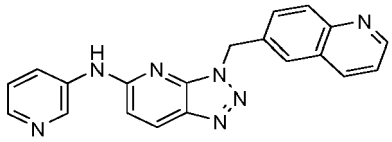
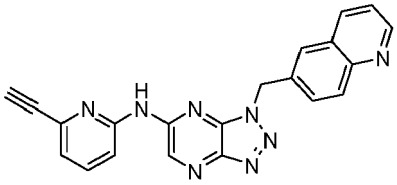
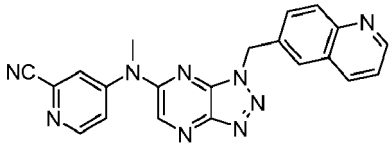
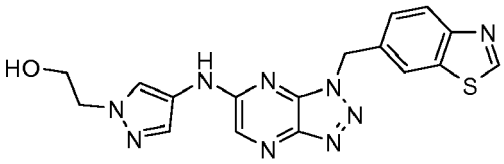
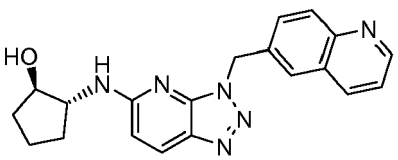
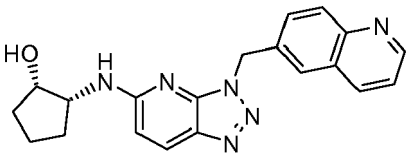
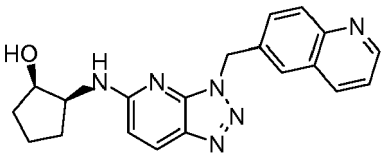
(continued)

Compound	Structure	LC/MS data
216		429 (M+1)$^+$
217	 Chiral	441 (M+1)$^+$
218	 Chiral	441 (M+1)$^+$
219		453 (M+1)$^+$
220		423 (M+1)$^+$
221		423 (M+1)$^+$
222		440 (M+1)$^+$
223		380 (M+1)$^+$
224		383 (M+1)$^+$

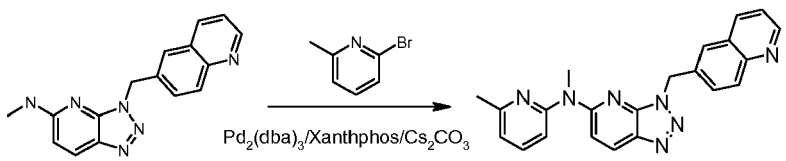
(continued)

Compound	Structure	LC/MS data
225		379 $(M)^+$
226		455 $(M+1)^+$
227		428 $(M)^+$
228		456 $(M+1)^+$
229		453 $(M+1)^+$
230		440 $(M+1)^+$
231		384 $(M+1)^+$
232		447 $(M+1)^+$
233		427 $(M)^+$
234		384 $(M+1)^+$

(continued)

Compound	Structure	LC/MS data
235		368 $(M+1)^+$
236		354 $(M+1)^+$
237		354 $(M+1)^+$
238		379 $(M+1)^+$
239[10]		394 $(M+1)^+$
240		394 $(M+1)^+$
241	 Chiral	361 $(M+1)^+$
242	 Chiral	361 $(M+1)^+$
243	 Chiral	361 $(M+1)^+$

[0288] [10] Under similar conditions described in Compound **152,** Compound **154** was synthesized by using Intermediate **154-a** that was prepared according to the procedure of Compound **244,** under appropriate conditions that will be recognized by one skilled in the art.

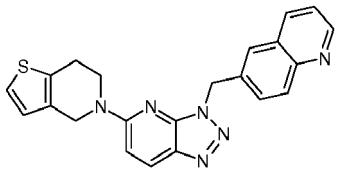


154-a 154

[0289] According to the procedure of Compound **154, Compound 177** and **239** were prepared using the corresponding intermediates and reagents under appropriate conditions that will be recognized by one skilled in the art.

Compound 244: 6-((6-(Pyridin-4-ylthio)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)-quinoline

[0290]

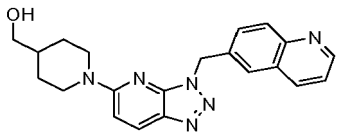
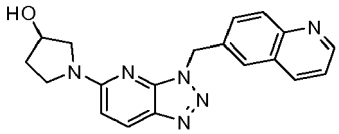
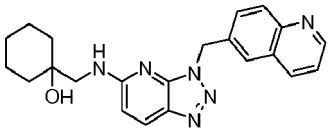
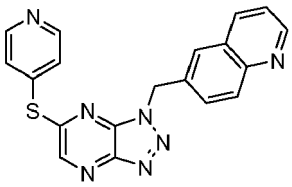


[0291] The mixture 6-((5-chloro-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)methyl)quinoline (60 mg, 0.2 mmol) (prepared according to Compound **60**), Cs_2CO_3 (195 mg, 0.6 mmol) and 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (52 mg, 0.3 mmol) in DMF (1.5 mL) was stirred at 120°C overnight, then concentrated. The residue was purified by chromatography to afford the title compound MS (m/z): 399 $(M+1)^+$.

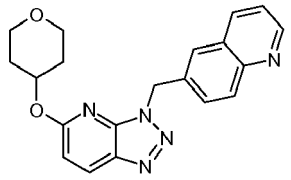
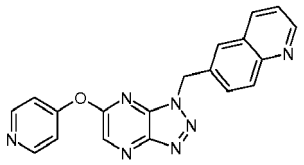
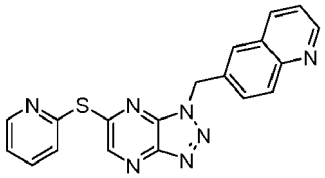
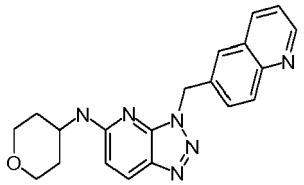
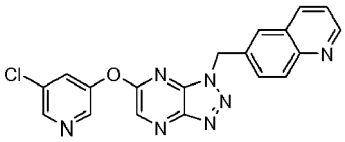
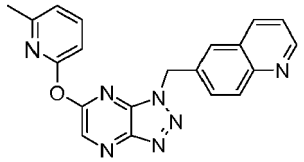
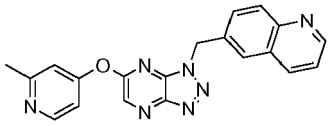
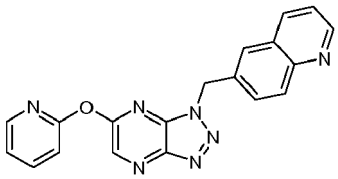
Compounds 245-260

[0292] The following compounds **245-260** were prepared according to the procedures of Compound **244** using the corresponding intermediates under similar conditions that will be recognized by one skilled in the art.

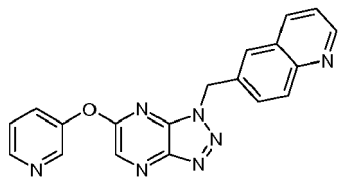
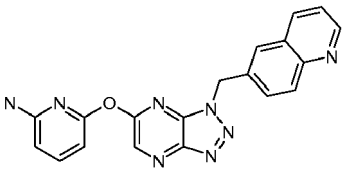
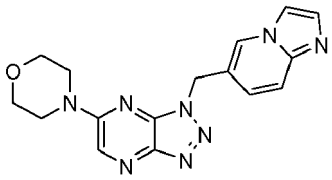
Table 4

Compound	Structure	LC/MS data
245		375 $(M+1)^+$
246		347 $(M+1)^+$
247		389 $(M+1)^+$
248		372 $(M+1)^+$

(continued)

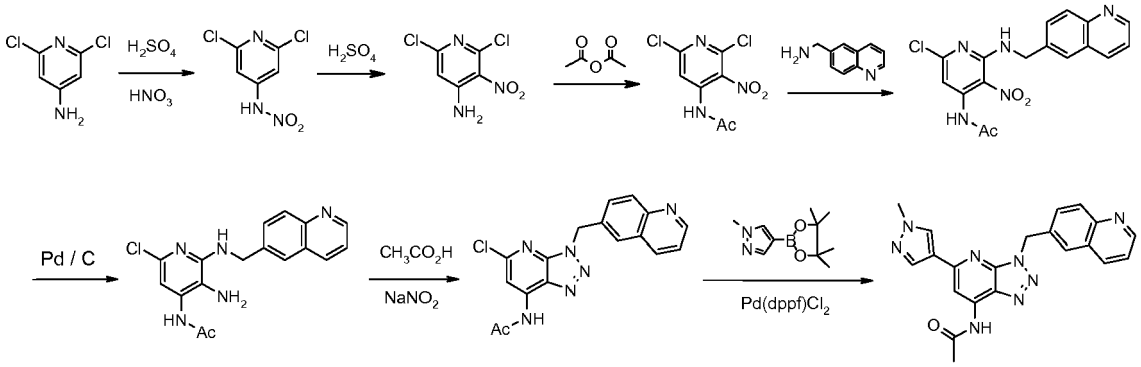
Compound	Structure	LC/MS data
249		362 $(M+1)^+$
250		356 $(M+1)^+$
252		372 $(M+1)^+$
253		361 $(M+1)^+$
254		389 $(M)^+$
255		370 $(M+1)^+$
256		370 $(M+1)^+$
257		356 $(M+1)^+$

(continued)

Compound	Structure	LC/MS data
258		356 $(M+1)^+$
259		371 $(M+1)^+$
260		337 $(M+1)^+$

Compound 261: *N*-(5-(1-methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)acetamide

[0293]



***N*-(2,6-Dichloropyridin-4-yl)nitramide**

[0294] 2,6-Dichloropyridin-4-amine (3.0 g, 18 mmol) was carefully added to concentrated sulfuric acid (20 mL). The mixture was cooled in an ice bath, and fuming nitric acid (2.6 mL) was added dropwise via pipette. The mixture was warmed to room temperature and stirred for 1h, then poured onto crushed ice, resulting in a white precipitate. The white precipitate was collected by filtration, washed with cold water, and dried to afford the title compound (3.7 g), which was used for next step without further purification.

2,6-Dichloro-3-nitropyridin-4-amine

[0295] *N*-(2,6-Dichloropyridin-4-yl)nitramide (3.7 g, 18 mmol) was added to concentrated sulfuric acid (5 mL), and the reaction mixture was heated at 60 °C for 30 mins After cooled to room temperature, the reaction mixture was poured onto crushed ice, and concentrated ammonium hydroxide was addded until the pH reached about 7. The precipitate was collected by filtration, washed with ice cold water, and dried to afford the title compound (2.5 g). MS (m/z): 208 $(M+1)^+$.

***N*-(2,6-Dichloro-3-nitropyridin-4-yl)acetamide**

[0296] 2,6-Dichloro-3-nitropyridin-4-amine (208 mg, 1 mmol) was added to acetic anhydride (2 mL), and the reaction mixture was refluxed overnight. After cooled to room temperature, the reaction mixture was basified with aqueous Na_2CO_3 until the pH was 8. The resulting mixture was then extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and concentrated to afford the title compound (240 mg), which was used for the next step without further purification. MS (m/z): 250 $(M+1)^+$.

***N*-(6-Chloro-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4-yl)acetamide**

[0297] To a mixture of *N*-(2,6-dichloro-3-nitropyridin-4-yl)acetamide (240 mg, 0.96 mmol) and quinolin-6-ylmethanamine (150 mg, 0.96 mmol) in CH3CN (10 mL) was added Et_3N (0.5 mL). The reaction mixture was stirred at 80 °C for 1h. After being cooled to room temperature, the mixture was purified by chromatography on silica gel eluting with DCM/MeOH =50/1 to afford the title compound (220 mg). MS (m/z): 372 $(M+1)^+$.

***N*-(3-Amino-6-chloro-2-(quinolin-6-ylmethylamino)pyridin-4-yl)acetamide**

[0298] To a solution of *N*-(6-chloro-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4 yl)acetamide (220 mg, 0.593 mmol) in methanol (5 mL) and CH_2Cl_2(5 mL) was added 10% catalytical amount Pd/C. The reaction mixture was stirred at room temperature under 1 atm of H_2 for 1h, then filtered. The filtrate was concentrated to afford the title compound, which was used for the next step without further purification. MS (m/z): 342 $(M+1)^+$.

***N*-(5-Chloro-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)acetamide**

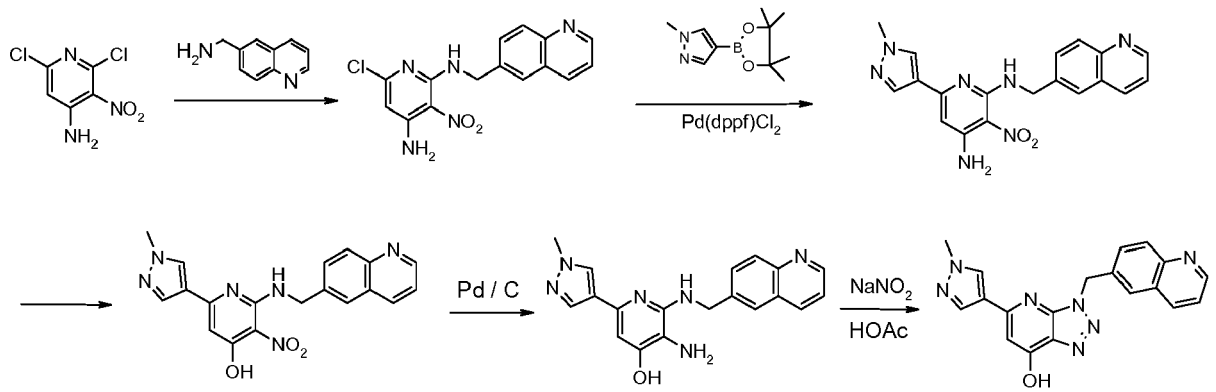
[0299] *N*-(3-amino-6-chloro-2-(quinolin-6-ylmethylamino)pyridin-4-yl)acetamide was added to a solution of acetic acid (2 mL) and water (2 mL) at 0 °C, followed by the addition of $NaNO_2$ (180 mg, 2.6 mmol) in H_2O (0.2 mL). The reaction was stirred at 0°C for 1h, and then basified with 30% NaOH to pH = 7. The resulting precipitate was collected by filtration to afford the title compound (80 mg), which was used for the next step without further purification. MS (m/z): 353 $(M+1)^+$.

***N*-(5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)acetamide**

[0300] To a mixture of *N*-(5-chloro-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl)acetamide (80 mg, 0.227 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (50 mg, 0.24 mmol) and Na_2CO_3 (48 mg, 0.25 mmol) in dioxane (10 mL) and H_2O (1 mL) under N_2 was added $Pd(dppf)Cl_2$ (20 mg, 0.02 mmol). The reaction mixture was stirred at 100°C under N_2 overnight. After cooled to room temperature, the reaction mixture was concentrated and purified by chromatography to afford the title compound (7 mg). MS: 400 $(M+1)^+$.

Compound 262: 5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo-[4,5-b]pyridin-7-ol

[0301]



6-Chloro-3-nitro-N2-(quinolin-6-ylmethyl)pyridine-2,4-diamine

[0302] To a mixture of 2,6-dichloro-3-nitropyridin-4-amine (624 mg, 3 mmol) and quinolin-6-ylmethanamine (316 mg,

2 mmol) in CH_3CN (10 mL) was added Et_3N (0.5 mL). The reaction mixture was stirred at 80°C for 1h. After cooled to room temperature, the mixture was concentrated to afford the title compound (658 mg). MS (m/z): 330 $(M+1)^+$.

6-(1-Methyl-1H-pyrazol-4-yl)-3-nitro-N2-(quinolin-6-ylmethyl) pyridine-2,4-diamine

[0303] To a mixture of 6-chloro-3-nitro-N2-(quinolin-6-ylmethyl)pyridine-2,4-diamine (658 mg, 2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 2.4 mmol) and Na_2CO_3 (424 mg, 4 mmol) in dioxane (20 mL) and H_2O (2 mL) under N_2 was added $Pd(dppf)Cl_2$ (160 mg, 0.2 mmol). The reaction mixture was stirred at 100°C under N_2 overnight. After cooled to room temperature, the mixture was concentrated and purified by chromatography to afford the title compound (300 mg). MS (m/z): 376 $(M+1)^+$.

6-(1-Methyl-1H-pyrazol-4-yl)-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4-ol

[0304] To a mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitro-N^2-(quinolin-6-ylmethyl) pyridine-2,4-diamine (260 mg, 0.69 mmol) in HBF4 (5 mL) at 0°C was added HNO_2 (96 mg, 1.4 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at 0°C overnight, then basified with aqueous $NaHCO_3$ to pH = 6-7. The resulting mixture was filtered. The filtrate was concentrated and purified by chromatography on silica gel to afford the title compound (200 mg). MS (m/z): 377 $(M+1)^+$.

3-Amino-6-(1-methyl-1H-pyrazol-4-yl)-2-(quinolin-6-ylmethylamino) pyridin-4-ol

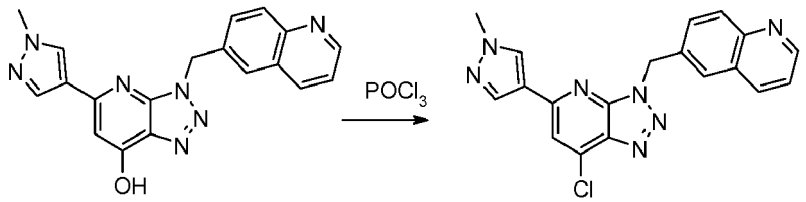
[0305] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitro-N2-(quinolin-6-ylmethyl)pyridine-2,4-diamine (200 mg, 0.53 mmol) in methanol (10 mL) was added 10% Pd/C (20 mg, 0.1 eq). The reaction mixture was stirred at room temperature under 1 atm of H_2 for 2h, then filtered. The filtrate was concentrated to afford the title compound (170 mg), which was used for the next step without further purification. MS (m/z): 347 $(M+1)^+$.

5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-ol

[0306] 3-amino-6-(1-methyl-1H-pyrazol-4-yl)-2-(quinolin-6-ylmethylamino)pyridin-4-ol (170 mg, 0.49 mmol) was added to a solution of acetic acid (3 mL) and H_2O (3 mL) at 0°C, followed by the addition of $NaNO_2$ (69 mg, 10 mmol) in H_2O (0.3 mL). The reaction mixture was stirred at 0°C for 1h, then basified with aqueous 30% NaOH to pH = 6-7 and purified by chromatography to afford the title compound (120 mg). MS (m/z): 358 (M+1)+.

Compound 263: 6-((7-Chloro-5-(1-methyl-1H-pyrazol-4-yl)-3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)methyl)quinoline

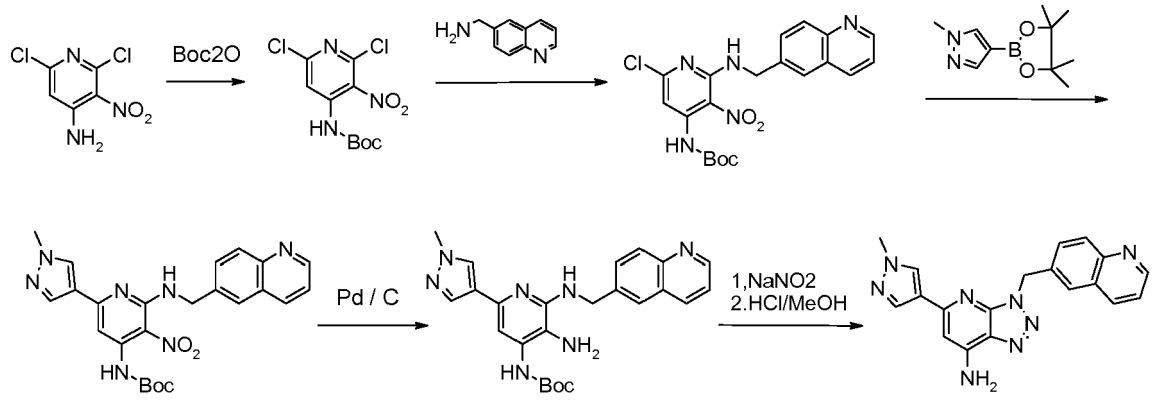
[0307]



[0308] 5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-ol (120 mg, 0.336 mmol) was dissolved in $POCl_3$ (2 ml). The reaction mixture was stirred at 110 °C for 1h. After cooled to 0 °C, the mixture was basified with aqueous $NaHCO_3$ to pH = 7, and extracted with EtOAc. The organic layer was separated, dried over anhydrous Na_2SO_4, concentrated, and purified by chromatography to afford the title compound (25 mg). MS: 376 $(M+1)^+$.

Compound 264: 5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo-[4,5-b]pyridin-7-amine

[0309]



***tert*-Butyl 2,6-dichloro-3-nitropyridin-4-ylcarbamate**

[0310] To a solution of 2,6-dichloro-3-nitropyridin-4-amine (832 mg. 4 mmol) in THF (10 mL) was added DMAP (50 mg, 0.4 mmol) and $(Boc)_2O$ (1.0 g, 4.6 mmol) in that order. The reaction mixture was stirred at room temperature for 2h, then concentrated. The residue was purified by chromatography on silica gel eluting with Pet/EtOAc=50/1 to afford the title compound (1.20 g).

***tert*-Butyl 6-chloro-3-nitro-2-(quinolin-6-ylmethylamino) pyridin-4-ylcarbamate**

[0311] A solution of *tert*-butyl 2,6-dichloro-3-nitropyridin-4-ylcarbamate (1.2 g, 3.9 mmol) and quinolin-6-ylmethanamine (616 mg, 3.9 mmol) in CH_3CN (15 mL) and Et_3N (1 mL) was stirred at 80 °C for 1h. After cooled to room temperature, the mixture was concentrated. The residue was purified by chromatography to afford the title compound (1.60 g). MS (m/z): 430 $(M+1)^+$.

***tert*-Butyl 6-(1-methyl-1H-pyrazol-4-yl)-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4-ylcarbamate**

[0312] To a mixture of *tert*-butyl 6-chloro-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4-ylcarbamate (860 mg, 2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (416 mg, 2 mmol) and Na_2CO_3 (424 mg, 4 mmol) in dioxane (20 mL) and H_2O (2 mL) under N_2 was added $Pd(dppf)Cl_2$ (163 mg, 0.2 mmol). The reaction was stirred at 80°C under N_2 overnight. After cooled to room temperature, the mixture was concentrated and purified by chromatography to afford the title compound (950 mg). MS (m/z): 476 $(M+1)^+$.

***tert*-Butyl 3-amino-6-(1-methyl-1H-pyrazol-4-yl)-2-(quinolin-6-ylmethylamino) pyridin-4-ylcarbamate**

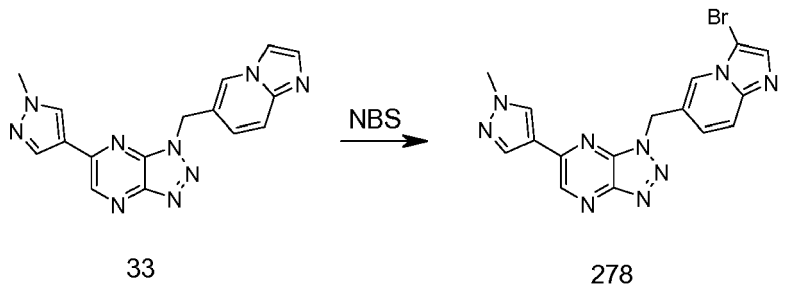
[0313] To a solution of *tert*-butyl 6-(1-methyl-1H-pyrazol-4-yl)-3-nitro-2-(quinolin-6-ylmethylamino)pyridin-4-ylcarbamate (950 mg, 2 mmol) in methanol (10 mL) was added 10% Pd/C (95 mg, 0.1 eq). The reaction was stirred at room temperature under 1 atm of H_2 for 1h, then filtered. The filtrate was concentrated to afford the title compound (890 mg), which was used for the next step without further purification. MS (m/z): 446 $(M+1)^+$.

5-(1-Methyl-1H-pyrazol-4-yl)-3-(quinolin-6-ylmethyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-amine

[0314] *tert*-Butyl 3-amino-6-(1-methyl-1H-pyrazol-4-yl)-2-(quinolin-6-ylmethylamino)pyridin-4-ylcarbamate (890 mg, 2 mmol) was added to a solution of acetic acid (5 mL) and water (5 mL) at 0°C, followed by the addition of $NaNO_2$ (300 mg, 4 mmol) in H_2O (0.5 mL). The reaction was stirred at 0°C for 1h, then basified with 30% NaOH to pH = 8. The resulting mixture was filtered to afford a solid. The solid was treated with TFA (3 mL), and then stirred at room temperature for another 0.5h, before treated with aqueous Na_2CO_3 to adjust the pH to 8. The resulting mixture was purified by chromatography to afford the title compound (190 mg). MS: 358 $(M+1)^+$.

Compound 278: 1-((3-Bromoimidazo[1,2-a]pyridin-6-yl)methyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine

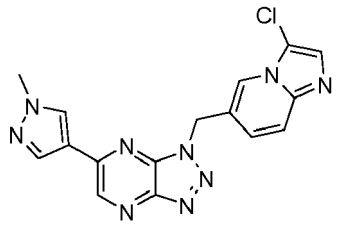
[0315]



[0316] To a solution of Compound **33** (10 mg, 0.03 mmol) in $CHCl_3$ (3 mL) was added NBS (5.4 mg, 0.031 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by chromatography to afford the title compound (11 mg). MS (m/z): 411.7 $(M+1)^+$.

Compound **300:**

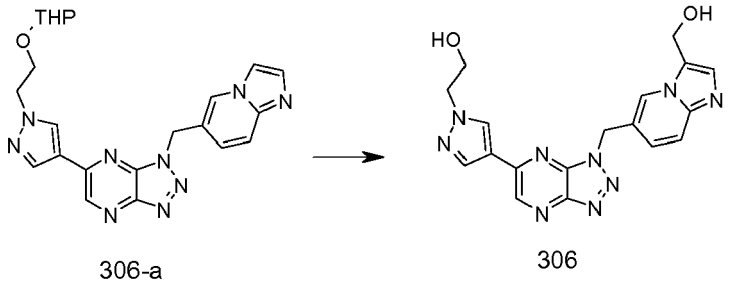
[0317]



[0318] **Compound 300** was prepared with NCS according to the procedure of Compound **278.** MS (m/z): 365.9 $(M+1)^+$.

Compound 306: 2-(4-(1-((3-(Hydroxymethyl)imidazo[1,2-a]pyridin-6-yl)methyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol

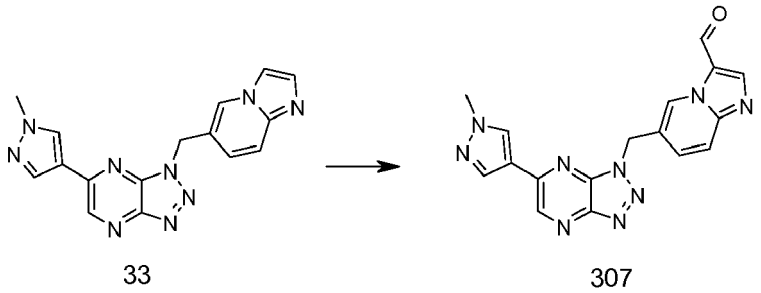
[0319]



[0320] To a solution of **306-a** (60 mg, 0.13 mmol) (prepared according to the procedure of **Compound 1**) in 0.1 mL of acetic acid were added sodium acetate (39 mg, 0.48 mmol) and then formaldehyde (0.13 mL, 37% in water). The mixture was stirred at 100 °C overnight. After cooled, the mixture was adjusted to pH>7 with aqueous NaOH.. The resulting precipitate was collected and purified by chromatography to afford the title compound (10 mg). MS (m/z): 392.0 $(M+H)^+$

Compound 307: 6-((6-(1-Methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)-imidazo[1,2-a]pyridine-3-carbaldehyde

[0321]

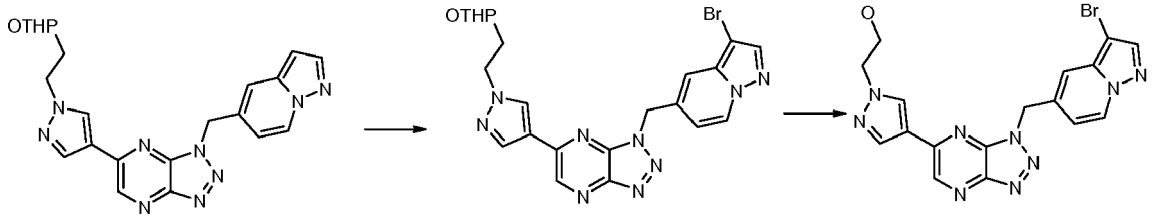


33 307

[0322] To a mixture of **Compound 33** (33 mg, 0.1 mmol) in 0.2 mL of acetic acid and 0.4 mL of water was added hexamethylenetetramine (16 mg, 0.11 mmol). The mixture was stirred at 120°C overnight. After cooled, the mixture was adjusted to pH>7 with aqueous NaOH and purified by chromatography to afford the title compound (5 mg). MS (m/z): 360.0 $(M+H)^+$.

Compound 311: 2-(4-(1-(Pyrazolo[1,5-a]pyridin-5-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol

[0323]

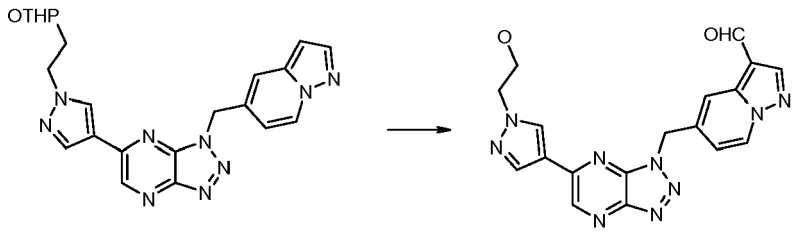


311-a 311

[0324] To a solution of 1-(pyrazolo[1,5-a]pyridin-5-ylmethyl)-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine **311-a** (10 mg, 0.022 mmol) (prepared according to the procedure of Compound **1**) in $CHCl_3$ was added NBS (4.4 mg, 0.025 mmol). The reaction mixture was stirred at rt for 1 h, then concentrated. The resulting residue was dissolved in $CHCl_3$ (2 mL) and MeOH (2 mL), followed by the addition of 6N HCl in MeOH. The resulting mixture was stirred for 30 min, then treated with NH3.H2O to bring pH to 8. The mixture was concentrated and purified by prep-TLC to afford the title compound. MS (m/z): 439.9 $(M+1)^+$.

Compound 312: 5-((6-(1-(2-Hydroxyethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)pyrazolo[1,5-a]pyridine-3-carbaldehyde

[0325]

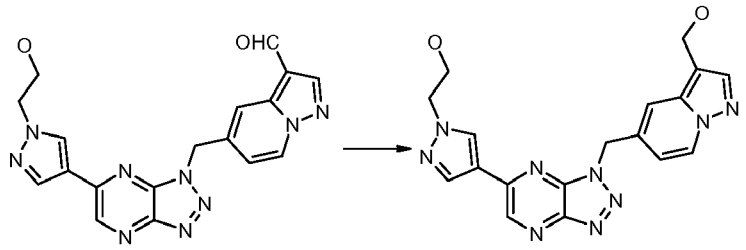


311-a 312

[0326] To a solution of 1-(pyrazolo[1,5-a]pyridin-5-ylmethyl)-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine **311-a** (125 mg, 0.28 mmol) in $AcOH/H_2O$ (2 mL/1 mL) was added HMTA (79 mg, 0.56 mmol). The reaction mixture was stirred at 110°C for 2 h, then treated with $NH_3.H_2O$ to bring pH to 8. The resulting mixture was then concentrated and purified by prep-TLC to afford the title compound (67 mg). MS (m/z): 389.37 $(M+1)^+$.

Compound 313: 2-(4-(1-((3-(Hydroxymethyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol

[0327]

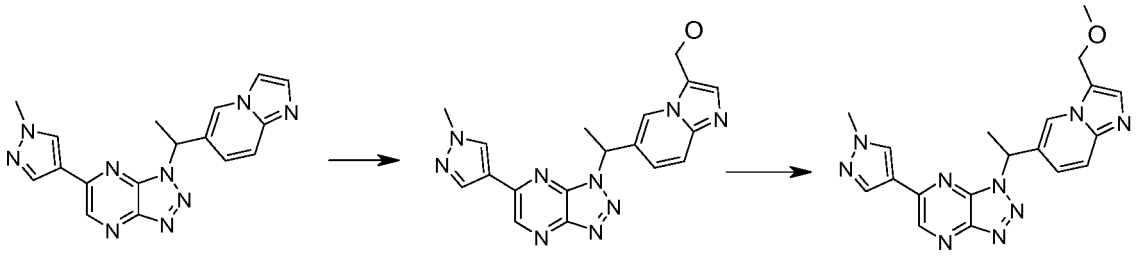


312 313

[0328] To a solution of **compound 312** (10 mg, 0.025 mmol) in MeOH was added $NaBH_4$ (4 mg, 0.051 mmol). The reaction was stirred at room temperature for 1 h, then concentrated and purified by prep-TLC to afford the title compound.

Compound 318: 1-(1-(3-(methoxymethyl)imidazo[1,2-a]pyridin-6-yl)ethyl)-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine

[0329]



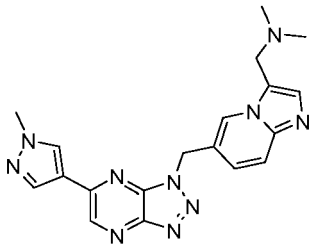
331 318-a 318

[0330] Intermediate **318-a** was prepared according to the procedure of **Compound 306** by using Compound **331.**

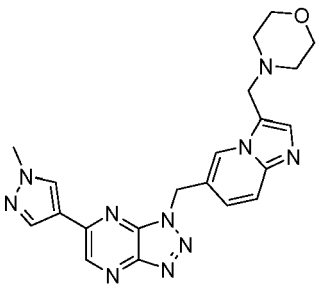
[0331] To a mixture of (6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)ethyl)H-imidazo[1,2-a]pyridin-3-yl)methanol **318-a** (40 mg, 0.11 mmol) in 30 mL of THF was added sodium hydride (22 mg, 0.53 mmol, 60% in mineral oil) at 0°C. The mixture was stirred at 0 °C for 1 h, then iodomethane (60 mg, 0.43 mmol) was added. The mixture was stirred at room temperature overnight, then treated with sat. Na_2CO_3, then concentrated. The residue was diluted with water, and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated and purified by chromatography on silica gel to afford the title compound (30 mg) MS (m/z): 389.9 $(M+H)^+$

Compounds **319** and **320:**

[0332]



319

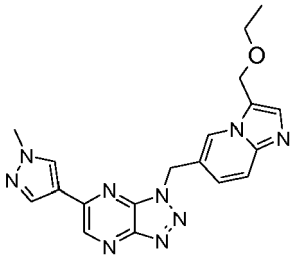


320

[0333] Compounds **319 and 320** were prepared according to the procedure of Compound **327.** Compound **319:** MS: 388.9$(M+1)^+$; Compound **320** MS: 431$(M+1)^+$

Compounds 321:

[0334]

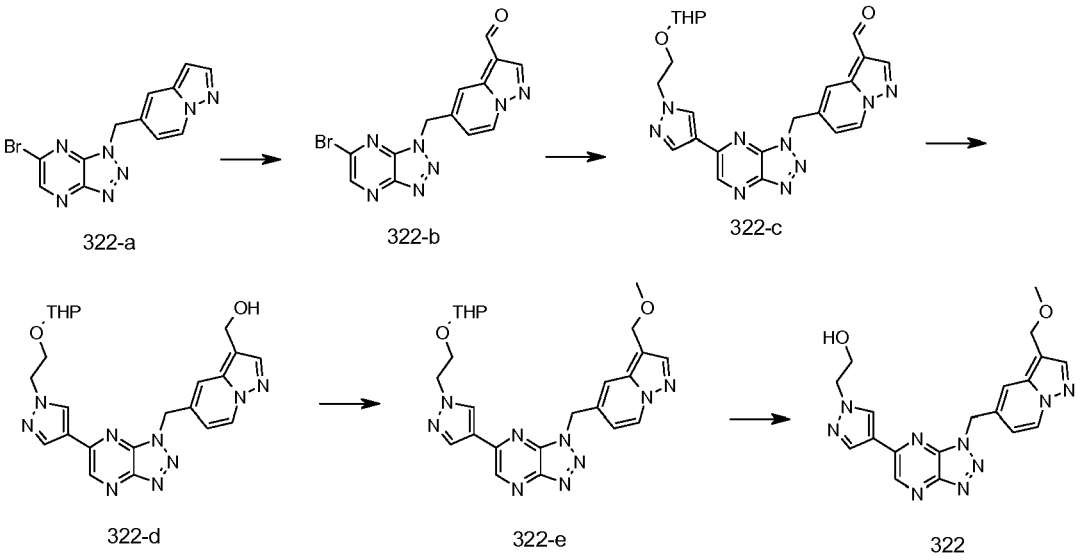


321

[0335] Compound **321** was prepared according to the procedure of Compound 318 starting from Compound **272.** MS: 389.9$(M+1)^+$.

Compound 322:

[0336]



5-((6-Bromo-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)pyrazolo[1,5-a]pyridine-3-carbaldehyde (**322-b**)

[0337] The title compound (Intermediate **322-b**) was prepared according to the procedure of Compound **307.**

5-((6-(1-(2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)pyrazolo[1,5-a]pyridine-3-carbaldehyde (322-c)

[0338] The title compound (Intermediate **322-c**) was prepared from **322-b** according to the procedure of Compound **1.**

(5-((6-(1-(2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)pyrazolo[1,5-a]pyridin-3-yl)methanol (332-d)

[0339] The title compound (Intermediate **322-d**) was prepared from **322-c** according to the procedure of Compound **313.** MS (m/z): 476.1 $(M+H)^+$.

1-((3-(Methoxymethyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazine (332-e)

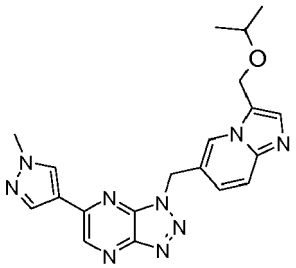
[0340] The title compound (Intermediate **322-e**) was prepared from **322-d** according to the procedure of Compound **318.**

2-(4-(1-((3-(Methoxymethyl)pyrazolo[1,5-a]pyridin-5-yl)methyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)-1H-pyrazol-1-yl)ethanol (compound 322)

[0341] To a mixture of **322-e** (40 mg, 0.082 mmol) in methanol (15mL) was added a solution of HCl in methanol (0.5 mL, 5 N). The mixture was stirred at 0°C for 1 h, then treated with ammonia to adjust pH to > 7. The resulting solution was concentrated and purified by chromatography to afford the title compound (15 mg).

Compounds 323:

[0342]

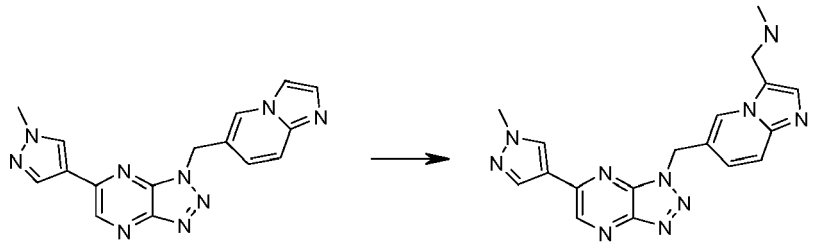


323

[0343] Compound **323** was prepared from compound **272** according to the procedure of **Compound 318.** MS: 403.9$(M+1)^+$

Compound 327: *N*-methy)-1-(6-((6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)imidazo[1,2-a]pyridin-3-yl)methanamine

[0344]

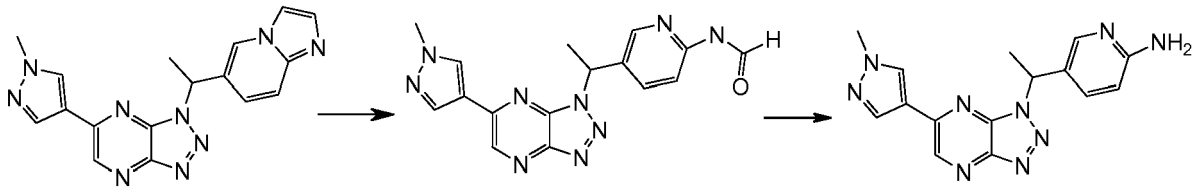


33 327

[0345] To a mixture of compound **33** (50 mg, 0.15 mmol) in acetic acid (0.5mL) were added ammonium chloride (61 mg, 0.9 mmol) and formaldehyde (61 mg, 0.75 mmol, 37% in water). The mixture was stirred at 55°C for 24h. The reaction was treated with ammonia to adjust the pH to >7, then concentrated and purified by chromatography to afford the title compound (15 mg). MS (m/z): 374.8 $(M+H)^+$.

Compound 330:

[0346]



331 330-a 330

***N*-(5-(1-(6-(1-Methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)ethyl)pyridin-2-yl)formamide (330-a)**

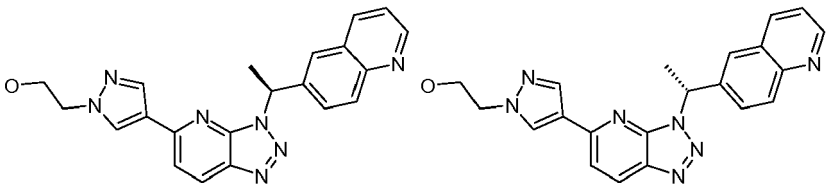
[0347] To a solution of the compound **331** (1.0 g) in 100 mL of CH_2Cl_2 was bubbled O_3 at-60 - -70°C for 30 mins, then N_2 for 10 mins. The reaction mixture was treated with Na_2SO_3 solution, and stirred for 10 mins. The resulting mixture was extracted with CH_2Cl_2. The organic layer was concentrated and purified by chromatography to afford the title compound as a solid (300 mg). MS (m/z): 322 $(M+H)^+$.

5-(1-(6-(1-Methyl-1H-pyrazol-4-yl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)ethyl)pyridin-2-amine (Compound 330)

[0348] A solution of compound **330-a** (300 mg) in 10 mL of HCl/CH_3OH was stirred overnight, then concentrated and basified with Na_2CO_3 solution. The resulting mixture was purified by chromatography to afford the title compound as a solid, 155 mg.

Compound 77 and 78

[0349]



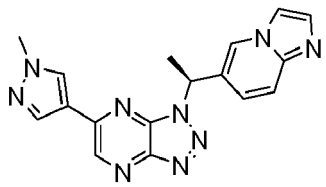
Compound 77 Compound 78

[0350] The racemic Compound **332** (4 mg) was resolved by chiral HPLC to produce the optically pure enantiomers Compound **77** (0.7 mg) and **78** (1.1 mg) (HPLC conditions: Gilson system, Column: Dicel IA 4.6 x 250 mm; mobile phase:

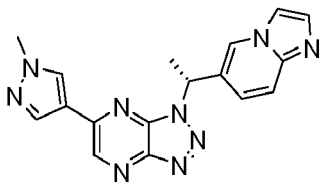
n-hexane/i-PrOH/ DEA = 70/ 30/ 0.1; flow rate, 1 mL/min; detector: UV 254 nm). Compound **77** is the first eluent with at least 98% ee, MS (m/z): 386 $(M+1)^+$. Compound **78** is the second eluent with at least 98% ee, MS (m/z): 386 $(M+1)^+$.

Compound 270 and 271

[0351]



Compound 270

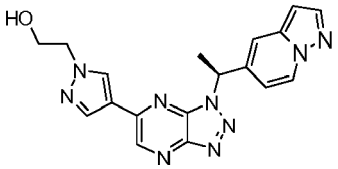


Compound 271

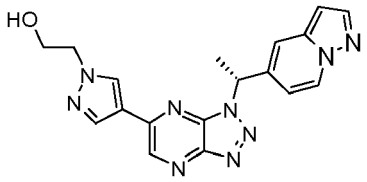
[0352] The racemic compound **331** (3 mg) was resolved by chiral HPLC to produce the optically pure enantiomers Compound **270** (0.9 mg) and **271** (1.1 mg). (HPLC conditions: Gilson system, column: Dicel IA 20 x 250 mm; mobile phase: EtOH/CH_3CN =9/1; flow rate = 8 mL/min; detector: UV 254 nm), Compound **270** is the first eluent with at least 98% ee, MS (m/z): 346 $(M+1)^+$. and Compound **271** is the second eluent with 93% ee, MS (m/z): 346 $(M+1)^+$.

Compounds 314 and 315 :

[0353]



314

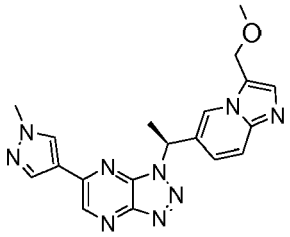


315

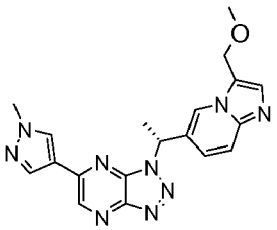
[0354] The racemic compound **310** (5 mg) was resolved by chiral HPLC to produce optically pure enantiomers Compound **314** (1.0 mg) and Compound **315** (1.9 mg). (HPLC conditions: Gilson system, Column: Dicel IA 20 x 250 mm; Mobile phase: *n*-Hexane/i-PrOH/ DEA=6/4/0.1; Flow rate: 8 ml/min; Detector: 254 nm;).Compound **314** is the first eluent with 95% ee, MS (m/z): 376 $(M+1)^+$. Compound **315** is the second eluent with 80% ee, MS (m/z): 376 $(M+1)^+$.

Compounds 324 and 325:

[0355]



324



325

[0356] Racemic Compound **318** (50 mg) was resolved by chiral HPLC to produce enantiomeic Compounds **324** (15 mg) and **325** (8 mg). (HPLC conditions: Gilson system; column: dicel IA, 20 x 250 mm IA; mobile phase: ethanol / methanol/ DEA = 70/30/0.1; detector: UV 254 nm). Compound **324** is the first eluent with at least 98% ee, MS (m/z): 390 $(M+1)^+$. Compound **325** is the second eluent with at least 90% ee, MS (m/z): 390 $(M+1)^+$.

Example 2: Inhibition of c-Met kinase activity using Transcreener FP assay

1. Reagents

[0357] Transcreenen™ KINASE Assay kit: Bellbrook Labs., 3003-10K;
Recombinant human Met : Invitrogen, PV3143;
Poly E4Y (substrate): Sigma, P0275; 5 mg/mL, dissolved in H_2O;
Assay buffer: 67 mM HEPES, 0.013% Triton X-100, 27 mM $MgCl_2$, 0.67 mM $MnCl_2$, 1.25 mM DTT, PH 7.4;
10 mM ATP: Invitrogene, PV3227;
500 mM EDTA: Invitrogene, 15575-038;
96 well black Greiner plate: Greiner, 675076.

2. Solution Preparation

[0358] Compound dilution: dilute test articles to 5 folds of the testing concentration using 20% DMSO.
[0359] Prepare Enzyme/Substrate stock: dilute recombinant human c-Met and Poly E4Y in assay buffer to 0.5 μg/mL for c-Met, and 62.5 μg/mL for Poly E4Y. The mixture is kept on ice until use;
Prepare ATP Diluent: dilute 10 mM ATP stock to 25 μM with assay buffer;
Prepare ADP Diluent: dilute 500 μM ADP stock to 25 μM with assay buffer;
Prepare ATP standard curve stock as following:

Column	ADP diluent (uL)	ATP diluent (uL)
1	50	0
2	25	25
3	10	40
4	5	45
5	5	95
6	5	195
7	5	495
8	4	496
9	3	497
10	2	498
11	1	499
12	1	999

3. Enzymatic reaction: in 96-well reaction plate

[0360] Add 5 μL of test article or 5 μL of 20% DMSO or 5 μL of 500 mM EDTA;
Add 10 μL of Enzyme/Substrate stock;
Add 10 μL of ATP Diluent to begin the enzyme reaction and mix on plate shaker;
Add 5 μL of 20% DMSO, 10 μL of assay buffer and 10 μL of ATP standard curve stock into standard curve wells;
Gently shake at 28 °C for 45 min.

4. Stop reaction and detect ADP

[0361] Prepare Detection Mix: According to the procedures described in the Assay kit, Alexa633 tracer, ADP antibody and stop & detect buffer were added into H_2O and mixed thoroughly. Prepare Tracer Only control: According to the procedures described in the Assay kit, ADP Alexa633 tracer and stop & detect buffer were added to H_2O and mixed throughly. Prepare No Tracer control: According to the procedures described in the Assay kit, the stop & detect buffer was diluted with H_2O;
Add 25 μL of detection mix, Tracer Only control and No Tracer control into corresponding wells, respectively;

The reaction plate was gently shaken at 28 °C for 1h;
Florescence polarization (FP) was measured on TECAN F500. Excitation wavelength: 610 nm, Emission wavelength: 670 nm.

5. Data analysis

[0362]

$$\text{Inhibition (\%)}=100-\frac{\text{Compound well}[\text{ADP}]}{\text{Positive control well}[\text{ADP}]}\times 100$$

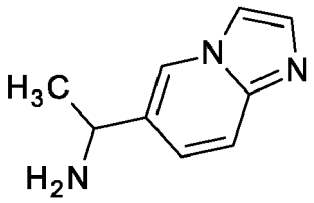
[0363] Where:
Compound well [ADP] represents the ADP concentration of the compound well.
Positive control well [ADP] represents the ADP concentration of the 20% DMSO well. Conversion of mP value to ADP concentration is based on the formula which is determined by standard curve. Measurement of mP value follows the suggestion of the instructions provided by BellBrook Labs (www.bellbrooklabs.com).

IC_{50}: calculated using XL-Fit 2.0 software.

[0364] IC_{50} values of compounds **7, 8, 11, 12, 16, 19, 20, 25, 33, 34, 35, 36, 42, 43, 44, 45, 47, 48, 49, 50, 56, 57, 77, 127, 128, 129, 153, 156, 158, 161, 163, 169, 190, 192, 193, 195, 197, 198, 203, 207, 210, 212, 220, 222, 223, 224, 225, 227, 228, 229, 230, 254, 265, 269, 270, 278, 279, 280, 300, 301, 303, 308, 309, 314, 318, 325, 328, 332, 1, 13, 14, 15, 21, 24, 26, 27, 46, 51, 52, 54, 58, 59, 61, 62, 63, 65, 70, 72, 76, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 95, 97, 102, 104, 111, 112, 113, 115, 117, 130, 131, 132, 133, 134, 135, 136, 137, 140, 141, 144, 145, 146, 147, 150, 152, 155, 157, 160, 162, 164, 165, 166, 168, 172, 173, 176, 177, 179, 180, 182, 183, 185, 186, 188, 189, 191, 194, 196, 199, 200, 202, 213, 214, 215, 217, 218, 221, 226, 235, 237, 238, 239, 240, 245, 246, 248, 250, 252, 253, 255, 258, 259, 266, 267, 268, 271, 272, 274, 275, 276, 277, 281, 282, 283, 287, 290, 295, 298, 302, 304, 305, 306, 307, 310, 311, 312, 313, 315, 319, 321, 322, 323, 324, 326, 327, 329, 331** are in the range of 0.001 to less than 0.1 uM. IC_{50} values of compounds **2, 5, 6, 9, 17, 18, 22, 23, 28, 30, 37, 38, 41, 53, 55, 64, 66, 71, 73, 74, 78, 79, 80, 92, 93, 94, 96, 98, 99, 100, 101, 103, 105, 107, 108, 109, 110, 116, 118, 119, 120, 121, 122, 123, 126, 138, 142, 143, 154, 170, 174, 181, 187, 201, 204, 205, 206, 208, 209, 216, 219, 231, 234, 236, 241, 244, 247, 249, 257, 260, 261, 263, 273, 284, 285, 286, 288, 289, 292, 293, 294, 296, 299, 316, 317, 320,** are from 0.1 uM to less than 1 uM.

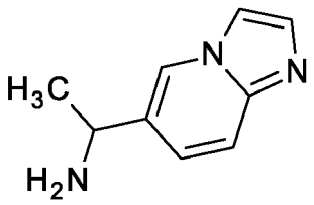
Claims

1. A compound of the formula:



or a salt thereof.

2. A compound according to claim 1, of the formula:



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EUROPEAN SEARCH REPORT

Application Number
EP 19 15 1824

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 2007/132308 A1 (PFIZER PROD INC [US]; CHEN HENGMIAO [US]; CUI JINGRONG JEAN [US]; HOFF) 22 November 2007 (2007-11-22) * Scheme 1; page 21; claim 1 * -----	2	INV. C07D471/04
A	WO 2005/004607 A1 (SUGEN INC [US]; CUI JINGRONG [US]; BOTROUS IRINY [US]) 20 January 2005 (2005-01-20) * claims 1-4; example 8 * -----	2	

TECHNICAL FIELDS SEARCHED (IPC)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	26 March 2019	Johnson, Claire

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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1

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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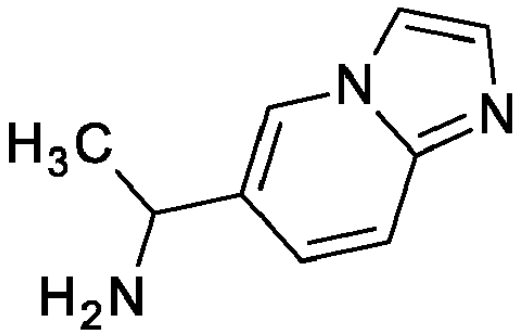
摘要

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