6-O-SUBSTITUTED BENZOXAZOLE AND BENZOTHIAZOLE COMPOUNDS AND METHODS OF INHIBITING CSF-1R SIGNALING

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application Serial Nos. 60/793,517, filed April 19, 2006, and No. 60/893,857, filed March 8, 2007, both of which are hereby incorporated by reference into this application in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to 6-O-substituted benzoxazole and benzothiazole compounds, their tautomers, stereoisomers, solvates, oxides, esters, metabolites, and prodrugs, and to the pharmaceutically acceptable salts thereof. This invention also relates to compositions of the compounds together with pharmaceutically acceptable carriers. In another aspect, this invention relates to uses of the compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer.

State of the Art

CSF-1R is the receptor for M-CSF (macrophage colony stimulating factor, also called CSF-1) and mediates the biological effects of this cytokine (Sherr 1985). The cloning of the colony stimulating factor-1 receptor (also called c-fms) was described for the first time in Roussel et al., *Nature* 325:549-552 (1987). In that publication, it was shown that CSF-1R had transforming potential dependent on changes in the C-terminal tail of the protein including the loss of the inhibitory tyrosine 969 phosphorylation which binds Cbl and thereby regulates receptor down regulation (Lee1999).

CSF-1R is a single chain, transmembrane receptor tyrosine kinase (RTK) and a member of the family of immunoglobulin (Ig) motif containing RTKs characterized by repeated Ig domains in the extracellular portion of the receptor. The intracellular protein

tyrosine kinase domain is interrupted by a unique insert domain that is also present in the other related RTK class III family members that include the platelet derived growth factor receptors (PDGFR), stem cell growth factor receptor (c-Kit) and fms-like cytokine receptor (FLT3). In spite of the structural homology among this family of growth factor receptors, they have distinct tissue-specific functions. CSF-1R is mainly expressed on cells of the monocytic lineage and in the female reproductive tract and placenta. In addition expression of CSF-1R has been reported in Langerhans cells in skin, a subset of smooth muscle cells (Inaba 1992), B cells (Baker 1993) and microglia (Sawada 1990).

The main biological effects of CSF-1R signaling are the differentiation, proliferation, migration, and survival of the precursor macrophages and osteoclasts from the monocytic lineage. Activation of CSF-1R is mediated by its only ligand, M-CSF. Binding of M-CSF to CSF-1R induces the formation of homodimers and activation of the kinase by tyrosine phosphorylation (Stanley 1997). Further signaling is mediated by the p85 subunit of PI3K and Grb2 connecting to the PI3K/AKT and Ras/MAPK pathways, respectively. These two important signaling pathways can regulate proliferation, survival and apoptosis. Other signaling molecules that bind the phosphorylated intracellular domain of CSF-1R include STAT1, STAT3, PLCγ, and Cbl (Bourette 2000).

CSF-1R signaling has a physiological role in immune responses, in bone remodeling and in the reproductive system. The knockout animals for either M-CSF-1 (op/op mouse; Pollard 1996) or CSF-1R (Dai 2002) have been shown to have osteopetrotic, hematopoietic, tissue macrophage, and reproductive phenotypes consistent with a role for CSF-1R in the respective cell types.

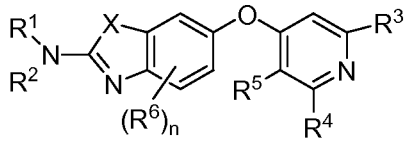
The recent success of targeted therapeutics, such as Herceptin® and Avastin®, has underscored the importance in developing "cleaner" less promiscuous drugs with a more specific mechanism of action. These drugs can minimize adverse events, have greater predictability, give physicians greater flexibility in their treatments, and provide researchers with a better understanding of a particular target. Additionally, targeted therapy may allow treatment of multiple indications affected by the same signaling pathway with fewer and potentially easier to manage toxicities. (*BioCentury*, V. 14(10) Feb, 2006) Inhibition of an individual kinase, such as CSF-1R, which is integrated within a pathway associated with cancer or other diseases, can effectively modulate downstream kinases as well, thereby affecting the entire pathway. However, the active sites of 491 human protein kinase

domains are highly conserved, which makes the design of selective inhibitors a formidable challenge (Cohen 2005). Accordingly, there is a need for selective kinase inhibitors, such as selective CSF-1R inhibitors.

SUMMARY OF THE INVENTION

A continuing need exists for compounds that inhibit cellular proliferation, inhibit the growth of tumors, treat cancer, modulate cell cycle arrest, and/or specifically inhibit molecules such as CSF-1R, and for pharmaceutical formulations and medicaments that contain such compounds. A need also exists for selective CSF-1R inhibitory compounds. A need also exists for methods of administering such compounds, pharmaceutical formulations, and medicaments to patients or subjects in need thereof.

One embodiment is directed to compounds, stereoisomers, tautomers, solvates, oxides, esters, and prodrugs of Formula (I), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (I) is:



(I)

and wherein X is O, S, or S(O);

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; or R^1 and R^2 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, halo, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbonitrile, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl;

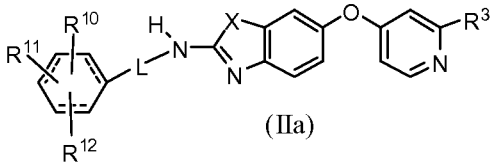
each R^6 is independently alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, or halo;

n is 0, 1, or 2; and

when X is O, R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl, or R^4 and R^5 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

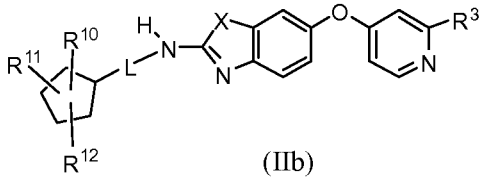
when X is S or S(O), R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIa) or (IIb), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IIa) and (IIb) are



(IIa)

or



(IIb)

and wherein X is O or S;

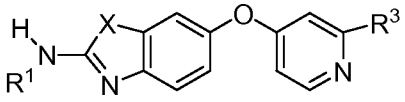
the dashed lines are saturated bonds or unsaturated bonds;

L is a covalent bond or is alkylidene or substituted alkylidene;

R^{10}, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or R^{11} is taken together with R^{12} to form a group selected from the group consisting of aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIIa), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IIIa) is



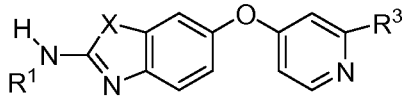
(IIIa)

and wherein X is O or S;

R^1 is alkyl or alkyl substituted with a substituent selected from the group consisting of aryl, cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIIb), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IIIb) is



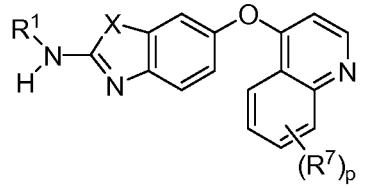
(IIIb)

and wherein X is O or S;

R^1 is selected from the group consisting of acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IV), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IV) is



(IV)

and wherein X is O or S;

R^7 is independently selected from the group consisting of alkoxy, haloalkoxy, halo, and carbonitrile;

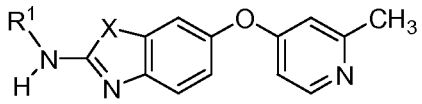
p is 0, 1, or 2;

R^1 is $-LR^8$ or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

L is a covalent bond, alkylidene, or substituted alkylidene; and

R^8 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, pyridyl, and when p is 0, R^8 is optionally 2-methoxyphenyl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (V), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (V) is



(V)

and wherein X is O or S;

R^1 is $-LR^9$ or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

L is a covalent bond, alkylidene, or substituted alkylidene; and

R^9 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, and pyridyl.

Another embodiment is directed to a method of treating a CSF-1R mediated disorder with a CSR-1R inhibitory compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V).

In a more particular embodiment said compound does not substantially inhibit Raf kinase. In a more particular embodiment said compound preferentially inhibits CSF-1R over Raf kinase. In a more particular embodiment said compound inhibits Raf kinase at an

IC_{50} of greater than about 1 μM. In a more particular embodiment said compound inhibits CSF-1R at an IC_{50} of at less than about 1 μM. More particular still, said compound inhibits CSF-1R at an IC_{50} of at less than about 0.1 μM.

DETAILED DESCRIPTION

Throughout this application, the text refers to various embodiments of the present compounds, compositions, and methods. The various embodiments described are meant to provide a variety illustrative examples and should not be construed as descriptions of alternative species. Rather it should be noted that the descriptions of various embodiments provided herein may be of overlapping scope. The embodiments discussed herein are merely illustrative and are not meant to limit the scope of the present invention.

Definitions

Unless specifically defined otherwise, the terms used herein are defined below.

"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), isopropyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), isobutyl ($(CH_3)_2CHCH_2$-), *sec*-butyl ($(CH_3)(CH_3CH_2)CH$-), *t*-butyl ($(CH_3)_3C$-), *n*-pentyl ($CH_3CH_2CH_2CH_2CH_2$-), and neopentyl ($(CH_3)_3CCH_2$-).

"Substituted alkyl" refers to an alkyl group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, azido, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cyanate, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, hydroxyamino, alkoxyamino, hydrazino, substituted hydrazino, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio,

substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, spirocycloalkylidene, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiocyanate, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Alkylidene" or "alkylene" refers to divalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms and preferably 1 to 6 carbon atoms. The alkylidene and alkylene groups include branched and straight chain hydrocarbyl groups.

"Substituted alkylidene" or "substituted alkylene" refers to an alkylidene group having from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, azido, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cyanate, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, hydroxyamino, alkoxyamino, hydrazino, substituted hydrazino, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, oxo, thione, spirocycloalkylidene, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiocyanate, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Alkoxy" refers to the group –O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, and *n*-pentoxy.

"Substituted alkoxy" refers to the group –O-(substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-,

cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, substituted hydrazino-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, substituted hydrazino, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$-.

"Acylamino" refers to the groups $-NR^{20}C(O)$alkyl, $-NR^{20}C(O)$substituted alkyl, $-NR^{20}C(O)$cycloalkyl, $-NR^{20}C(O)$substituted cycloalkyl, $-NR^{20}C(O)$cycloalkenyl, $-NR^{20}C(O)$substituted cycloalkenyl, $-NR^{20}C(O)$alkenyl, $-NR^{20}C(O)$substituted alkenyl, $-NR^{20}C(O)$alkynyl, $-NR^{20}C(O)$substituted alkynyl, $-NR^{20}C(O)$aryl, $-NR^{20}C(O)$substituted aryl, $-NR^{20}C(O)$heteroaryl, $-NR^{20}C(O)$substituted heteroaryl, $-NR^{20}C(O)$heterocyclic, and $-NR^{20}C(O)$substituted heterocyclic wherein R^{20} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, cycloalkenyl-C(O)O-, substituted cycloalkenyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein.

"Amino" refers to the group $-NH_2$.

"Substituted amino" refers to the group $-NR^{21}R^{22}$ where R^{21} and R^{22} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl,

substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cylcoalkyl, -SO_2-cycloalkenyl, -SO_2-substituted cylcoalkenyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, and -SO_2-substituted heterocyclic and wherein R^{21} and R^{22} are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R^{21} and R^{22} are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein. When R^{21} is hydrogen and R^{22} is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R^{21} and R^{22} are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it is meant that either R^{21} or R^{22} is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R^{21} nor R^{22} are hydrogen.

"Hydroxyamino" refers to the group –NHOH.

"Alkoxyamino" refers to the group –NHO-alkyl wherein alkyl is defined herein.

"Aminocarbonyl" refers to the group -C(O)$NR^{23}R^{24}$ where R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, hydroxy, alkoxy, substituted alkoxy, amino, substituted amino, and acylamino, and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonyl" refers to the group -C(S)$NR^{23}R^{24}$ where R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl,

alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the group $-NR^{20}C(O)NR^{23}R^{24}$ where R^{20} is hydrogen or alkyl and R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the group $-NR^{20}C(S)NR^{23}R^{24}$ where R^{20} is hydrogen or alkyl and R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the group $-O-C(O)NR^{23}R^{24}$ where R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted

heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyl" refers to the group $-SO_2NR^{23}R^{24}$ where R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyloxy" refers to the group $-O\text{-}SO_2NR^{23}R^{24}$ where R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonylamino" refers to the group $-NR^{20}-SO_2NR^{23}R^{24}$ where R^{20} is hydrogen or alkyl and R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to

form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkyenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Amidino" refers to the group $-C(=NR^{25})NR^{23}R^{24}$ where R^{25}, R^{23}, and R^{24} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and where R^{23} and R^{24} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Preferred aryl groups include phenyl and naphthyl.

"Substituted aryl" refers to aryl groups which are substituted with 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, azido, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cyanate, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, hydroxyamino, alkoxyamino, hydrazino, substituted hydrazino, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio,

substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiocyanate, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Aryloxy" refers to the group –O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

"Substituted aryloxy" refers to the group –O-(substituted aryl) where substituted aryl is as defined herein.

"Arylthio" refers to the group –S-aryl, where aryl is as defined herein.

"Substituted arylthio" refers to the group –S-(substituted aryl), where substituted aryl is as defined herein.

"Alkenyl" refers to alkenyl groups having from 2 to 6 carbon atoms and preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1 to 2 sites of vinyl unsaturation (>C=C<). Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-yl.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy or thiol substitution is not attached to a vinyl (unsaturated) carbon atom.

"Alkynyl" refers to hydrocarbyl groups having from 2 to 6 carbon atoms and preferably 2 to 3 carbon atoms and having at least 1 and preferably from 1 to 2 sites of acetylenic unsaturation (-C≡C-).

"Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and preferably 1 to 2 substituents, selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein and with the proviso that any hydroxy or thiol substitution is not attached to an acetylenic carbon atom.

"Azido" refers to the group $-N_3$.

"Hydrazino" refers to the group $-NHNH_2$.

"Substituted hydrazino" refers to the group $-NR^{26}NR^{27}R^{28}$ where R^{26}, R^{27}, and R^{28} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, carboxyl ester, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cylcoalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-substituted cycloalkenyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, and $-SO_2$-substituted heterocyclic and wherein R^{27} and R^{28} are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that $R^{27}$and

R^{28} are both not hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein.

"Cyano" or "carbonitrile" refers to the group -CN.

"Cyanate" refers to the group -OCN.

"Carbonyl" refers to the divalent group –C(O)– which is equivalent to -C(=O)-.

"Carboxyl" or "carboxy" refers to –COOH or salts thereof.

"Carboxyl ester" or "carboxy ester" refers to the groups -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-alkynyl, -C(O)O-substituted alkynyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -C(O)O-substituted cycloalkyl, -C(O)O-cycloalkenyl, -C(O)O-substituted cycloalkenyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and -C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein.

"(Carboxyl ester)amino" refers to the group -NR^{20}-C(O)O-alkyl, -NR^{20}-C(O)O-substituted alkyl, -NR^{20}-C(O)O-alkenyl, -NR^{20}-C(O)O-substituted alkenyl, -NR^{20}-C(O)O-alkynyl, -NR^{20}-C(O)O-substituted alkynyl, -NR^{20}-C(O)O-aryl, -NR^{20}-C(O)O-substituted aryl, -NR^{20}-C(O)O-cycloalkyl, -NR^{20}-C(O)O-substituted cycloalkyl, -NR^{20}-C(O)O-cycloalkenyl, -NR^{20}-C(O)O-substituted cycloalkenyl, -NR^{20}-C(O)O-heteroaryl, -NR^{20}-C(O)O-substituted heteroaryl, -NR^{20}-C(O)O-heterocyclic, and -NR^{20}-C(O)O-substituted heterocyclic wherein R^{20} is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein.

"(Carboxyl ester)oxy" refers to the group -O-C(O)O-alkyl, -O-C(O)O-substituted alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)O-substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted aryl,

-O-C(O)O-cycloalkyl, -O-C(O)O-substituted cycloalkyl, -O-C(O)O-cycloalkenyl, -O-C(O)O-substituted cycloalkenyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl are as defined herein.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, heterocyclic, aryl, or heteroaryl provided that the point of attachment is through the cycloalkyl ring. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

"Cycloalkenyl" refers to non-aromatic cyclic alkyl groups of from 4 to 10 carbon atoms having single or multiple cyclic rings and having at least one >C=C< ring unsaturation and preferably from 1 to 2 sites of >C=C< ring unsaturation.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to a cycloalkyl or cycloalkenyl group having from 1 to 5 or preferably 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, azido, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cyanate, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, hydroxyamino, alkoxyamino, hydrazino, substituted hydrazino, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl,

sulfonyloxy, thioacyl, thiocyanate, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

"Cycloalkyloxy" refers to –O-cycloalkyl.

"Substituted cycloalkyloxy refers to –O-(substituted cycloalkyl).

"Cycloalkylthio" refers to –S-cycloalkyl.

"Substituted cycloalkylthio" refers to –S-(substituted cycloalkyl).

"Cycloalkenyloxy" refers to –O-cycloalkenyl.

"Substituted cycloalkenyloxy" refers to –O-(substituted cycloalkenyl).

"Cycloalkenylthio" refers to –S-cycloalkenyl.

"Substituted cycloalkenylthio" refers to –S-(substituted cycloalkenyl).

"Guanidino" refers to the group $–NHC(=NH)NH_2$.

"Substituted guanidino" refers to $–NR^{29}C(=NR^{29})N(R^{29})_2$ where each R^{29} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, and substituted heterocyclyl and two R^{29} groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R^{29} is not hydrogen, and wherein said substituents are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Haloalkyl" refers to substitution of alkyl groups with 1 to 5 or preferably 1 to 3 halo groups.

"Haloalkoxy" refers to substitution of alkoxy groups with 1 to 5 or preferably 1 to 3 halo groups.

"Hydroxy" or "hydroxyl" refers to the group –OH.

"Heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (*e.g.*, pyridinyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein the condensed rings may or may

not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Preferred heteroaryls include pyridinyl, pyrrolyl, indolyl, thiophenyl, and furanyl.

"Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, preferably 1 to 3, or more preferably 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

"Heteroaryloxy" refers to –O-heteroaryl.

"Substituted heteroaryloxy refers to the group –O-(substituted heteroaryl).

"Heteroarylthio" refers to the group –S-heteroaryl.

"Substituted heteroarylthio" refers to the group –S-(substituted heteroaryl).

"Heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a saturated, partially saturated, or unsaturated group (but not aromatic) having a single ring or multiple condensed rings, including fused bridged and spirocycyl ring systems, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, sulfonyl moieties.

"Substituted heterocyclic" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 5 or preferably 1 to 3 of the same substituents as defined for substituted cycloalkyl.

"Heterocyclyloxy" refers to the group –O-heterocycyl.

"Substituted heterocyclyloxy" refers to the group –O-(substituted heterocycyl).

"Heterocyclylthio" refers to the group –S-heterocycyl.

"Substituted heterocyclylthio" refers to the group –S-(substituted heterocycyl).

Examples of heterocycle and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine,

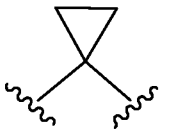
isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, and tetrahydrofuranyl.

"Nitro" refers to the group $-NO_2$.

"Oxo" refers to the atom (=O).

"Oxide" refers to products resulting from the oxidation of one or more heteroatoms. Examples include N-oxides, sulfoxides, and sulfones.

"Spirocyclyl" refers to divalent cyclic groups from 3 to 10 carbon atoms having a cycloalkyl or heterocyclyl ring with a spiro union (the union formed by a single atom which is the only common member of the rings) as exemplified by the following structure:



"Spirocycloalkyl" or "spirocycloalkylidene" refers to divalent cyclic groups having a cycloalkyl ring with a spiro union, as described for spirocyclyl.

"Sulfonyl" refers to the divalent group $-S(O)_2-$.

"Substituted sulfonyl" refers to the group $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cylcoalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-substituted cylcoalkenyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Substituted sulfonyl includes groups such as methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-.

"Sulfonyloxy" refers to the group –OSO_2-alkyl, -OSO_2-substituted alkyl, -OSO_2-alkenyl, -OSO_2-substituted alkenyl, -OSO_2-cycloalkyl, -OSO_2-substituted cylcoalkyl, -OSO_2-cycloalkenyl, -OSO_2-substituted cylcoalkenyl, -OSO_2-aryl, -OSO_2-substituted aryl, -OSO_2-heteroaryl, -OSO_2-substituted heteroaryl, -OSO_2-heterocyclic, -OSO_2-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thioacyl" refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiol" refers to the group -SH.

"Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

"Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

"Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to -C(=S)-.

"Thione" refers to the atom (=S).

"Thiocyanate" refers to the group -SCN.

"Solvate" or "solvates" refer compounds or a salt thereof that are bound to a stoichiometric or non-stoichiometric amount of a solvent. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts. Suitable solvates include water.

"Stereoisomer" or "stereoisomers" refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers.

"Tautomer" refer to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moeity such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

"Prodrug" refers to any derivative of a compound of the embodiments that is capable of directly or indirectly providing a compound of the embodiments or an active metabolite or residue thereof when administered to a subject. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of the embodiments when such compounds are administered to a subject (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species. Prodrugs include ester forms of the compounds of the invention. Examples of ester prodrugs include formate, acetate, propionate, butyrate, acrylate, and ethylsuccinate derivatives. An general overview of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate. The term also includes pharmaceutically acceptable salts of stereoisomers, tautomers, esters, and prodrugs of the compound.

"Patient" refers to mammals and includes humans and non-human mammals.

"Treating" or "treatment" of a disease in a patient refers to 1) preventing the disease from occurring in a patient that is predisposed or does not yet display symptoms of the disease; 2) inhibiting the disease or arresting its development; or 3) ameliorating or causing regression of the disease.

Reference to "selective" inhibition, refers to a compound, composition, or chemotype that preferentially inhibits a particular target or class of targets. Reference to "selective inhibition of CSF-1R" indicates the preferential inhibition of CSF-1R and optionally like kinase receptors such as PDGFR. In some embodiments, selective inhibition of CSF-1R refers to preferential inhibition of CSF-1R over Raf kinase. "Selective," "targeted," "specific," or "preferential" inhibition is not intended to mean complete absence of inhibitory activity with respect to all other kinases or receptors.

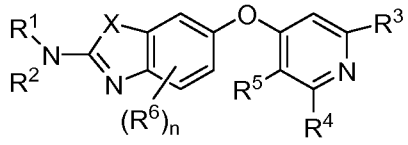
"CSF-1R inhibitor" refers to a compound that can inhibit CSF-1R. Preferably, a CSF-1R inhibitor is selective of CSF-IR over other targets. In an embodiment, a CSF-1R inhibitor has selective inhibition of CSF-1R over Raf kinase. In a preferred embodiment, such selective inhibition refers to at least a 2:1 binding preference of a compound of this invention to CSF-1R relative to Raf kinase, more preferably at least 5:1, and even more preferably at least 10:1.

Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxycabonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

It is understood that in all substituted groups defined above, polymers arrived at by defining substituents with further substituents to themselves (e.g., substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, which is further substituted by a substituted aryl group etc.) are not intended for inclusion herein. In such cases, the maximum number of such substitutions is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to -substituted aryl-(substituted aryl)-substituted aryl.

Similarly, it is understood that the above definitions are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

One embodiment is directed to compounds, stereoisomers, tautomers, solvates, oxides, esters, and prodrugs of Formula (I), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (I) is:



(I)

and wherein X is O, S, or S(O);

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; or R^1 and R^2 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, halo, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbonitrile, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl;

each R^6 is independently alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, or halo;

n is 0, 1, or 2; and

when X is O, R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl, or R^4 and R^5 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

when X is S or S(O), R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl.

In some embodiments, X is O.

In some embodiments, X is S.

In some embodiments, X is S(O).

In some embodiments, the oxide of Formula (I) is an oxide wherein X is $S(O)_2$.

In some embodiments, R^2 is hydrogen or methyl.

In some embodiments, R^1 is alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxyl, and substituted sulfonyl. Substituted and unsubstituted R^1 alkyl groups include branched hydrocarbyl groups such as pent-2-yl.

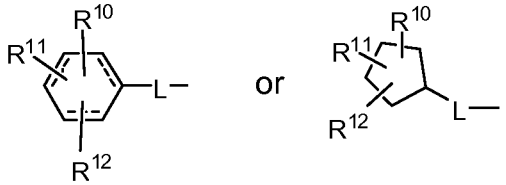
In some embodiments, R^1 is $-LR^{1a}$ wherein L is a covalent bond, alkylidene, or substituted alkylidene, and R^{1a} selected from cycloalkyl, cycloalkenyl, aryl, heterocyclyl, and heteroaryl, wherein each R^{1a} is substituted or unsubstituted.

In some aspects, R^{1a} is selected from phenyl, furan-2-yl, furan-3-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclohexenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2,3-dihydrobenzofuran, 2,3-dihydrobenzo[b][1,4]dioxine, 3,4-dihydro-2H-benzo[b][1,4]dioxepine, pyrazinyl, pyrrolidinyl, piperidinyl, piperidinone, pyrrolidinone, pyridin-2(1H)-one, morpholino, napthyl, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, and azepan-2-one, wherein each R^{1a} is substituted or unsubstituted. In some such aspects L is a covalent bond.

In some embodiments, L is a covalent bond.

In some embodiments of the compound of Formula (I), L is alkylidene substituted with 0, 1, 2, or 3 substituents independently selected from alkyl, substituted alkyl, hydroxy, alkoxy, haloalkoxy, aminocarbonyl, carboxyl ester, and carboxyl.

In some embodiments of the compound of Formula (I), R^1 is



wherein the dashed lines are saturated bonds or unsaturated bonds;

wherein L is a covalent bond or is alkylidene or substituted alkylidene; and

R^{10}, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted

aryl, heteroaryl, and substituted heteroaryl; or R^{11} is taken together with R^{12} to form a group selected from the group consisting of aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl. In some aspects, R^{10} is hydrogen.

In some embodiments, the dashed lines are saturated bonds, thereby forming a cyclohexyl group.

In some embodiments of the compound of Formula (I), L is a covalent bond.

In some embodiments of the compound of Formula (I), L is methylene or substituted methylene.

In some embodiments of the compound of Formula (I) when L is not a covalent bond,, L is substituted with alkyl, substituted alkyl, carboxyl, aminocarbonyl, and carboxyl ester.

In some embodiments of the compound of Formula (I), R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxyl, alkyl, substituted alkyl, and alkoxy.

In some embodiments of the compound of Formula (I), at least one of R^{10}, R^{11}, and R^{12} is hydroxyl.

In some embodiments, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, and alkoxy.

In some embodiments, R^{11} is taken together with R^{12} to form aryl or substituted aryl.

In some embodiments, R^1 is alkyl or substituted alkyl.

In some embodiments, R^1 is substituted alkyl, wherein the substituent of R^1 is selected from the group consisting of alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

In some embodiments, R^1 is substituted alkyl, wherein the substituent of R^1 is selected from the group consisting of alkyl, aryl, cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

In some embodiments, R^1 is substituted alkyl, wherein the substituent of R^1 is cycloalkyl or substituted cycloalkyl.

In some embodiments, R^1 is substituted alkyl, wherein the substituent of R^1 is cycloalkyl or substituted cycloalkyl.

In some embodiments, R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

In some embodiments, R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

In some embodiments, R^3 is acylamino or aminocarbonyl.

In some embodiments, R^3 is $-C(O)NH-LR^{3a}$ wherein L is a covalent bond, alkylidene, or substituted alkylidene, and R^{3a} is selected from the group consisting of alkyl, haloalkyl, amino, acylamino, (carboxyl ester)amino, hydroxy, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

In some embodiments, R^3 is $-C(O)NHCH_3$.

In some embodiments, R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

In some embodiments, R^3 is selected from the group consisting of pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, pyrimidin-4-yl, pyrimidin-3-yl, pyrimidin-2-yl, thiazoyl, tetrazolyl, imidazol-1-yl, imidazol-2-yl, imidazol-3-yl, pyrazinyl, phenyl, tetrahydropyridine, 1H-pyrrolo[2,3-b]pyridine, furanyl, oxazole, oxadiazole, cyclopropyl, cyclohexyl, cyclohexenyl, piperidinyl, morpholino, tetrahydro-1H-benzo[d]imidazole, pyrrolidinyl, piperazinyl, and piperzin-2-one, wherein each R^3 is substituted or unsubstituted.

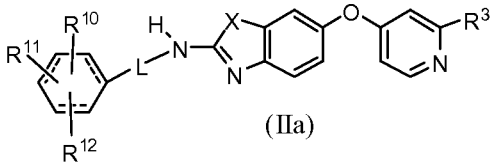
In some embodiments, R^4 is hydrogen.

In some embodiments, R^5 is hydrogen.

In some embodiments and in combination with any of the aforementioned embodiments, n is 0, R^4 and R^5 are hydrogen, and R^3 is selected from the group consisting of hydrogen, halo, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

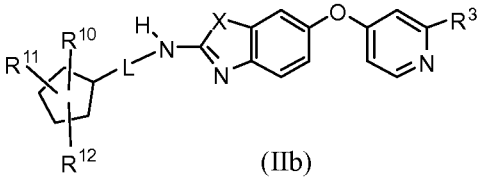
In some embodiments, R^4 and R^5 are taken together to form an aryl or substituted aryl group.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIa) or (IIb), the pharmaceutically acceptable salts thereof, and the related compositions and methods



(IIa)

or



(IIb)

wherein X is O or S;

wherein the dashed lines are saturated bonds or unsaturated bonds;

wherein L is a covalent bond or is alkylidene or substituted alkylidene;

R^{10}, R^{11} and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or R^{11} is taken together with R^{12} to form a group selected from the group consisting of aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

In some embodiments of the compound of Formula (IIa) or (IIb), X is O.

In some embodiments of the compound of Formula (IIa) or (IIb), X is S.

In some embodiments, the dashed lines are saturated bonds, thereby forming a cyclohexyl group.

In some embodiments of the compound of Formula (IIa) or (IIb), L is a covalent bond.

In some embodiments of the compound of Formula (IIa) or (IIb), L is methylene or substituted methylene.

In some embodiments of the compound of Formula (IIa) or (IIb), L is substituted with alkyl, substituted alkyl, carboxyl, aminocarbonyl, or carboxyl ester.

In some embodiments of the compound of Formula (IIa) or (IIb), R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxyl, alkyl, substituted alkyl, and alkoxy.

In some embodiments of the compound of Formula (IIa) or (IIb), at least one of R^{10}, R^{11}, and R^{12} is hydroxyl.

In some embodiments of the compound of Formula (IIa) or (IIb), R^{11} and R^{12} are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, and alkoxy.

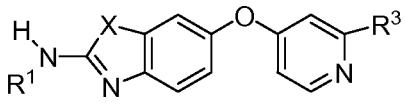
In some embodiments of the compound of Formula (IIa) or (IIb), R^{11} is taken together with R^{12} to form aryl or substituted aryl.

In some embodiments of the compound of Formula (IIa) or (IIb), R^3 is acylamino or aminocarbonyl.

In some embodiments of the compound of Formula (IIa) or (IIb), R^3 is $-C(O)NHCH_3$.

In some embodiments of the compound of Formula (IIa) or (IIb), R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIIa), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IIIa) is



(IIIa)

and wherein X is O or S;

R^1 is alkyl or alkyl substituted with a substituent selected from the group consisting of aryl, cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl,

substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

In some embodiments of the compound of Formula (IIIa), X is O.

In some embodiments of the compound of Formula (IIIa), X is S.

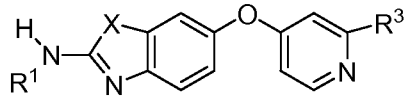
In some embodiments of the compound of Formula (IIIa), R^1 is alkyl substituted with cycloalkyl.

In some embodiments of the compound of Formula (IIIa), R^3 is acylamino or aminocarbonyl.

In some embodiments of the compound of Formula (IIIa), R^3 is $-C(O)NHCH_3$.

In some embodiments of the compound of Formula (IIIa), R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

Another embodiment is directed to compounds, stereoisomers, tautomers, and solvates of Formula (IIIb), the pharmaceutically acceptable salts thereof, and the related compositions and methods wherein Formula (IIIb) is



(IIIb)

and wherein X is O or S;

R^1 is selected from the group consisting of acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

In some embodiments of the compound of Formula (IIIb), X is O.

In some embodiments of the compound of Formula (IIIb), X is S.

In some embodiments of the compound of Formula (IIIb), R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

In some embodiments of the compound of Formula (IIIb), R^3 is acylamino or aminocarbonyl.

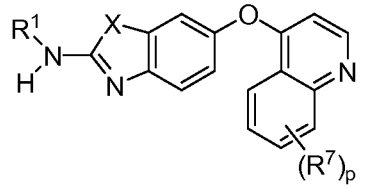
In some embodiments of the compound of Formula (IIIb), R^3 is -C(O)NHCH$_3$.

In some embodiments of the compound of Formula (IIIb), R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

In some embodiments of the compound of Formula (IIIb), R^3 is -C(O)NH-LR^{3a}, wherein L is a covalent bond, alkylidene, or substituted alkylidene, and R^{3a} is selected from the group consisting of alkyl, haloalkyl, amino, acylamino, (carboxyl ester)amino, hydroxy, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

In some embodiments of the compound of Formula (IIIb), R^3 is selected from the group consisting of pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, pyrimidin-4-yl, pyrimidin-3-yl, pyrimidin-2-yl, thiazoyl, tetrazolyl, imidazol-1-yl, imidazol-2-yl, imidazol-3-yl, pyrazinyl, phenyl, tetrahydropyridine, 1H-pyrrolo[2,3-b]pyridine, furanyl, oxazole, oxadiazole, cyclopropyl, cyclohexyl, cyclohexenyl, piperidinyl, morpholino, tetrahydro-1H-benzo[d]imidazole, pyrrolidinyl, piperazinyl, and piperzin-2-one, wherein each R^3 is substituted or unsubstituted.

Another embodiment is directed to a compound, stereoisomer, tautomer, solvate, oxide, ester, and prodrug of Formula (IV), a pharmaceutically acceptable salt therof, and the related compositions and methods wherein Formula (IV) is



(IV)

and wherein X is O or S;

R^7 is independently selected from the group consisting of alkoxy, haloalkoxy, halo, and carbonitrile;

p is 0, 1, or 2;

R^1 is –LR^8 or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

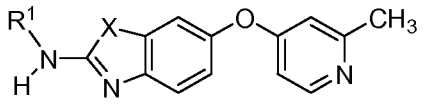
L is a covalent bond, alkylidene, or substituted alkylidene; and

R^8 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, pyridyl, and when p is 0, R^{1a} is optionally 2-methoxyphenyl.

In some embodiments, X is S.

In some embodiments, p is 0.

Another embodiment is directed to a compound, stereoisomer, tautomer, solvate, oxide, ester, and prodrug of Formula (V), the pharmaceutically acceptable salt thereof, and the related compositions and methods wherein Formula (V) is



(V)

wherein X is O or S;

R^1 is $-LR^9$ or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

L is a covalent bond, alkylidene, or substituted alkylidene; and

R^9 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, and pyridyl.

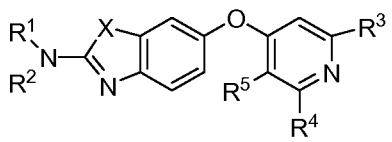
In some embodiments, X is S.

In some embodiments, L is a covalent bond or is alkylidene.

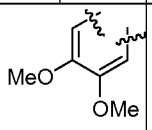
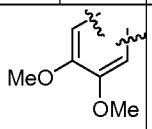
In some embodiments, R^9 is cyclohexyl or substituted cyclohexyl.

Representative compounds are presented in Table 1.

Table 1



Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
1	O	4-bromophenyl	H	H	H	$-C(O)NHCH_3$
2	O	2-(R)-1-phenylethyl	H	H	H	$-C(O)NHCH_3$

Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
3	O	2-morpholin-4-ylphenyl	H	H	H	$-C(O)NHCH_3$
4	O	2,3-dihydrobenzo[1,4]-dioxin-6-yl	H			H
5	O	(2,3-dihydrobenzo[1,4]dioxin-6-yl	H	H	H	$-C(O)NHCH_3$
6	O	(1-thiazol-2-yl-ethyl)	H	H	H	$-C(O)NHCH_3$
7	O	2-(S)-phenylethyl	H	H	H	$-C(O)NHCH_3$
8	O	2-chlorobenzyl	H	H	H	$-C(O)NHCH_3$
9	O	2,4-dichlorobenzyl	H	H	H	$-C(O)NHCH_3$
10	O	3-methylcyclohexyl	H	H	H	$-C(O)NHCH_3$
11	O	2-methoxyphenyl	H	H	H	$-C(O)NHCH_3$
12	O	2-ethoxyphenyl	H	H	H	$-C(O)NHCH_3$
13	O	(1S,2S,3S,5R)-2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl	H	H	H	$-C(O)NHCH_3$
14	O	1-(R)-phenylethyl	H			H
15	O	(1S,2R,4R)-7,7-dimethylbicyclo-[2.1.1]hept-2-ylmethyl	H	H	H	$-C(O)NHCH_3$
16	O	2-fluorobenzyl	H	H	H	$-C(O)NHCH_3$
17	O	2-methoxybenzyl	H	H	H	$-C(O)NHCH_3$
18	O	2-(R)-1-naphthalenylethyl	H	H	H	$-C(O)NHCH_3$
19	O	2-(R)-1-phenylpropyl	H	H	H	$-C(O)NHCH_3$
20	O	2-(S)-1-naphthalen-2-ylethyl	H	H	H	$-C(O)NHCH_3$
21	O	cyclohexylmethyl	H	H	H	$-C(O)NHCH_3$
22	O	cyclobutyl	H	H	H	$-C(O)NHCH_3$
23	O	cyclopentyl	H	H	H	$-C(O)NHCH_3$
24	O	cyclohexyl	H	H	H	$-C(O)NHCH_3$
25	O	(2-morpholin-4-ylmethyl)	H	H	H	$-C(O)NHCH_3$
26	O	phenyl	H	H	H	$-C(O)NHCH_3$
27	O	(4-chlorobenzyl)	H	H	H	$-C(O)NHCH_3$
28	O	2,4-dimethoxyphenyl	H	H	H	$-C(O)NHCH_3$
29	O	cyclohexyl	H	H	H	$-NHC(O)CH_3$
30	O	tetrahydropyran-4-yl	H	H	H	$-C(O)NHCH_3$
31	O	2-(R)-1-(2-methoxyphenyl)	H	H	H	$-C(O)NHCH_3$
32	O	2-chlorobenzyl	H	H	H	$-C(O)NHCH_3$
33	O	2,5-difluorobenzyl	H	H	H	$-NHC(O)CH_3$
34	O	cyclohexylmethyl	H	H	H	$-NHC(O)CH_3$
35	O	2-(R)-phenylacetic acid	H	H	H	$-C(O)NHCH_3$

Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
36	O	2-(R)-carboxylic acid methylamide	H	H	H	-C(O)NHCH$_3$
37	O	2-(R)-hydroxy-1-phenyl-ethyl	H	H	H	-C(O)NHCH$_3$
38	O	2-(S)-phenylacetic acid	H	H	H	-C(O)NHCH$_3$
39	O	2-(S)-carboxylic acid methylamide	H	H	H	-C(O)NHCH$_3$
40	O	Pyridine-2-ylmethyl	H	H	H	-C(O)NHCH$_3$
41	O	benzyl	H	H	H	-C(O)NHCH$_3$
42	O	3-chlorobenzyl	H	H	H	-C(O)NHCH$_3$
43	O	2-(2-pyrrolidin-1-ylethyl)phenyl	H	H	H	-C(O)NHCH$_3$
44	O	2-(2-piperidin-1-ylethyl)phenyl	H	H	H	-C(O)NHCH$_3$
45	O	2-(4-methyl-imidazol-1-yl)phenyl	H	H	H	-C(O)NHCH$_3$
46	O	2-oxazol-5-ylphenyl	H	H	H	-C(O)NHCH$_3$
47	O	2-(2-methylimidazol-1-yl)phenyl	H	H	H	-C(O)NHCH$_3$
48	O	2-morpholin-4-yl-ethyl	H	H	H	-C(O)NHCH$_3$
49	O	(1S,2R)-2-hydroxy-indan-1-yl	H	H	H	-C(O)NHCH$_3$
50	O	(1R,2S)-2-hydroxy-indan-1-yl	H	H	H	-C(O)NHCH$_3$
51	O	2-(R)-3-hydroxy-1-phenylpropyl	H	H	H	-C(O)NHCH$_3$
52	O	(1S,2S)-2-hydroxycyclohexyl	H	H	H	-C(O)NHCH$_3$
53	O	2-(R)-phenylacetic acid methyl ester	H	H	H	-C(O)NHCH$_3$
54	O	2-(R)-cyclohexylethyl	H	H	H	-C(O)NHCH$_3$
55	O	2-(S)-phenylacetic acid methyl ester	H	H	H	-C(O)NHCH$_3$
56	O	2-(S)-hydroxy-1-phenylethyl	H	H	H	-C(O)NHCH$_3$
57	O	Pyridine-4-ylmethyl	H	H	H	-C(O)NHCH$_3$
58	O	2-piperidin-1-ylethyl	H	H	H	-C(O)NHCH$_3$
59	O	Pyrindin-3-ylmethyl	H	H	H	-C(O)NHCH$_3$
60	O	cyclohexylmethyl	H	H	H	-C(O)OH
61	O	phenethyl	H	H	H	-C(O)NHCH$_3$
62	O	2-(R)-cyclohexylmethyl-carbamoylmethyl	H	H	H	-C(O)NHCH$_3$
63	O	2-pyrrolidin-1-ylethyl	H	H	H	-C(O)NHCH$_3$
64	O	2-piperidin-1-ylethyl	H	H	H	-C(O)NHCH$_3$
65	O	2,3-dihydrobenzo-[1,4]dioxin-5-ylmethyl	H	H	H	-C(O)NHCH$_3$
66	O	2-(S)-1-cyclohexyl-2-hydroxyethyl	H	H	H	-C(O)NHCH$_3$

Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
67	O	2-(R)-1-cyclohexyl-2-hydroxyethyl	H	H	H	-C(O)NHCH$_3$
68	O	cyclohexylmethyl	H	H	H	-C(O)NHNHC(O)OC(CH$_3$)$_3$
69	O	cyclohexylmethyl	H	H	H	-C(O)NH$_2$
70	O	Cyclohex-3-enyl	H	H	H	-C(O)NHCH$_3$
71	O	2,4-difluorobenzyl	H	H	H	-C(O)NHCH$_3$
72	O	2-bromobenzyl	H	H	H	-C(O)NHCH$_3$
73	O	2-fluoro-5-methoxybenzyl	H	H	H	-C(O)NHCH$_3$
74	O	3-(2-morpholin-4-ylethyl)phenyl	H	H	H	-C(O)NHCH$_3$
75	O	Cyclohexanecarboxylic acid ethyl ester	H	H	H	-C(O)NHCH$_3$
76	O	2,6-dichlorobenzyl	H	H	H	-C(O)NHCH$_3$
77	O	2,3-dichlorobenzyl	H	H	H	-C(O)NHCH$_3$
78	O	2-chloro-6-fluorobenzyl	H	H	H	-C(O)NHCH$_3$
79	O	2,3,-difluorobenzyl	H	H	H	-C(O)NHCH$_3$
80	O	cyclohexylmethyl	H	H	H	-CH$_2$OH
81	O	cyclohexylmethyl	H	H	H	oxadiazolyl
82	O	cyclohexylmethyl	H	H	H	-CN
83	O	2,5-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
84	O	2,6-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
85	O	2-dimethyaminobenzyl	H	H	H	-C(O)NHCH$_3$
86	O	2-aminobenzyl	H	H	H	-C(O)NHCH$_3$
87	O	2,6-difluorobenzyl	H	H	H	-C(O)NHCH$_3$
88	O	2-morpholin-4-ylbenzyl	H	H	H	-C(O)NHCH$_3$
89	O	2-methylbenzyl	H	H	H	-C(O)NHCH$_3$
90	O	3,4-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
91	O	2,3-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
92	O	2,4-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
93	O	Cyclohexanecarboxylic acid-methyl	H	H	H	-C(O)NHCH$_3$
94	O	2,3-dihydrobenzo-[1,4]dioxin-5-yl	H	H	H	-C(O)NHCH$_3$
95	O	Benzo[1,3]dioxol-5-yl	H	H	H	-C(O)NHCH$_3$
96	O	2-ethoxybenzyl	H	H	H	-C(O)NHCH$_3$
97	O	2-trifluoromethylbenzyl	H	H	H	-C(O)NHCH$_3$
98	O	isopropyl	H	H	H	-C(O)NHCH$_3$
99	O	isobutyl	H	H	H	-C(O)NHCH$_3$
100	O	Tert-butyl	H	H	H	-C(O)NHCH$_3$
101	O	cycloheptylmethyl	H	H	H	-C(O)NHCH$_3$
102	O	Tetrahydrofuran-2-ylmethyl	H	H	H	-C(O)NHCH$_3$
103	O	Benzyl-piperidin-4-yl	H	H	H	-C(O)NHCH$_3$
104	O	1,2,3,4-tetrahydronaphthalen-1-yl	H	H	H	-C(O)NHCH$_3$

Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
105	O	2-pyrazol-1-ylbenzyl	H	H	H	-C(O)NHCH$_3$
106	O	benzyl	CH$_3$	H	H	-C(O)NHCH$_3$
107	O	1-phenyl-piperidin-4-yl	H	H	H	-C(O)NHCH$_3$
108	O	3,4-dihydro-2H-benzo-[b][1,4]dioxepin-6ylmethyl	H	H	H	-C(O)NHCH$_3$
109	O	cyclohexylmethyl	H	H	H	5-methyl-1H-imidazol-2-yl
110	O	2,3-dihydrobenzo-[1,4]dioxine-5-carbonyl	H	H	H	-C(O)NHCH$_3$
111	O	cyclohexylmethyl	H	H	H	-CH$_2$NH$_2$
112	O	Carboxylic acid methylamide	H	H	H	-C(O)NHCH$_3$
113	O	2,4,6-trimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
114	O	5-chloro-2-methoxybenzyl	H	H	H	-C(O)NHCH$_3$
115	O	5-fluoro-2-methoxybenzyl	H	H	H	-C(O)NHCH$_3$
116	O	2-fluoro-6-methoxybenzyl	H	H	H	-C(O)NHCH$_3$
117	O	2-chloro-3,4-dimethoxybenzyl	H	H	H	-C(O)NHCH$_3$
118	O	2-piperidin-1-ylbenzyl	H	H	H	-C(O)NHCH$_3$
119	O	2,3-dihydro-benzo-[1,4]dioxin-2-ylmethyl	H	H	H	-C(O)NHCH$_3$
120	O	4-benzyl-morpholin-2-ylmethyl	H	H	H	-C(O)NHCH$_3$
121	O	2-chloro-6-methoxybenzyl	H	H	H	-C(O)NHCH$_3$
122	O	2,3-dihydrobenzo-[1,4]dioxin-6-ylmethyl	H	H	H	-C(O)NHCH$_3$
123	O	2-(2,3-dihydrobenzo-[1,4]dioxin-5-yl)ethyl	H	H	H	-C(O)NHCH$_3$
124	O	2,3-dihydrobenzofuran-5-ylmethyl	H	H	H	-C(O)NHCH$_3$
125	O	2-(2,3-dihydrobenzo-[1,4]dioxin-5-yl)ethyl	H	H	H	-C(O)NHCH$_3$
126	S	4-chloro-3-trifluoromethylphenyl	H	H	H	-C(O)NHCH$_3$
127	S	2-chlorobenzyl	H	H	H	-C(O)NHCH$_3$
128	S	cyclohexylmethyl	H	H	H	-C(O)NHCH$_3$
129	S	2-(R)-1-(2-methoxyphenyl)ethyl	H	H	H	-C(O)NHCH$_3$
130	S	2,4-dichlorobenzyl	H	H	H	-C(O)NHCH$_3$
131	S	2-(R)-1-phenylethyl	H	H	H	-C(O)NHCH$_3$
132	S	2-methoxylbenzyl	H	H	H	-C(O)NHCH$_3$
133	S	2-phenethyl	H	H	H	-C(O)NHCH$_3$
134	S	2,3-dichlorobenzyl	H	H	H	-C(O)NHCH$_3$
135	S	cyclohexyl	H	H	H	-C(O)NHCH$_3$
136	S	3-methylcyclohexyl	H	H	H	-C(O)NHCH$_3$
137	S	(1S,2S)-2-hydroxycyclohexyl	H	H	H	-C(O)NHCH$_3$

Cmpd. No.	X	R^1	R^2	R^4	R^5	R^3
138	S	2-(R)-cyclohexylethyl	H	H	H	$-C(O)NHCH_3$
139	S	2,5-difluorobenzyl	H	H	H	$-C(O)NHCH_3$
140	S	2-fluorobenzyl	H	H	H	$-C(O)NHCH_3$
141	S	Tetrahydropyran-4-ylmethyl	H	H	H	$-C(O)NHCH_3$
142	S	2-morpholin-4-ylbenzyl	H	H	H	$-C(O)NHCH_3$
143	S	2-pyrazol-1-yl-benzyl	H	H	H	$-C(O)NHCH_3$
144	S	2-dimethylaminobenzyl	H	H	H	$-C(O)NHCH_3$
145	S	2,6-dimethoxybenzyl	H	H	H	$-C(O)NHCH_3$
146	S	2,5-dimethoxybenzyl	H	H	H	$-C(O)NHCH_3$
147	S	2,3-difluorobenzyl	H	H	H	$-C(O)NHCH_3$
148	S	cycloheptylmethyl	H	H	H	$-C(O)NHCH_3$
149	S	2,6-difluorobenzyl	H	H	H	$-C(O)NHCH_3$
150	S	Pyridin-2-ylmethyl	H	H	H	$-C(O)NHCH_3$
151	S	3,4-dimethoxybenzyl	H	H	H	$-C(O)NHCH_3$
152	S	2,3-dihydrobenzo-[1,4]dioxin-5-ylmethyl	H	H	H	$-C(O)NHCH_3$
153	S	2-piperidin-1-yl-benzyl	H	H	H	$-C(O)NHCH_3$
154	S	Pyridin-3-ylmethyl	H	H	H	$-C(O)NHCH_3$
155	S	(1R,2R)-2-benzyloxycyclohexyl	H	H	H	$-C(O)NHCH_3$
156	S	(1S,2S)-2-benzyloxycyclohexyl	H	H	H	$-C(O)NHCH_3$
157	S	(1R,2R)-2-hydroxycyclohexyl	H	H	H	$-C(O)NHCH_3$
158	S	2,6-dichlorobenzyl	H	H	H	$-C(O)NHCH_3$
159	S	cyclohexylmethyl	H	H	H	$-C(O)NH(CH_2)_2OCH_3$
160	S	cyclohexylmethyl	H	H	H	$-C(O)NH(CH_2)_2N(CH_3)_2$
161	S	4-sulfonamido-benzyl	H	H	H	$-C(O)NHCH_3$

Representative compounds of Formula (I) include, for example,

4-[2-(4-Bromo-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Morpholin-4-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-[6-(6,7-dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-amine,

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(1-Thiazol-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((S)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(3-Methyl-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Methoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Ethoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1S,2S,3S,5R)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-3-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

[6-(6,7-Dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-((R)-1-phenyl-ethyl)-amine,

4-{2-[((1S,2R,4R)-7,7-Dimethyl-bicyclo[2.2.1]hept-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Naphthalen-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Phenyl-propylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((S)-1-Naphthalen-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-(2-Cyclobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-(2-Cyclopentylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Morpholin-4-ylmethyl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-(2-Phenylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(4-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4-Dimethoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

N-[4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridin-2-yl]-acetamide,

4-[2-(Tetrahydro-pyran-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

N-{4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide,

4-[2-(2,5-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

N-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide,

(R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid,

4-{2-[((R)-Methylcarbamoyl-phenyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

(S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid,

4-{2-[((S)-Methylcarbamoyl-phenyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[(Pyridin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-(2-Benzylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(3-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(2-Pyrrolidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(4-Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Oxazol-5-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(2-Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-(2-Amino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-(2-Hydroxy-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1R,2S)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-3-Hydroxy-1-phenyl-propylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

(R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester,

4-[2-((R)-1-Cyclohexyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

(S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester,

4-[2-((S)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(Pyridin-4-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[3-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[(Pyridin-3-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid,

4-(2-Phenethylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-{2-[((R)-Cyclohexyl-methylcarbamoyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Pyrrolidin-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Piperidin-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-((S)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

N'-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonyl}-hydrazinecarboxylic acid tert-butyl ester,

4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid amide,

4-[2-(Cyclohex-3-enylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Bromo-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Fluoro-5-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[3-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid ethyl ester,

4-[2-(2,6-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,3-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Chloro-6-fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,3-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-methanol,

Cyclohexylmethyl-[6-(2-[1,3,4]oxadiazol-2-yl-pyridin-4-yloxy)-benzooxazol-2-yl]-amine,

4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonitrile,

4-[2-(2,5-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,6-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Dimethylamino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Amino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,6-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Morpholin-4-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Methyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(3,4-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,3-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid,

4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(Benzo[1,3]dioxol-5-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Ethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Trifluoromethyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-(2-Isopropylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-(2-Isobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-(2-tert-Butylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(Cycloheptylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(Tetrahydro-furan-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(1-Benzyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Pyrazol-1-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(Benzyl-methyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(1-Phenyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

Cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine,

4-{2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

[6-(2-Aminomethyl-pyridin-4-yloxy)-benzooxazol-2-yl]-cyclohexylmethyl-amine,

4-{2-[(1-Methylcarbamoyl-cyclohexylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4,6-Trimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(5-Chloro-2-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(5-Fluoro-2-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Fluoro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Chloro-3,4-dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Piperidin-1-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[(4-Benzyl-morpholin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Chloro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-{2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, and

4-{2-[1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide.

Representative compounds of Formula (I) include, for example,

4-[2-(4-Chloro-3-trifluoromethyl-phenylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Chloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2,4-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Phenyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Methoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-(2-Phenethylamino-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(2,3-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-(2-Cyclohexylamino-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide,

4-[2-(3-Methyl-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((R)-1-Cyclohexyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,5-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Fluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(Tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Morpholin-4-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Pyrazol-1-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Dimethylamino-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,6-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,5-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,3-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(Cycloheptylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,6-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(Pyridin-2-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(3,4-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-(2-Piperidin-1-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-{2-[(Pyridin-3-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide,

4-[2-((1R,2R)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1S,2S)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide,

4-[2-(2,6-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, and

4-[2-(4-Sulfonamido-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide or a pharmaceutically acceptable salt, tautomer, solvate, or stereoisomer thereof.

In other embodiments, provided is a compound of Table 2, 3, or 4 or a stereoisomer, tautomer, solvate, oxide, ester, prodrug, or pharmaceutically acceptable salt thereof.

It will also be apparent to those skilled in the art that the compounds of the invention, including the compounds of compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) or their stereoisomers, as well as the pharmaceutically acceptable salts, esters, metabolites and prodrugs of any of them, may be subject to tautomerization and may therefore exist in various tautomeric forms wherein a proton of one atom of a molecule shifts to another atom and the chemical bonds between the atoms of the molecules are consequently rearranged. See, e.g., March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structures*, Fourth Edition, John Wiley & Sons, pages 69-74 (1992).

Preferred embodiments, including the compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) or their tautomers, as well as the pharmaceutically acceptable salts, esters, metabolites and prodrugs of any of them, may comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of preferred embodiments existing in enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, such as in (R)- or (S)-forms. As a result, all such possible isomers, individual stereoisomers in their optically pure forms, mixtures thereof, racemic mixtures (or "racemates"), mixtures of diastereomers, as well as single diastereomers of the compounds of the preferred embodiments are contemplated. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure*

Appl. Chem. *45*:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

Methods for treating CSF-1R mediated diseases

There are 3 distinct mechanisms by which CSF-1R signaling is likely involved in tumor growth and metastasis. The first is that expression of CSF-ligand and receptor has been found in tumor cells originating in the female reproductive system (breast, ovarian, endometrium, cervical) (Scholl 1994; Kacinski 1997; Nagan 199; Kirma 2007) and the expression has been associated with breast cancer xenograft growth as well as poor prognosis in breast cancer patients. Two point mutations were seen in CSF-1R in about 10-20% of acute myelocytic leukemia, chronic myelocytic leukemia and myelodysplasia patients tested in one study, and one of mutations was found to disrupt receptor turnover (Ridge 1990). However the incidence of the mutations could not be confirmed in later studies (Abu-Duhier 2003). Mutations were also found in some cases of hepatocellular cancer (Yang 2004) and idiopathic myelofibrosis (Abu-Duhier 2003).

Pigmented villonodular synovitis (PVNS) and Tenosynovial Giant cell tumors (TGCT) can occur as a result of a translocation that fuses the M-CSF gene to a collagen gene COL6A3 and results in overexpression of M-CSF (West 2006). A landscape effect is proposed to be responsible for the resulting tumor mass that consists of monocytic cells attracted by cells that express M-CSF. TGCTs are smaller tumors that can be relatively easily removed from fingers where they mostly occur. PVNS is more aggressive as it can recur in large joints and is not as easily controlled surgically.

The second mechanism is based on blocking signaling through M-CSF/CSF-1R at metastatic sites in bone which induces osteoclastogenesis, bone resorption and osteolytic bone lesions. Breast, kidney, and lung cancers are examples of cancers that have been found to metastasize to the bone and cause osteolytic bone disease resulting in skeletal complications. M-CSF released by tumor cells and stroma induces the differentiation of

hematopoietic myeloid monocyte progenitors to mature osteoclasts in collaboration with the receptor activator of nuclear factor kappa-B ligand—RANKL. During this process, M-CSF acts as a permissive factor by giving the survival signal to osteoclasts (Tanaka 1993). Inhibition of CSF-1R kinase activity during osteoclast differentiation and maturation with a small molecule inhibitor is likely to prevent unbalanced activity of osteoclasts that cause osteolytic disease and the associated skeletal related events in metastatic disease. Whereas breast, lung cancer and multiple myeloma typically result in osteolytic lesions, metastasis to the bone in prostate cancer initially has an osteoblastic appearance in which increased bone forming activity results in 'woven bone' which is different from typical lamellar structure of normal bone. During disease progression bone lesions display a significant osteolytic component as well as high serum levels of bone resorption and suggests that anti-resorptive therapy may be useful. Bisphosphonates have been shown to inhibit the formation of osteolytic lesions and reduced the number of skeletal-related events only in men with hormone-refractory metastatic prostate cancer but at this point their effect on osteoblastic lesions is controversial and bisphosphonates have not been beneficial in preventing bone metastasis or hormone responsive prostate cancer to date. The effect of anti-resorptive agents in mixed osteolytic/osteoblastic prostate cancer is still being studied in the clinic (Choueiri 2006; Vessella 2006).

The third mechanism is based on the recent observation that tumor associated macrophages (TAM) found in solid tumors of the breast, prostate, ovarian and cervical cancers correlated with poor prognosis (Bingle 2002; Pollard 2004). Macrophages are recruited to the tumor by M-CSF and other chemokines. The macrophages can then contribute to tumor progression through the secretion of angiogenic factors, proteases and other growth factors and cytokines and may be blocked by inhibition of CSF-1R signaling. Recently it was shown by Zins et al (Zins 2007) that expression of siRNA of Tumor necrosis factor alpha (TNFα), M-CSF or the combination of both would reduce tumor growth in a mouse xenograft model between 34% and 50% after intratumoral injection of the respective siRNA the xenograft. SiRNA targeting the TNFalpha secreted by the human SW620 cells reduced the mouse M-CSF and led to reduction of macrophages in the tumor. In addition treatment of MCF7 tumor xenografts with an antigen binding fragment directed against M-CSF antibody did result in 40% tumor growth inhibition, reversed the resistance

to chemotherapeutics and improved survival of the mice when given in combination with chemotherapeutics (Paulus 2006).

TAMs are only one example of an emerging link between chronic inflammation and cancer. There is additional evidence for a link between inflammation and cancer as many chronic diseases are associated with an increased risk of cancer, cancers arise at sites of chronic inflammation, chemical mediators of inflammation are found in many cancers; deletion of the cellular or chemical mediators of inflammation inhibits development of experimental cancers and long-term use of anti-inflammatory agents reduce the risk of some cancers. A link to cancer exists for a number of inflammatory conditions among those *H.pylori* induced gastritis for gastric cancer, Schistosomiasis for bladder cancer, HHV8 for Kaposi's sarcoma, endometriosis for ovarian cancer and prostatitis for prostate cancer (Balkwill 2005). Macrophages are key cells in chronic inflammation and respond differentially to their microenvironment. There are two types of macrophages that are considered extremes in a continuum of functional states: M1 macrophages are involved in Type 1 reactions. These reactions involve the activation by microbial products and consequent killing of pathogenic microorganisms that result in reactive oxygen intermediates. On the other end of the extreme are M2 macrophages involved in Type 2 reactions that promote cell proliferation, tune inflammation and adaptive immunity and promote tissue remodeling, angiogenesis and repair (Mantovani 2004). Chronic inflammation resulting in established neoplasia is usually associated with M2 macrophages. A pivotal cytokine that mediates inflammatory reactions is TNF-α that true to its name can stimulate anti-tumor immunity and hemorrhagic necrosis at high doses but has also recently been found to be expressed by tumor cells and acting as a tumor promoter (Zins 2007; Balkwill 2006). The specific role of macrophages with respect to the tumor still needs to be better understood including the potential spatial and temporal dependence on their function and the relevance to specific tumor types.

In another embodiment, a method for treating periodontitis, histiocytosis X, osteoporosis, Paget's disease of bone (PDB), bone loss due to cancer therapy, periprosthetic osteolysis, glucocorticoid-induced osteoporosis, rheumatoid arthritis, psiratic arthritis, osteoarthritis, inflammatory arthridities, and inflammation is provided.

Rabello 2006 has demonstrated that SNPs in the CSF1 gene exhibited a positive association with aggressive periodontitis: an inflammatory disease of the periodontal tissues that causes tooth loss due to resorption of the alveolar bone.

Histiocytosis X (also called Langerhans cell histiocytosis, LCH) is a proliferative disease of Langerhans dendritic cells that appear to differentiate into osteoclasts in bone and extraosseous LCH lesions. Langerhans cells are derived from circulating monocytes (Ginoux 2006). Increased levels of M-CSF that have been measured in sera and lesions where found to correlate with disease severity (da Costa 2005). The disease occurs primarily in a pediatric patient population and has to be treated with chemotherapy when the disease becomes systemic or is recurrent.

The pathophysiology of osteoporosis is mediated by loss of bone forming osteoblasts and increased osteoclast dependent bone resorption. Supporting data has been described by Cenci et al showing that an anti-M-CSF antibody injection preserves bone density and inhibits bone resorption in ovarectomized mice (Cenci 2000). Recently a potential link between postmenopausal bone loss due to estrogen deficiency was identified and found that the presence of TNF alpha producing T-cell affected bone metabolism (Roggia 2004). A possible mechanism could be the induction of M-CSF by TNF alpha *in vivo*. An important role for M-CSF in TNF-alpha-induced osteoclastogenesis was confirmed by the effect of an antibody directed against the M-CSF-inhibitor that blocked the TNF alpha induced osteolysis in mice and thereby making inhibitors of CSF-1R signaling potential targets for inflammatory arthritis (Kitaura 2005).

Paget's disease of bone (PDB) is the 2nd most common bone metabolism disorder after osteoporosis in which focal abnormalities of increased bone turnover lead to complications such as bone pain, deformity, pathological fractures, and deafness. Mutations in four genes have been identified that regulate normal osteoclast function and predispose individuals to PDB and related disorders: insertion mutations in TNFRSF11A, which encodes receptor activator of nuclear factor (NF) kappaB (RANK)-a critical regulator of osteoclast function, inactivating mutations of TNFRSF11B which encodes osteoprotegerin (a decoy receptor for RANK ligand), mutations of the sequestosome 1 gene (SQSTM1), which encodes an important scaffold protein in the NFkappaB pathway and mutations in the valosin-containing protein (VCP) gene. This gene encodes VCP, which has a role in targeting the inhibitor of NFkappaB for degradation by the proteasome (Daroszewska,

2006). Targeted CSF-1R inhibitors provide an opportunity to block the deregulation of the RANKL signaling indirectly and add an additional treatment option to the currently used bisphosphonates.

Cancer therapy induced bone loss especially in breast and prostate cancer patients is an additional indication where a targeted CSF-1R inhibitor could prevent bone loss (Lester 2006).With the improved prognosis for early breast cancer the long-term consequences of the adjuvant therapies become more important as some of the therapies including chemotherapy, irradiation, aromatase inhibitors and ovary ablation affect bone metabolism by decreasing the bone mineral density, resulting in increased risk for osteoporosis and associated fractures (Lester 2006). The equivalent to adjuvant aromatase inhibitor therapy in breast cancer is androgen ablation therapy in prostate cancer which leads to loss of bone mineral density and significantly increases the risk of osteoporosis-related fractures (Stoch 2001).

Targeted inhibition of CSF-1R signaling is likely to be beneficial in other indications as well when targeted cell types include osteoclasts and macrophages e.g. treatment of specific complications in response to joint replacement as a consequence of rheumatoid arthritis. Implant failure due to periprosthetic bone loss and consequent loosing of protheses is a major complication of joint replacement and requires repeated surgery with high socioeconomic burdens for the individual patient and the health-care system. To date, there is no approved drug therapy to prevent or inhibit periprosthetic osteolysis (Drees 2007).

Glucocorticoid-induced osteoporosis (GIOP) is another indication in which a CSF-1R inhibitor could prevent bone loss after longterm glucocorticocosteroid use that is given as a result of various conditions among those chronic obstructive pulmonary disease, asthma and rheumatoid arthritis (Guzman-Clark 2007; Feldstein 2005).

Rheumatoid arthritis, psiratic arthritis and inflammatory arthridities are in itself potential indications for CSF-1R signaling inhibitors in that they consist of a macrophage component a to a varying degree bone destruction (Ritchlin 2003). Osteoarthritis and rheumatoid arthritis are inflammatory autoimmune disease caused by the accumulation of macrophages in the connective tissue and infiltration of macrophages into the synovial fluid, which is at least partially mediated by M-CSF. Campbell et al. (2000) demonstrated that M-

CSF is produced by human-joint tissue cells (chondrocytes, synovial fibroblasts) *in vitro* and is found in synovial fluid of patients with rheumatoid arthritis, suggesting that it contributes to the synovial tissue proliferation and macrophage infiltration which is associated with the pathogenesis of the disease. Inhibition of CSF-1R signaling is likely to control the number of macrophages in the joint and alleviate the pain from the associated bone destruction. In order to minimize adverse affects and to further understand the impact of the CSF-1R signaling in these indications, one method is to specifically inhibit CSF-1R without targeting a myriad other kinases, such as Raf kinase.

Recent literature reports correlate increased circulating M-CSF with poor prognosis and atherosclerotic progression in chronic coronary artery disease (Saitoh 2000; Ikonomidis 2005); M-CSF influences the atherosclerotic process by aiding the formation of foam cells (macrophages with ingested oxidized LDL) that express CSF-1R and represent the initial plaque (Murayama 1999).

Expression and signaling of M-CSF and CSF-1R is found in activated microglia. Microglia, which are resident macrophages of the central nervous system, can be activated by various insults, including infection and traumatic injury. M-CSF is considered a key regulator of inflammatory responses in the brain and M-CSF levels increase in HIV-1 encephalitis, Alzheimer's disease (AD) and brain tumors. Microgliosis as a consequence of autocrine signaling by M-CSF/CSF-1R results in induction of inflammatory cytokines and nitric oxides being released as demonstrated by e.g. using an experimental neuronal damage model (Hao 2002; Murphy 1998). Microglia that have increased expression of CSF-1R are found to surround plaques in AD and in the amyloid precursor protein V717F transgenic mouse model of AD (Murphy 2000). On the other hand op/op mice with fewer microglia in the brain resulted in fibrilar deposition of Aβ and neuronal loss compared to normal control suggesting that microglia do have a neuroprotective function in the development of AD lacking in the op/op mice (Kaku 2003).

In one aspect, the preferred embodiments provide methods for treating CSF-1R related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) effective to reduce or prevent the disorder. In a preferred embodiment, the disorder is tumor growth and/or metathesis in the subject.

In other aspects, the preferred embodiments provide methods for treating CSF-1R related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) effective to reduce or prevent osteoclastogenesis, bone resorption and/or bone lesions in the subject.

In yet other aspects, the preferred embodiments provide methods for treating CSF-1R related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) effective to treat the disorder in the subject in combination with at least one additional agent. In a more particular embodiment the additional agent is a bisphosphonate. In one embodiment the disorder is tumor growth and/or metastasis, osteoclastogenesis, bone resorption and/or bone lesions

In yet other aspects, the preferred embodiments provide compounds of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) that are capable of selectively or preferentially inhibiting CSF-1R. In preferred embodiments the selective inhibitors of CSF-1R are capable of inhibiting CSF-1R at greater than about 5-fold, or about 10 fold, or about 20 fold, or about 30 fold, or about 50 fold, or about 100 fold, or about 250 fold, or about 500 fold, or about 750 fold, or about 1,000 fold, or about 2,000 the inhibitory activity (with respect to IC_{50} values, for example) in Raf kinase.

In other aspects provided is a method of inhibiting CSF-1R comprising contacting a cell with a compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V). In some aspects said compound is 4-{2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide or 4-[2-((1R,2R)-2-Benzyloxy-cyclo-hexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide.

In one aspect, the inhibitory effect of compounds on Raf is determined using the following biotinylated assay. The Raf kinase activity is measured by providing ATP, a recombinant kinase inactive MEK substrate and assaying the transfer of phosphate moiety to the MEK residue. Recombinant full length MEK with an inactivating K97R ATP binding site mutation (rendering kinase inactive) is expressed in *E. coli* and labelled with biotin post purification. The MEK cDNA is subcloned with an N-terminal $(His)_6$ tag and expressed in E. coli and the recombinant MEK substrate is purified from *E. coli* lysate by

nickel affinity chromatography followed by anion exchange. The final MEK substrate preparation is biotinylated (Pierce EZ-Link Sulfo-NHS-LC-Biotin) and concentrated to about 11.25μM. Recombinant Raf (including c-Raf and mutant B-Raf isoforms) is obtained by purification from sf9 insect cells infected with the corresponding human Raf recombinant expression vectors. The recombinant Raf isoforms are purified via a Glu antibody interaction or by Metal Ion Chromatography.

For each assay, the compound is serially diluted, for instance, starting at 25 μM with 3-fold dilutions, in DMSO and then mixed with various Raf isoforms (about 0.50 nM each). The kinase inactive biotin-MEK substrate (50 nM) is added in reaction buffer plus ATP (1 μM). The reaction buffer contains 30 mM Tris-HCl_2 pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 4mM EDTA, 25 mM beta-glycerophosphate, 5 mM $MnCl_2$, and 0.01% BSA/PBS. Reactions are subsequently incubated for about 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture is transferred to a neutradavin-coated plate and incubated for about 1 hour. Phosphorylated product is measured with the DELFIA time-resolved fluorescence system, using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence can be read on a Wallac 1232 DELFIA fluorometer. The concentration of the compound for 50% inhibition (IC_{50}) is calculated by non-linear regression using XL Fit data analysis software.

In yet other aspects, the preferred embodiments provide methods for treating CSF-1R related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer. In a more particular embodiment the additional agent is a bisphosphonate.

A number of suitable anticancer agents to be used as combination therapeutics are contemplated for use in the methods of the preferred embodiments. Indeed, the preferred embodiments include administration of numerous additional anticancer agents such as, but not limited to, agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies

conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g. interferons [e.g. IFN-α, etc.] and interleukins [e.g. IL-2, etc.], etc.); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g. all-trans-retinoic acid, etc.); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) are known to those skilled in the art.

In preferred embodiments, additional anticancer agents to be used in combination with compounds of the preferred embodiments comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation (e.g., ω); kinase inhibitors (e.g., Epidermal Growth Factor Receptor [EGFR] kinase inhibitor, Vascular Endothelial Growth Factor Receptor [VEGFR] kinase inhibitor, Fibroblast Growth Factor Receptor [FGFR] kinase inhibitor, Platelet-derived Growth Factor Receptor [PDGFR] I kinase inhibitor, and Bcr-Abl kinase inhibitors such as STI-571, Gleevec, and Glivec]); antisense molecules; antibodies [e.g., Herceptin and Rituxan]; anti-estrogens [e.g., raloxifene and tamoxifen]; anti-androgens [e.g., flutamide, bicalutamide, finasteride, amino-glutethamide, ketoconazole, and corticosteroids]; cyclooxygenase 2 (COX-2) inhibitors [e.g., Celecoxib, meloxicam, NS-398, and non-steroidal antiinflammatory drugs (NSAIDs)]; and cancer chemotherapeutic drugs [e.g., irinotecan (Camptosar), CPT-11, fludarabine (Fludara), dacarbazine (DTIC), dexamethasone, mitoxantrone, Mylotarg, VP-16, cisplatinum, 5-FU, Doxrubicin, Taxotere or taxol; cellular signaling molecules; ceramides and cytokines; and staurosprine, and the like.

The compounds of the preferred embodiments are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient.

In other aspects, the preferred embodiments provide pharmaceutical compositions comprising at least one compound of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

In other aspects, the preferred embodiments provide methods of manufacture of compounds of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) as described herein.

In other aspects provided is a pharmaceutical composition comprising an effective amount of a compound, stereoisomer, tautomer, solvate, oxide, ester, or prodrug of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. In some aspects the compound preferentially inhibits CSF-1R over Raf kinase. More particularly said compound inhibits Raf kinase at greater than about 1 μM.

Other aspects further comprise an additional agent. More particularly, said additional agent is a bisphosphonate.

Other aspects provide compounds of Formula (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) effective to inhibit CSF-1R activity in a human or animal subject when administered thereto. More particularly, said compound exhibits an IC_{50} value with respect to CSF-1R inhibition of less than about 1 μM. More particularly, said compound exhibits an IC_{50} value with respect to Raf inhibition of greater than about 1 μM.

Another embodiment provides a method of inhibiting CSF-1R, wherein said compound selectively inhibits CSF-1R.

The compounds of the embodiments are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), incorporated herein by reference.

Administration and Pharmaceutical Composition

In general, the compounds of preferred embodiments will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents

that serve similar utilities. The actual amount of the compound of preferred embodiments, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors. The drug can be administered more than once a day, preferably once or twice a day. All of these factors are within the skill of the attending clinician.

Effective amounts of the compounds of the preferred embodiments generally include any amount sufficient to detectably inhibit CSF-1R activity by any of the assays described herein, by other CSF-1R kinase activity assays known to those having ordinary skill in the art or by detecting an inhibition or alleviation of symptoms of cancer.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

For purposes of the preferred embodiments, a therapeutically effective dose generally can be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from about 0.001 to about 1000 mg/kg body weight daily and more preferred from about 1.0 to about 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The choice of formulation depends on various factors such as the mode of drug administration and bioavailability of the drug substance. In general, compounds of preferred embodiments can be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen that can be adjusted according to the degree of affliction. Compositions can take the form of tablets,

pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions. Another preferred manner for administering compounds of preferred embodiments is inhalation. This is an effective method for delivering a therapeutic agent directly to the respiratory tract (see U.S. Patent 5,607,915).

Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Liquid and semisolid excipients can be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), incorporated herein by reference.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V). These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V), or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with agents such as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl,

and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the preferred embodiments which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the embodiments. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent

compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

It will be apparent to those skilled in the art that the compounds of the preferred embodiments, including the compounds of Formulas (I), (IIa), (IIb), (IIIa), (IIIb), (IV), or (V) or their tautomers, prodrugs, and stereoisomers, as well as the pharmaceutically acceptable salts, esters and prodrugs of any of them, may be processed *in vivo* through metabolism in a human or animal body or cell to produce metabolites. The term "metabolite" as used herein refers to the formula of any derivative produced in a subject after administration of a parent compound. The derivatives may be produced from the parent compound by various biochemical transformations in the subject such as, for example, oxidation, reduction, hydrolysis, or conjugation and include, for example, oxides and demethylated derivatives. The metabolites of a compound of the embodiments may be identified using routine techniques known in the art. See, e.g., Bertolini, G. et al., *J. Med. Chem. 40*:2011-2016 (1997); Shan, D. et al., *J. Pharm. Sci. 86*(7):765-767; Bagshawe K., *Drug Dev. Res. 34*:220-230 (1995); Bodor, N., *Advances in Drug Res. 13*:224-331 (1984); Bundgaard, H., *Design of Prodrugs* (Elsevier Press 1985); and Larsen, I. K., *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991). It should be understood that individual chemical compounds that are metabolites of the compounds of Formulas (I), (IIa), (IIb), or (III) or their tautomers, prodrugs, and stereoisomers, as well as the pharmaceutically acceptable salts, esters and prodrugs of any of them, are included within the preferred embodiments.

The compounds of the preferred embodiments may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intrathecal, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The compounds of the preferred embodiments can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present

compositions in liposome form can contain, in addition to a compound of the preferred embodiments, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq.* (1976).

Compressed gases may be used to disperse a compound of preferred embodiments in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc. Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

For delivery via inhalation the compound can be formulated as liquid solution, suspensions, aerosol propellants or dry powder and loaded into a suitable dispenser for administration. There are several types of pharmaceutical inhalation devices-nebulizer inhalers, metered dose inhalers (MDI) and dry powder inhalers (DPI). Nebulizer devices produce a stream of high velocity air that causes the therapeutic agents (which are formulated in a liquid form) to spray as a mist that is carried into the patient's respiratory tract. MDI's typically are formulation packaged with a compressed gas. Upon actuation, the device discharges a measured amount of therapeutic agent by compressed gas, thus affording a reliable method of administering a set amount of agent. DPI dispenses therapeutic agents in the form of a free flowing powder that can be dispersed in the patient's inspiratory air-stream during breathing by the device. In order to achieve a free flowing powder, the therapeutic agent is formulated with an excipient such as lactose. A measured amount of the therapeutic agent is stored in a capsule form and is dispensed with each actuation.

Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from about 10 to about 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Patent No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of about 400 nm) in the presence of a surface modifier and then

dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

Combination Therapies

While the compounds of the preferred embodiments can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment of cancer. The compounds of the preferred embodiments are also useful in combination with known therapeutic agents and anti-cancer agents, and combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the preferred embodiments. Examples of such agents can be found in *Cancer Principles and Practice of Oncology*, V. T. Devita and S. Hellman (editors), 6th edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The compounds of the preferred embodiments are also useful when co-administered with radiation therapy.

Therefore, in one embodiment, the compounds are also used in combination with known anticancer agents including, for example, estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

Estrogen receptor modulators are compounds that can interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethyl-propanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

Androgen receptor modulators are compounds which can interfere with or inhibit the binding of androgens to an androgen receptor. Representative examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate. Retinoid receptor modulators are compounds which interfere or inhibit the binding of retinoids to a retinoid receptor. Examples of retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, LX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N4-carboxyphenyl retinamide.

Cytotoxic and/or cytostatic agents are compounds which can cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors. Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032). A representative example of a hypoxia activatable compound is tirapazamine. Proteasome inhibitors include, but are not limited to, lactacystin and bortezomib. Examples of microtubule inhibitors/microtubule-stabilizing agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-

norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. Representative examples of topoisomerase inhibitors include topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa, 9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroOxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylene-dioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis [(2-amino-ethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1'-de]acridin-6-one, N-[1-[2(diethylamino)-ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna. Examples of inhibitors of mitotic kinesins, such as the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768 and WO 01/98278, WO 03/050,064 (Jun. 19, 2003), WO 03/050,122 (Jun. 19, 2003), WO 03/049,527 (Jun. 19, 2003), WO 03/049,679 (Jun. 19, 2003), WO 03/049,678 (Jun. 19, 2003) and WO 03/39460 (May 15, 2003) and pending PCT Appl. Nos. US03/06403 (filed Mar. 4, 2003), US03/15861 (filed May 19, 2003), US03/15810 (filed May 19, 2003), US03/18482 (filed Jun. 12, 2003) and US03/18694 (filed Jun. 12, 2003). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

Inhibitors of kinases involved in mitotic progression include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (e.g., inhibitors of PLK-1),

inhibitors of bub-1 and inhibitors of bub-1R. Antiproliferative agents include antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,1-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include, for example, Bexxar. HMG-CoA reductase inhibitors are inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art such as those described or cited in U.S. Pat. No. 4,231,938 and WO 84/02131. Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®.; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 Feb. 1996) and U.S. Pat. Nos. 4,782,084 and 4,885,314. In an embodiment, the HMG-CoA reductase inhibitor is selected from lovastatin or simvastatin.

Prenyl-protein transferase inhibitors are compounds which inhibit any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1H)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imnidazolylmethyl-2-piperazinone, (S)-1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl)-2-piperazinone, 5(S)-n-butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl)-4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine, 4-{-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{-5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimnidazol-1-ylmethyl}-benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol-4-yl-methyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl]-3H-imidazol4-yl-methyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-midazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5H,17H-6,10:12,16-dimetheno-1H-imidazo[4,3-c][1,11,4]dioxaazacyclo-nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k]-[1,6,9,12]oxatriaza-cyclooctadecine-9-carbonitrile, 19,20-dihydro-19-oxo-5H,17H-18,21-ethano-6,10:12,16-dimetheno-22H-imidazo[3,4-h][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (.+-.)-19,20-dihydro-3-methyl-19-oxo-5H-18,21-ethano-12,14-etheno-6,10-metheno-22H-benzo[d]imidazo[4,3-k][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile. Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European

Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer 35*(9):1394-1401 (1999).

Angiogenesis inhibitors refers to compounds that can inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-.alpha., interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS 89*:7384 (1992); *JNCI 69*:475 (1982); *Arch. Ophthalmol. 108*:573 (1990); *Anat. Rec.*, (238):68 (1994); *FEBS Letters 372*:83 (1995);*Clin, Orthop. 313*:76 (1995); *J. Mol. Endocrinol. 16*:107 (1996); *Jpn. J. Pharmacol. 75*:105 (1997); *Cancer Res. 57*:1625 (1997); *Cell 93*:705 (1998); *Intl. J. Mol. Med. 2*:715 (1998); *J. Biol. Chem. 274*:9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, 17:963-968 (October 1999); Kim et al., *Nature*, 362:841-844 (1993); WO 00/44777; and WO 00/61186). Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the preferred

embodiments include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med. 38*:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost. 80*:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res. 101*:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed Jan. 18, 2002). The preferred embodiments also encompass combinations of the compounds of the preferred embodiments with NSAIDs which are selective COX-2 inhibitors (generally defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least about 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays). Such compounds include, but are not limited to those disclosed in U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, U.S. Pat. No. 5,710,140, issued Jan. 20, 1998, WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S. Pat. No. 5,633,272, issued May 27, 1997, and U.S. Pat. No. 5,932,598, issued Aug. 3, 1999, all of which are hereby incorporated by reference. Representative inhibitors of COX-2 that are useful in the methods of the preferred embodiments include 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine. Compounds which are described as specific inhibitors of COX-2 and are therefore useful in the preferred embodiments, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published Jul. 21, 1994, U.S. Pat. No. 5,344,991, issued Jun. 6, 1994, U.S. Pat. No. 5,134,142, issued Jul. 28, 1992, U.S. Pat. No. 5,380,738, issued Jan. 10, 1995, U.S. Pat. No. 5,393,790, issued Feb. 20, 1995, U.S. Pat. No. 5,466,823, issued Nov. 14, 1995, U.S.

Pat. No. 5,633,272, issued May 27, 1997, U.S. Pat. No. 5,932,598, issued Aug. 3, 1999, U.S. Pat. No. 5,474,995, issued Dec. 12, 1995, U.S. Pat. No. 5,861,419, issued Jan. 19, 1999, U.S. Pat. No. 6,001,843, issued Dec. 14, 1999, U.S. Pat. No. 6,020,343, issued Feb. 1, 2000, U.S. Pat. No. 5,409,944, issued Apr. 25, 1995, U.S. Pat. No. 5,436,265, issued Jul. 25, 1995, U.S. Pat. No. 5,536,752, issued Jul. 16, 1996, U.S. Pat. No. 5,550,142, issued Aug. 27, 1996, U.S. Pat. No. 5,604,260, issued Feb. 18, 1997, U.S. Pat. No. 5,698,584, issued Dec. 16, 1997, and U.S. Pat. No. 5,710,140, issued Jan. 20,1998. Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

Agents that interfere with cell cycle checkpoints are compounds that can inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

Inhibitors of cell proliferation and survival signaling pathway can be pharmaceutical agents that can inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779). Such agents include small molecule inhibitor compounds and antibody antagonists.

Apoptosis inducing agents include activators of TNF receptor family members (including the TRAIL receptors).

In certain presently preferred embodiments, representative agents useful in combination with the compounds of the preferred embodiments for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, as well as other cancer chemotherapeutic agents.

The above compounds to be employed in combination with the compounds of the preferred embodiments can be used in therapeutic amounts as indicated in the *Physicians' Desk Reference* (PDR) 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

The compounds of the preferred embodiments and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the preferred embodiments may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

General Synthetic Methods

The compounds of preferred embodiments can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in

the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

Furthermore, the compounds of preferred embodiments contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the embodiments, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's *Reagents for Organic Synthesis*, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's *Chemistry of Carbon Compounds*, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), *Organic Reactions*, Volumes 1-40 (John Wiley and Sons, 1991), March's *Advanced Organic Chemistry*, (John Wiley and Sons, 4th Edition), and Larock's *Comprehensive Organic Transformations* (VCH Publishers Inc., 1989).

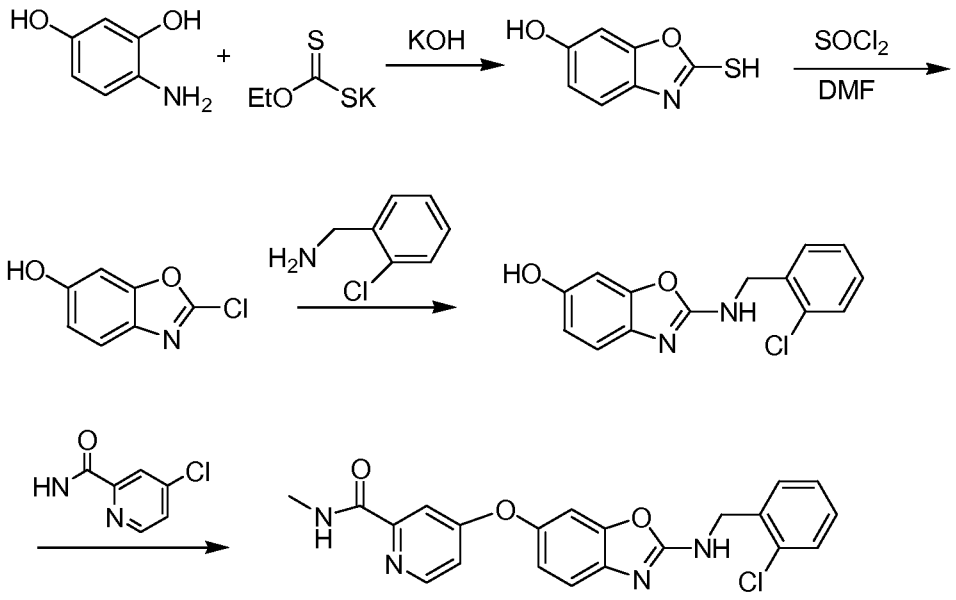
The various starting materials, intermediates, and compounds of the preferred embodiments may be isolated and purified where appropriate using conventional techniques such as precipitation, filtration, crystallization, evaporation, distillation, and chromatography. Characterization of these compounds may be performed using conventional methods such as by melting point, mass spectrum, nuclear magnetic resonance, and various other spectroscopic analyses.

Compounds of the embodiments may generally be prepared using a number of methods familiar to one of skill in the art, such as, for example, the methods disclosed in

U.S. patent application Publication Nos. US20040087626 A1 and US20040122237 A1, the disclosures of which are incorporated herein in their entirety, in connection with the following description and examples. The compounds of the embodiments may be generally made in accordance with the following reaction Schemes 1-8, which are described in detail in the Examples, below.

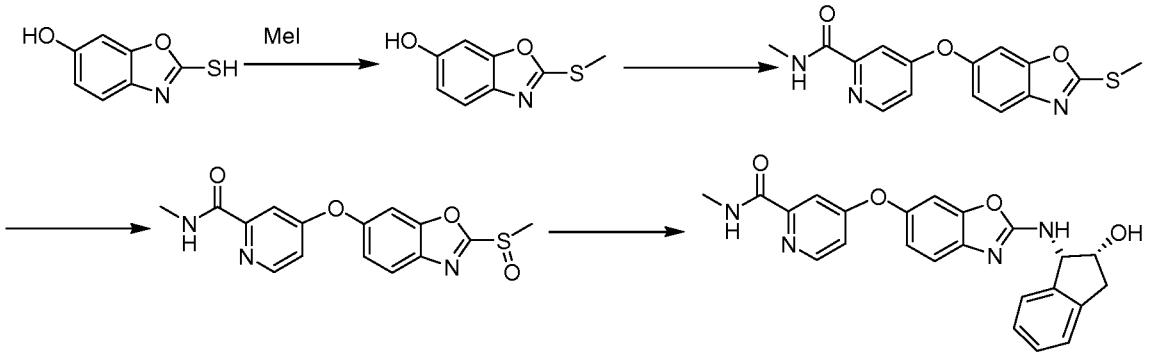
Schemes 1-8 illustrate general methods for the preparation of intermediates and compounds of the embodiments. These compounds are prepared from starting materials either known in the art or are commercially available. The specific compounds are for illustrative purposes only.

Scheme 1



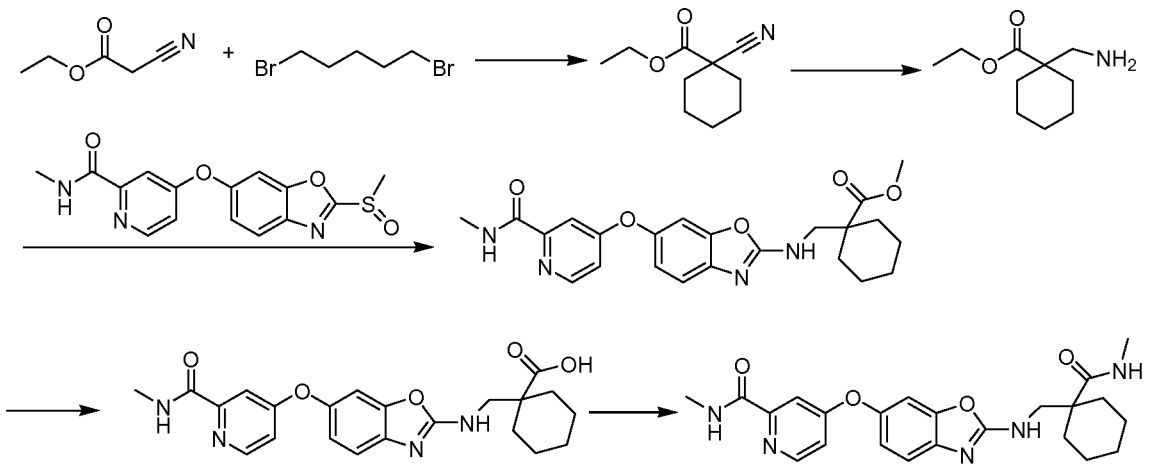
In Scheme 1, 2-hydroxyaniline or a derivative thereof reacts with ethylxanthic acid to give a thiol-benzoxazole. The thiol-benzoxazole is converted to a chloro-benzoxazole with reaction with thionyl chloride. Alternatively, the thiol benzoxazole can be converted to halogenated benzoxazole with a array of halogenating agents, such as, but not limited to phosphorus trichloride, phosphorus tribromide, phosgene, or oxalyl chloride. The chloro-benzoxazole is then reacted with a benzylamine such as 2-chlorobenzylamine to give a benzylamino-benzoxazole. The benzylamino-benzoxazole is coupled with chloro-pyridine in the presence of a base such as, cesium carbonate to give a compound of the invention. Alternatively, a halogenated pyridine can be used for the coupling.

Scheme 2



In Scheme 2, a thiol-benzoxazole or derivative thereof is alkylated at the thiol moiety. The alkylated thiol-benzoxazole is coupled with the corresponding halo pyridine such as chloro-pyridine in the presence of a base such as cesium carbonate to give a compound of the invention. The resulting benzoxazolyloxy-pyridine is oxidized, for instance, with mCPBA. Other oxidizing agents can be used to oxidize the thiol to a sulfoxide. Other oxidizing agents include, but are not limited to, hydrogen peroxide, sodium periodate, pyridinium chlorochromate or chromium trioxide. The sulfoxide of the benzoxazolyloxy-pyridine is subjected to nucleophilic attack with an amine to give a compound of the invention.

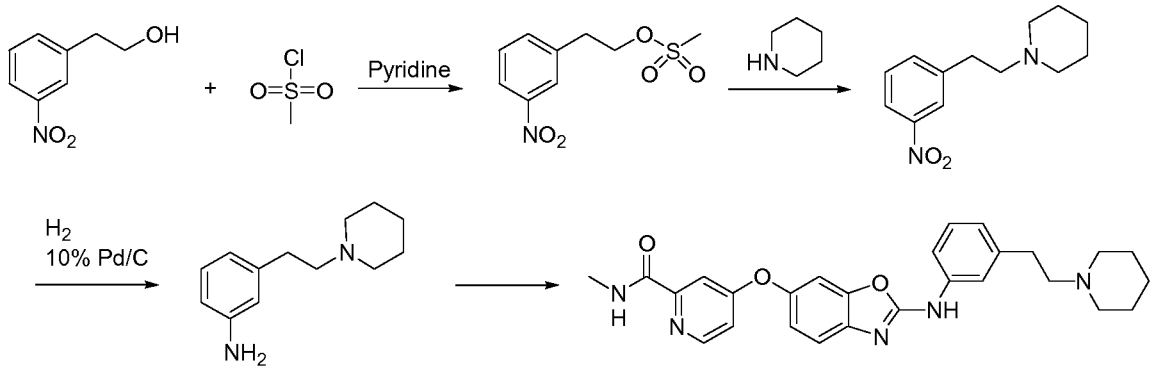
Scheme 3



In Scheme 3, cyanoacetate and 1,5-dibromopentane are coupled to form 1-cyano-cyclohexanecarboxylic acid ethyl ester after cyclization. This product is reduced with

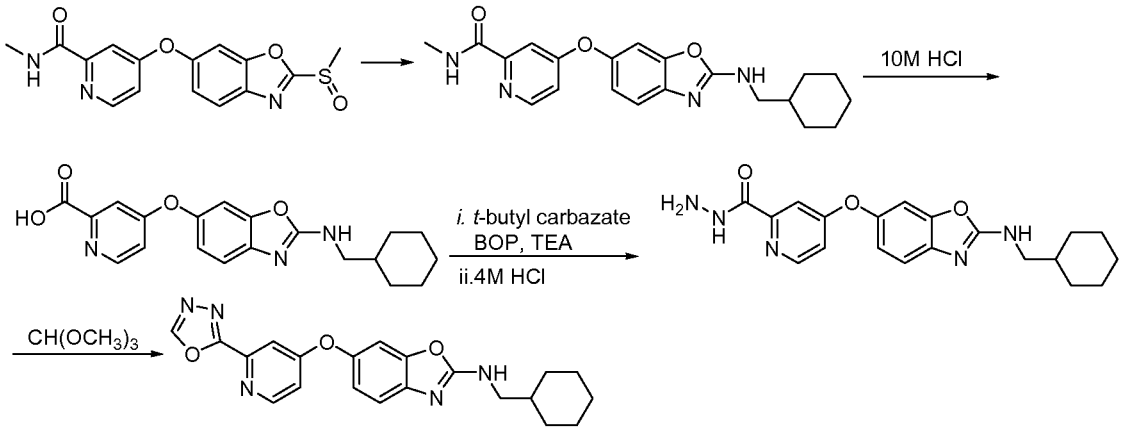
hydrogen and Raney nickel. Other reducing agents can be used to reduce the nitrile group to an amine. Other reducing agents include, but are not limited to, catalytic hydrogenation using platinum oxide or Raney nickel or lithium aluminum hydride, diisobutyl aluminum hydride, sodium borohydride, or lithium triethylborohydride. The reduced product is coupled with sulfoxo-benzoxazolyloxy-pyridine. The resulting product from the coupling reaction can be further functionalized or derivatized. For example, in Scheme 3, an ester group can be converted to a carboxylic acid group from hydrolysis and then converted to an amide from reaction with an amine. These reactions are well-known conversions to one skilled in the art.

Scheme 4



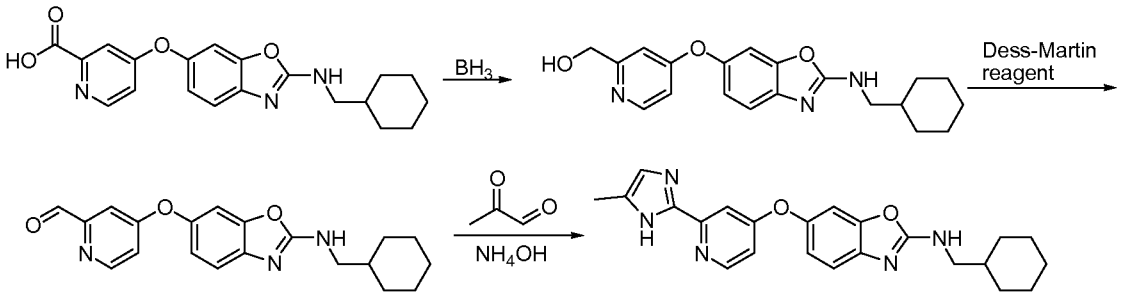
In Scheme 4, 3-(2-piperidin-1-yl-ethyl)-phenylamine is an example of an amine that can be used to form a compound of the embodiments. 3-(2-Piperidin-1-yl-ethyl)-phenylamine is formed from sulfonation of 2-(3-nitrophenyl)-ethanol, then aminating the resulting methanesulfonic acid 2-(3-nitrophenyl)-ethyl ester, and subsequently reducing the resulting 1-[2-(3-nitrophenyl)-ethyl]-piperidine.

Scheme 5



In Scheme 5, 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide is aminated with cyclohexylmethanamine. The resulting 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide is then hydrolyzed to form 4-[2-(cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid. 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid then reacts with benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate, *tert*-butyl carbazate, and triethyl amine to form 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide. 4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide then reacts with trimethyl orthoformate to form a compound of the embodiments.

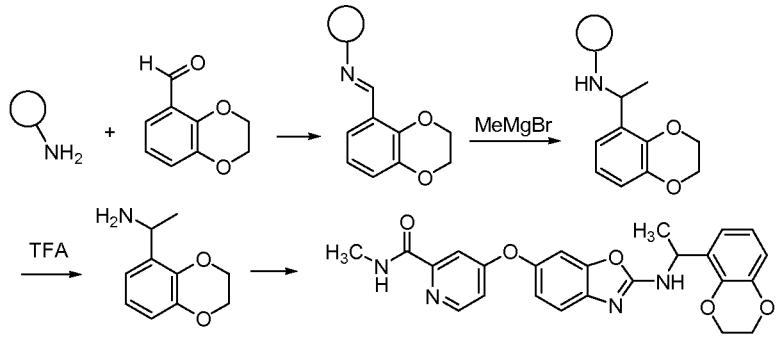
Scheme 6



In Scheme 6, a compound of the embodiment can be further functionalized. For instance, 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carboxylic acid

is reduced to {4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-yl}-methanol with borane. Other suitable reducing agents include, but are not limited to, lithium aluminum hydride, aluminum hydride, diisobultyl aluminum hydride, sodium borohydride, or lithium triethylborohydride. {4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-yl}-methanol is then oxidized to 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde with Dess-Martin reagent. Other suitable oxidizing agents include, but are not limited to, pyridinium chlorochromate, SO_3·pyridine in DMSO, or conditions commonly refered to as a Swern or Moffet oxidation. 4-(2-(Cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde is then converted to cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine by reaction with pyruvic aldehyde.

Scheme 7

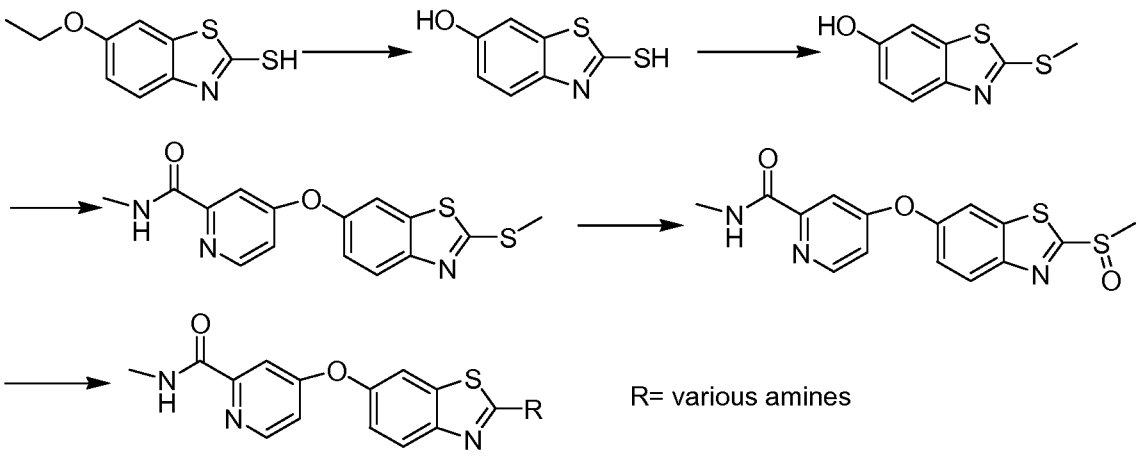


In Scheme 7, a compound of the embodiments is synthesized from reaction of 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (from Example 2) with 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine. In one instance, 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine is synthesized via a resin.

An amine linked to a resin is reacted with 2,3-dihydro-benzo[1,4]dioxine-5-carbaldehyde, thus giving C-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine. C-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine is derivatized with alkylation at the imino site, such as with methyl magnesium bromide. Other alkylating agents can be used according to the desired molecule. The resulting 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine is cleaved from the resin. An example of a resin-cleaving agent is trifluoroacetic acid (TFA). The resulting 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine

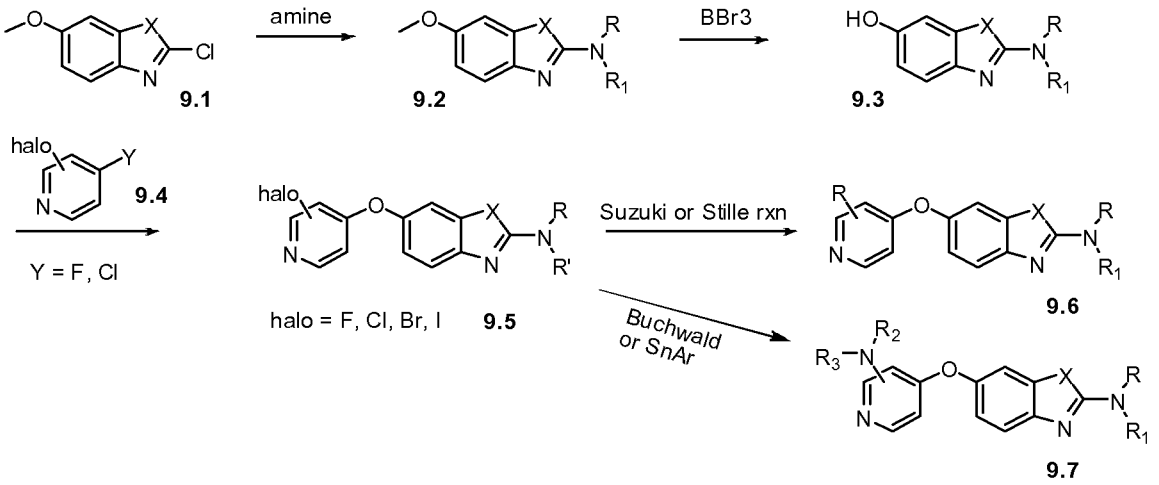
can be used for synthesis of a compound of the embodiments. For instance, 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine can be used to react with 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide to form 4-{2-[1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide.

Scheme 8



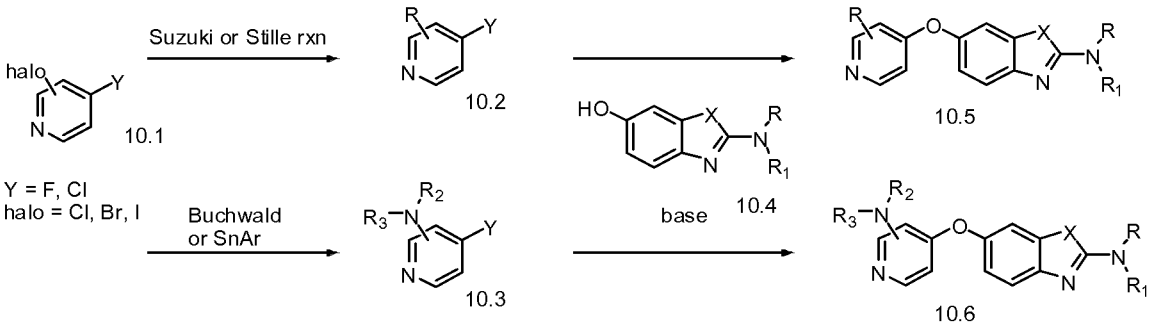
In Scheme 8, 2-mercapto-benzothiazol-6-ol was prepared as per United States Patent No. 4,873,346. 2-Mercapto-benzothiazol-6-ol is then converted to 2-methylsulfanyl-benzothiazol-6-ol *via* conventional procedures to remove an ethereal protecting group. Reaction of 2-methylsulfanyl-benzothiazol-6-ol with methyl iodide provides alkylation at the thiol position. Reaction of 2-methylsulfanyl-benzothiazol-6-ol with 4-chloro-pyridine-2-carboxylic acid methylamide gives 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide. Subsequent oxidation of 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide gives 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide. 4-(2-Methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide can be a substrate for reaction with various amines. For instance, 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide can react with cyclohexylmethylamine to give 4-[2-(cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide.

Scheme 9



In Scheme 9 benzoxazoles or benzothiazoles of formula 9.1 can be reacted with a substituted amine to provide intermediates of the formula 9.2. Treatement of intermediates of formula 9.2 with a reagent such as, for example, BBr_3 provides phenols of the formula 9.3. Subsequent treatment of intermediates of formula 9.3 with 4-halo pyridines of formula 9.4 at temperatures generally ranging from, but not limited to, room temperature to 130°C provides in the presence of a base such as, for example, potassium or cesium carbonate provides compounds for formula 9.5. Further treatment with boronic acids or stannanes under conditions known to those practiced in the art as Suzuki or Stille reactions provides compounds of formula 9.6. In addition, treatment of a compound of formula 9.5 with a substituted amine under conditions known to those practiced in the art for a Buchwald reaction or SnAr reaction provides compounds of formula 9.7.

Scheme 10



In Scheme 10 benzoxazoles or benzothiazoles of formula 10.5 and 10.6 can be prepared starting with a 4-halopyridine for formula 10.1 which can be (1) treated with boronic acids or stannanes under conditions known to those practiced in the art as Suzuki or Stille reactions provides intermediates of formula 10.2 or (2) reacted with a substituted amine under conditions known to those practiced in the art for a Buchwald reaction or SnAr

reaction to provide intermediates of formula 10.3. Subsequent reaction of intermediates of formula 10.2 or 10.3 with a phenolic intermediate of formula 10.4 in the presence of a base such as, for example, potassium or cesium carbonate in a solvent such as, for example, dimethyl formamide, acetonitrile or dioxane provides compounds of formula 10.5 and 10.6.

EXAMPLES

Referring to the examples that follow, compounds of the preferred embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 μ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% (or 35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature 40°C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; gradient: 5-95% acetonitrile in water with 0.05% TFA over a 4 min period ; flow rate 0.8 mL/min; molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

GCMS analysis is performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 μL; initial column temperature: 50°C; final column temperature: 250°C; ramp time: 20 minutes; gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 300 MHz NMR (Palo Alto, CA). The spectral reference was either TMS or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (e.g., 75°C) to promote increased sample solubility.

The purity of some of the compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ).

Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

Preparative separations are carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography are dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

It should be understood that the organic compounds according to the preferred embodiments may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the preferred embodiments encompasses any tautomeric form of the drawn structure.

It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

The examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

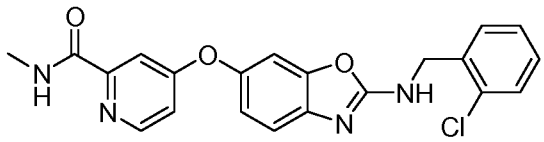
Abbreviations

ACN	Acetonitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
DCM	Dichloromethane
DIEA	diisopropylethylamine
DIPEA	N,N-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EtOAc	ethyl acetate
EtOH	ethanol
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
MCPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidone
RT	room temperature
THF	tetrahydrofuran

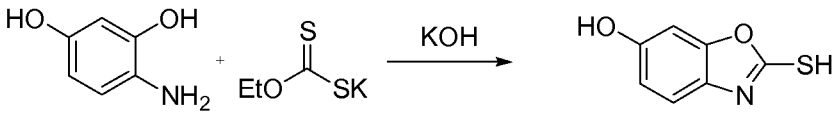
COMPOUNDS OF FORMULA I

Example 1

Synthesis of 4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide (Table 2, Compound 8)

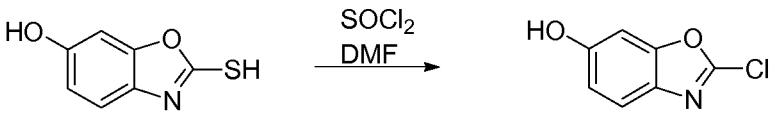


Step 1. Synthesis of 2-Mercapto-benzooxazol-6-ol



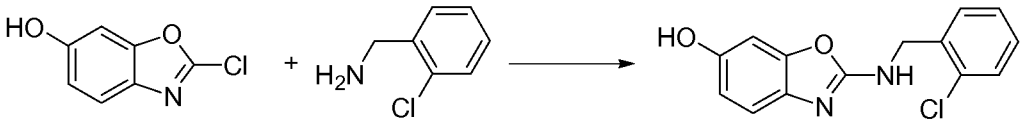
To a solution of 4-aminoresorcinol (1 eq) and ethylxanthic acid (3 eq) in ethanol was added potassium hydroxide (2.1 eq). The mixture was refluxed for two hours then diluted with water and acidified using 1N HCl to a pH of 4. The product was extracted into ethyl acetate then concentrated. The resulting solid was triturated with dichloromethane to give pure product with a 90% yield. MH+ = 168.1.

Step 2. Synthesis of 2-Chloro-benzooxazol-6-ol



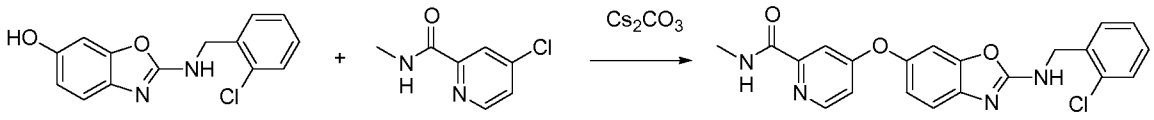
2-Mercapto-benzoxazol-6-ol (1 eq) was dissolved in thionyl chloride (10 eq). DMF (0.6 eq) was slowly added to this solution at room temperature. The mixture was heated to 80°C and refluxed for 15 minutes. The reaction mixture was cooled to room temperature and the solvent was removed. The resulting solid was azeotroped three times with xylenes. The solid was dissolved in a 10% solution of THF in ethyl acetate and washed once with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried with anhydrous sodium sulfate, filtered, and the solvent removed. The solid was triturated with acetonitrile to yield pure product with a 68% yield. MH + = 170.0.

Step 3. Synthesis of 2-(2-Chloro-benzylamino)-benzooxazol-6-ol



2-Chloro-benzooxazol-6-ol (1 eq) and 2-chloro-benzylamine (2 eq) was dissolved in NMP. Using a Personal Chemistry microwave system, the mixture was reacted at 180°C for six minutes. The crude reaction mixture was diluted with ethyl acetate and washed once with brine and once with 1N HCl, or washed twice with brine, depending on the amine used. The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. This material was purified by silica gel column using hexane and ethyl acetate. MH+ = 275.1.

Step 4. Synthesis of 4-[2-(2-Chloro-benzylamino)-benzoxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

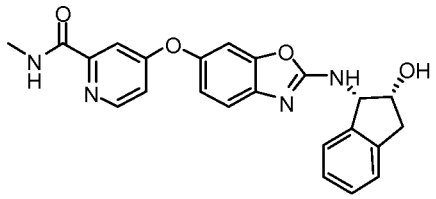


To a solution of 2-(2-chloro-benzylamino)-benzooxazol-6-ol (1 eq) in DMSO was added the 4-chloro-pyridine-2-carboxylic acid methylamide (1 eq). This was allowed to stir for 15 minutes at room temperature at which point cesium carbonate (1.2 eq) was added. The solution was heated in a Personal Chemistry microwave reactor at 150°C for a total of 30 minutes. The crude reaction mixture was diluted with ethyl acetate, washed three times with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was then purified by reverse phase preparatory HPLC to give the pure product **8**. MH+ = 409.1.

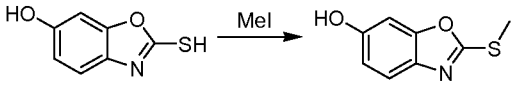
Compounds **9**, **11**, **12**, **18**, **19**, **20**, **26**, **27**, **28,** and **40** in Table 2, below, were synthesized following similar procedures in Example 1.

Example 2

4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzoxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide (Table 2, Compound 50)



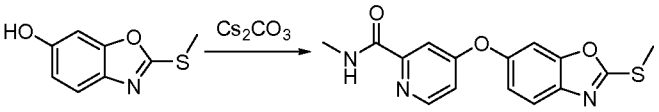
Step 1. Synthesis of 2-(methylthio)benzo[d]oxazol-6-ol



To a solution of the 2-mercaptobenzo[d]oxazol-6-ol (1.55 g, 9.28 mmol, 1.0 eq) in 20 mL of methylene chloride was added triethylamine (1.87 g, 18.56 mmol, 2.0 eq) and methyl iodide (1.77 g, 13.92 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred at rt for 3 hours. The mixture was diluted with 100 mL of methylene chloride. The resulting mixture was washed with water (10 mL), brine (10mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified

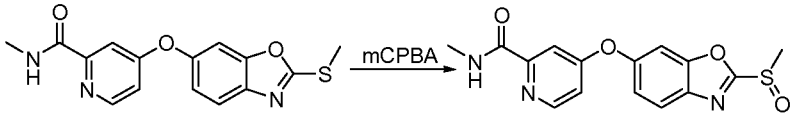
by silica gel column eluted with ethyl acetate and hexane to give the titled compound. MH+ = 182.

Step 2. Synthesis of 4-(2-(methylthio)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide



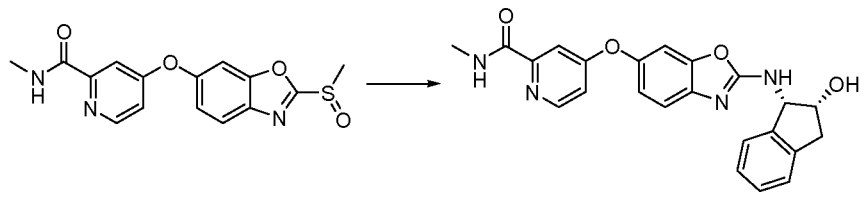
To a solution of 2-(methylthio)benzo[d]oxazol-6-ol (8.5 g, 46.7 mmol, 1 eq) in 80 mL of *N*,*N*-dimethylformamide was added 4-chloro-*N*-methylpyridine-2-carboxamide (16.0 g, 93.4 mmol, 2.0 eq) and cesium carbonate (45.7 g, 140.1 mmol, 3.0 eq). The reaction mixture was stirred at 75°C for 6 hours. After the mixture was cooled to room temperature, the mixture was added 120 mL of water. After filtration, the solid was purified by silica gel column eluted with ethyl acetate and hexane to give the titled compound. MH+ = 316.

Step 3. Synthesis of 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide



To a solution of the 4-(2-(methylthio)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide (1.26 g, 4.0 mmol, 1.0 eq) in 40 mL of methylene chloride was added 3-chloroperoxybenzoic acid (70%, 989 mg, 4.4 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 5 hours and then was diluted with 200 mL of methylene chloride. The resulting mixture was washed with aqueous sodium bicarbonate and brine then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was used to next step without further purification. MH+ = 332.

Step 4. 4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

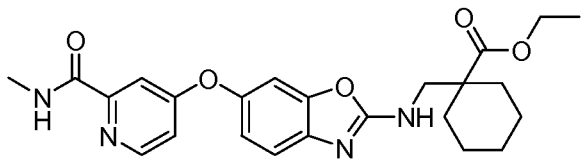


A solution of 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide (17 mg, 0.05 mmol, 1.0 eq) and (1*S*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-ol (30 mg, 0.2 mml, 4.0 eq) in 1 mL of *N*,*N*-dimethylacetamide was heated in the microwave at 90°C for 600 seconds. The crude product was purified by reverse phase prep HPLC to give the title compound. MH= = 417.0.

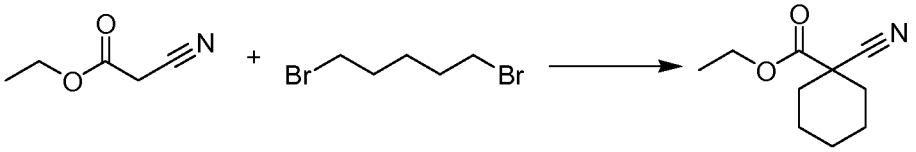
Compounds **45**, **46**, and **47**, in Table 2, below, were synthesized following the similar procedures as in Example 2 varying the temperature to 140°C. Compounds **42, 57, 59, and 94** in Table 2, below, were synthesized following the similar procedures as in Example 2 varying the temperature to 120°C.

Example 3

Synthesis of 1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino] methyl}-cyclohexanecarboxylic acid ethyl ester (Table 2, Compound 75)



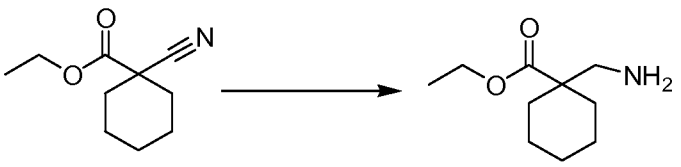
Step 1. Synthesis of 1-Cyano-cyclohexanecarboxylic acid ethyl ester



To a solution of cyanoacetate (1 eq) in DMF at 0°C was slowly added cesium carbonate (2.5 eq), followed by the slow addition of 1,5-dibromopentane. This mixture was allowed to stir for 30 minutes at 0°C and at room temperature for two hours. The crude reaction mixture was diluted with ethyl acetate and washed three times with water, dried

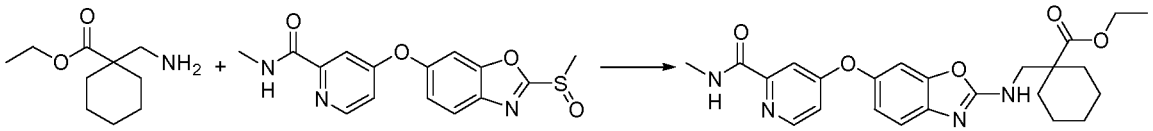
with anhydrous sodium sulfate, filtered, and concentrated. The compound was clean enough to continue without purification. 57% yield. ^{1}H NMR (300MHz, $CDCl_3$) δ 4.25 (q, 2H), 2.12-1.68 (m, 10H), 1.31 (t, 3H).

Step 2. Synthesis of 1-Aminomethyl-cyclohexanecarboxylic acid ethyl ester



Excess Raney Nickel in an ethanol slurry was added to a solution of 1-cyano-cyclohexanecarboxylic acid ethyl ester in ethanol under a nitrogen atmosphere. The nitrogen atmosphere was replaced with excess hydrogen gas and the mixture was allowed to stir overnight. The reaction mixture was filtered through celite and the solvent was removed. The compound was clean enough to continue without purification. 80% yield. MH+ = 186.2.

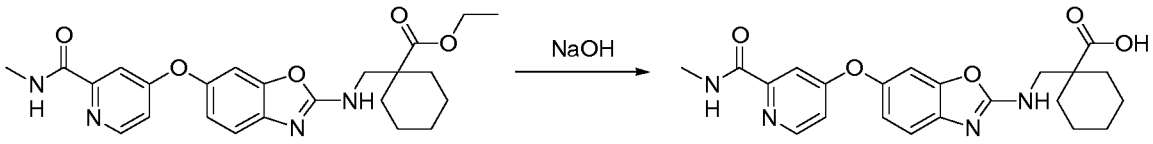
Step 3. Synthesis of 1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino] methyl}-cyclohexanecarboxylic acid ethyl ester



To a solution of 1-aminomethyl-cyclohexanecarboxylic acid ethyl ester in THF was added 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide from Step 3 of Example 2. After reacting at room temperature for 2 hours the solvent was removed and the crude product was diluted with ethyl acetate and some dichloromethane, then washed three times with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The final product was purified by reverse phase preparatory HPLC. MH+ = 453.1.

Example 4

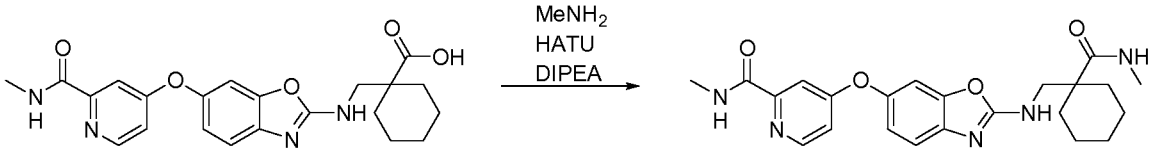
Synthesis of 1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid (Table 2, Compound 93)



1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino] methyl}-cyclohexanecarboxylic acid ethyl ester (1 eq) was dissolved in 3 M sodium hydroxide (20 eq); THF and methanol were added to homogenize the solution. The mixture was allowed to react at room temperature overnight. The solvents were removed. The crude product was brought to a pH of 4 with 1 N HCl, then to pH of 7 with saturated aqueous sodium bicarbonate. This solution was saturated with solid sodium chloride then extracted three times with ethyl acetate. The combined organic extracts were washed once with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The product was purified by silica gel column in isopropanol and dichloromethane (50%) MH+ = 425.1.

Example 5

Synthesis Of 4-{2-[(1-Methylcarbamoyl-cyclohexylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide (Table 2, Compound 112)

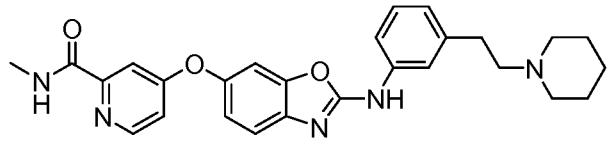


To a solution of 1-{[6-(2-methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid (1 eq) in DMF was added DIPEA (3 eq) and [dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl- ammonium hexafluoro phosphate (1 eq). This was stirred at room temperature for 2 hours, then a 2 M solution of methylamine in THF (5 eq) was added and allowed to react overnight at 70°C. The mixture was diluted with ethyl acetate and washed twice with a saturated aqueous solution of ammonium chloride and once with brine, then dried with anhydrous sodium

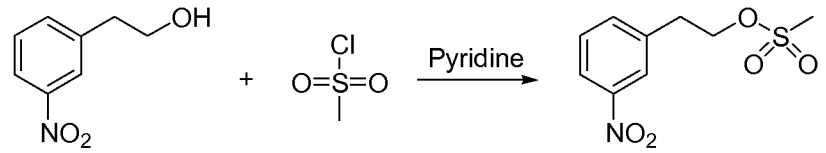
sulfate, filtered and concentrated, then purified by preparatory reverse phase HPLC. MH+ = 438.1.

Example 6

Synthesis of 4-{2-[3-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide (Table 2, Compound 44)

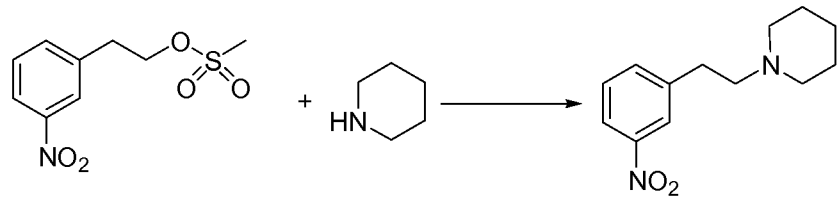


Step 1. Synthesis of Methanesulfonic acid 2-(3-nitro-phenyl)-ethyl ester



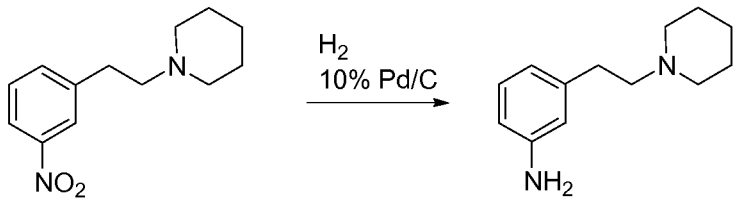
To a solution of 2-(3-nitro-phenyl)-ethanol (1 eq) in dichloromethane at 0°C was added pyridine (4 eq) and methanesulfonyl chloride (2 eq). After stirring at 0°C for one hour, then room temperature overnight, the mixture was diluted with dichloromethane and washed once with water, once with 1 N HCl, dried with anhydrous sodium sulfate, filtered and concentrated. The product was clean enough to be taken on to the next step without purification. MH+ = 246.0.

Step 2. Synthesis of 1-[2-(3-Nitro-phenyl)-ethyl]-piperidine



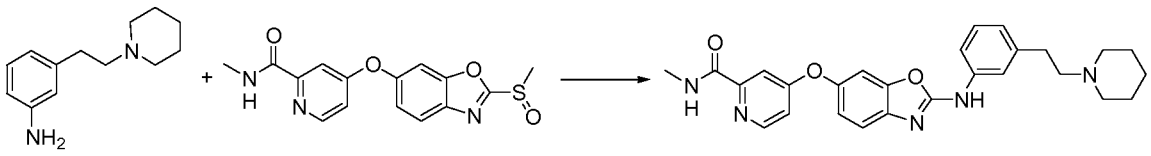
Methanesulfonic acid 2-(3-nitro-phenyl)-ethyl ester was dissolved in piperidine (20 eq) and THF and stirred at 60°C for one hour. The solvent was removed. The crude product was diluted with ethyl acetate, washed three times with water, dried with anhydrous sodium sulfate, filtered and concentrated. The product was clean enough to carry forward without purification. 44% yield. MH+ = 235.1.

Step 3. Synthesis of 3-(2-Piperidin-1-yl-ethyl)-phenylamine



To a solution of 1-[2-(3-Nitro-phenyl)-ethyl]-piperidine in ethanol was added a catalytic amount 10% activated palladium on carbon and excess hydrogen gas. This mixture was allowed to stir overnight, then filtered and concentrated. The product was clean enough for the next reaction. 60% yield. MH+ = 205.1.

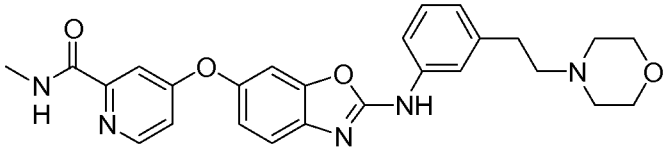
Step 4. Synthesis of 4-{2-[3-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide



The 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide from step 3 of Example 2 and 3-(2-piperidin-1-yl-ethyl)-phenylamine were dissolved in DMAC and heated in a CEM microwave reactor at 120°C for 10 to 20 minutes. The crude reaction mixture was purified by preparatory reverse phase HPLC. MH+ = 472.2.

Example 7

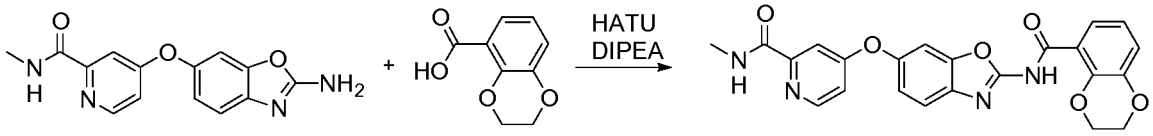
4-{2-[3-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide (Table 2, Compound 74)



The compound Table 2, Entry **74** was synthesized following the similar procedure as in Example 6. MH+ = 474.2.

Example 8

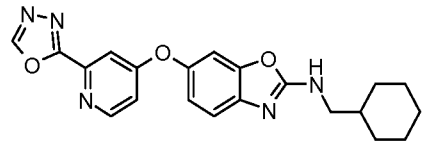
Synthesis of 4-{2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide (Table 2, Compound 110)



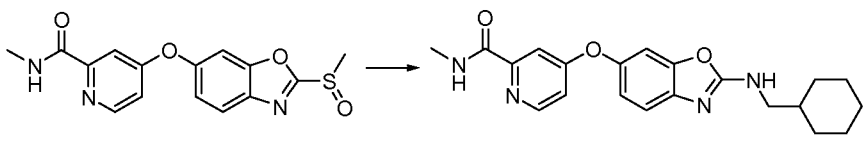
4-(2-Amino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (1 eq) and 2,3-dihydro-1,4-benzodioxane-5-carboxylic acid (1 eq) were dissolved in DMF. To this solution were added DIPEA (3 eq) and [dimethylamino-([1,2,3]triazolo[4,5-b]pyridin-3-yloxy)-methylene]-dimethyl-ammonium hexafluoro phosphate (1 eq). The mixture was stirred at 40°C overnight, then diluted with ethyl acetate and washed once each with 1N HCl, saturated aqueous sodium bicarbonate, and brine, and finally dried with anhydrous sodium sulfate, filtered, and concentrated. This was purified by preparatory reverse phase HPLC. MH+ = 447.0.

Example 9

Synthesis of Cyclohexylmethyl-[6-(2-[1,3,4]oxadiazol-2-yl-pyridin-4-yloxy)-benzooxazol-2-yl]-amine (Table 2, Compound 81)

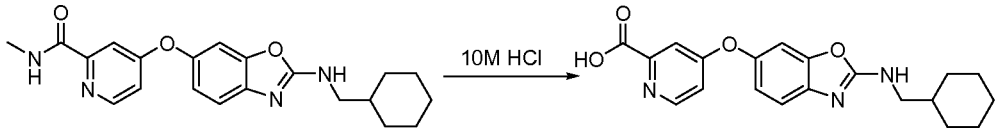


Step 1. Synthesis of 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)-N-methylpyridine-2-carboxamide



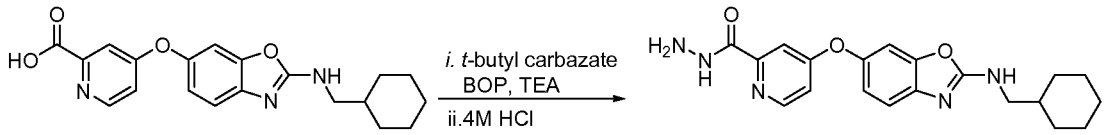
To a solution of 4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide (1.40 g, 4.23 mmol, 1.0 eq) in 15 mL of THF was added cyclohexylmethanamine (955 mg, 8.46 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at that temperature for 2 hours. After the solvent was removed under reduced pressure, the residue was dissolved in 150 mL of ethyl acetate. The resulting mixture was washed with water (20 mL), brine (20mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified by silica gel column eluted with ethyl acetate and hexane to give the titled compound. $MH^+ = 381$.

Step 2. Synthesis of 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid



A solution of 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)-*N*-methylpyridine-2-carboxamide (300 mg, 0.79 mmol, 1.0 eq) in 10 mL of 10M aqueous hydrochloric acid solution was stirred at 100°C for 24 hours. The reaction mixture was cooled to room temperature. Most of water was removed under reduced pressure. And then aqueous sodium bicarbonate was added to the mixture until pH > 7.0. After filtration, the solid was washed with water and dried to give the titled compound. MH+ = 368.0.

Step 3. Synthesis of 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide

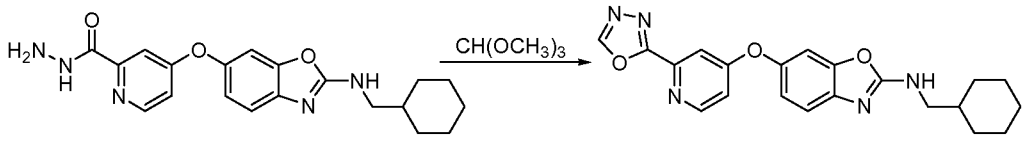


To a solution of the 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid (110 mg, 0.30 mmol, 1.0 eq) in 2 mL of *N*,*N*-dimethylformamide was added benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (199 mg, 0.45 mmol, 1.5 eq), *tert*-butyl carbazate (47 mg, 0.36 mmol, 1.2 eq) and triethyl amine (60mg, 0.60 mmol, 2.0 eq) at room temperature. The reaction mixture was stirred at that temperature for 2 hours. Then the mixture was added 20 mL of water. After filtration,

the solid was purified again by silica gel column eluted with ethyl acetate and hexane to give the Boc protected titled compound.

The Boc protected titled compound (54 mg, 0.112 mmol, 1.0 eq) was dissolved in 1 mL of methanol. And then the mixture was added 3 mL of 4M hydrogen chloride in dioxane. The reaction mixture was stirred at room temperature overnight. The solvents were removed to give the titled compound, which was used to next step without further purification. MH+ = 382.0.

Step 4. Synthesis of cyclohexylmethyl-[6-(2-[1,3,4]oxadiazol-2-yl-pyridin-4-yloxy)-benzooxazol-2-yl]-amine

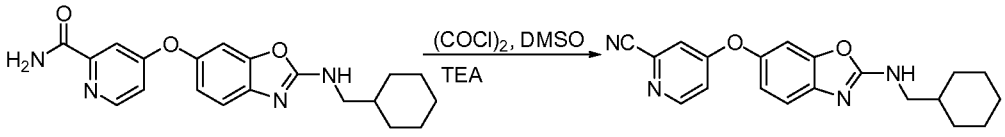


A solution of 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbohydrazide (8 mg, 0.019 mmol, 1.0 eq) and 0.1 mL of 4 M hydrogen chloride in 1 mL trimethyl orthoformate was heated in the microwave at 120°C for 1200 seconds. The crude product was purified by reverse phase prep HPLC to give the title compound. MH^+ = 392.0

Compound **81** was also isolated from the reaction. MH+ = 367.0.

Example 10

Synthesis of 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonitrile (Table 2, Compound 82)

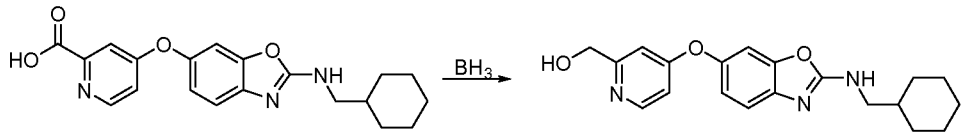


To a solution of the methylsulfoxide (32 mg, 0.41 mmol, 6.0 eq) in 1 mL of methylene chloride was added oxalyl chloride (2M, 0.135 mL, 0.27 mmol, 4.0 eq) at -78°C. After 15 minutes, the 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carboxamide (25 mg, 0.068 mmol, 1.0 eq) in 2 mL of methylene chloride was added to the reaction mixture. After being stirred at that temperature for 20 minutes, triethyl amine (83

mg, 0.83 mmol, 12 eq) was added to mixture. The reaction mixture was stirred at –78°C for 2 hours, and then was quenched with aqueous ammonium chloride solution. The resulting mixture was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified by reverse phase prep HPLC to give the title compound. MH+ = 349.0.

Example 11

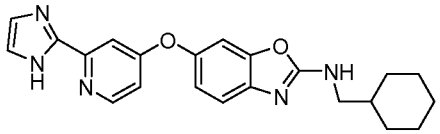
Synthesis of {4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-methanol (Table 2, Compound 80)



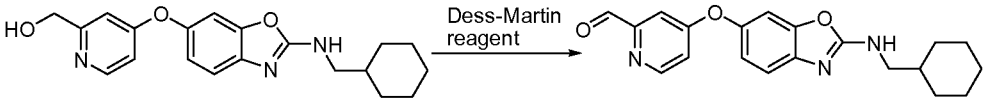
To a solution of the 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carboxylic acid (120 mg, 0.33 mmol, 1.0eq) in 5 mL of THF was added borane-tetrahydrofuran complex (1M, 1mL, 1mmol) at 0°C. The reaction mixture was stirred at that temperature for 5 hours. The reaction was quenched with 1M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (2 × 60 mL). The combined organic layers were washed with water (10 mL), brine (10mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified by silica gel column eluted with ethyl acetate and hexane to give the titled compound. MH+ = 354.0.

Example 12

Synthesis of Cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine (Table 2, Compound 109)

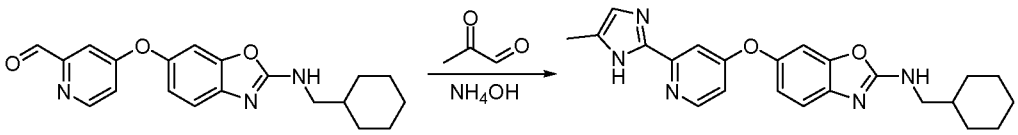


Step 1. Synthesis of 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde



To a solution of the 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridin-2-yl)methanol (20 mg, 0.057 mmol, 1.0eq) in 2 mL of methylene chloride and 2 mL of THF was added Dess-Martin reagent (26 mg, 0.062 mmol, 1.1eq) at room temperature. The reaction mixture was stirred at that temperature for 4 hours. Then the mixture was diluted with 50 mL of ethyl acetate. The resulting mixture was washed with aq sodium bicarbonate (5 mL), water (5 mL), brine (5 mL), then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was purified by preparative TLC sheet to give the titled compound. MH+ = 352.0.

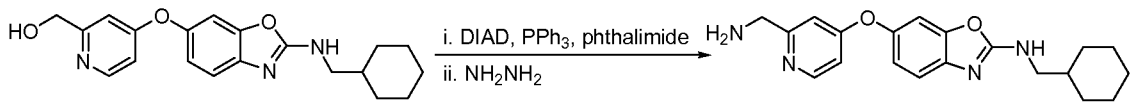
Step 2. Synthesis of Cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine



To a solution of the 4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridine-2-carbaldehyde (5 mg, 0.014 mmol, 1.0eq) in 0.6 mL of methanol was added pyruvic aldehyde (40%, 0.1 mL) and 0.15 mL ammonium hydroxide at room temperature. The reaction mixture was stirred at that temperature for 2 hours. The crude product was purified by reverse phase prep HPLC to give the title compound. MH+ = 404.0.

Example 13

Synthesis of [6-(2-Aminomethyl-pyridin-4-yloxy)-benzooxazol-2-yl]-cyclohexylmethyl-amine (Table 2, Compound 111)

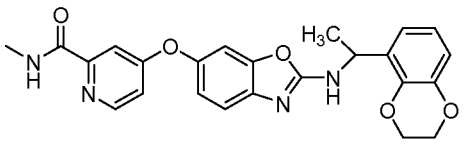


To a solution of the (4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridin-2-yl)methanol (20 mg, 0.057 mmol, 1.0eq) in 2 mL of THF was added triphenyl phosphine (22 mg, 0.085 mmol, 1.5eq), phthalimide (12.5 mg, 0.085 mmol, 1.5 eq) and diisopropyl azodicarboxylate (17 mg, 0.085 mmol, 1.5 eq) at room temperature. The reaction mixture was stirred at that temperature for 16 hours. Then the solvent was removed. The crude product was purified by preparative TLC sheet to give 2-((4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridin-2-yl)methyl)isoindoline-1,3-dione.

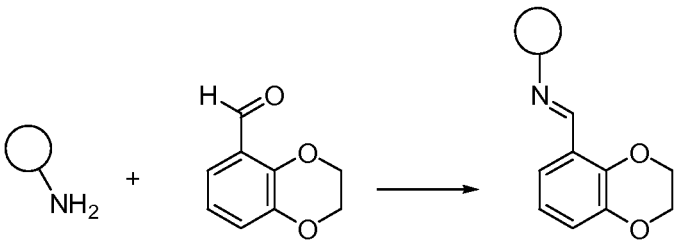
The 2-((4-(2-(cyclohexylmethylamino)benzo[d]oxazol-6-yloxy)pyridin-2-yl)methyl)isoindoline-1,3-dione (6.2 mg, 0.013 mmol, 1 eq) was dissolved in 0.5 mL of ethanol. And then hydrazine monohydrate (6.4 mg, 0.13 mmol, 10 eq) was added to the reaction mixture. The mixture was stirred at room temperature for 3 hours. And then the solvents were removed. The crude product was purified by reverse phase prep HPLC to give the title compound. MH+ = 353.0.

Example 14

Synthesis of 4-{2-[1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide (Table 2, Compound 125)

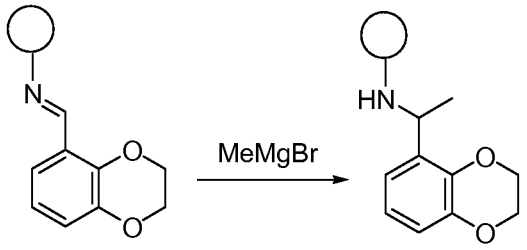


Step 1. Synthesis of C-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine



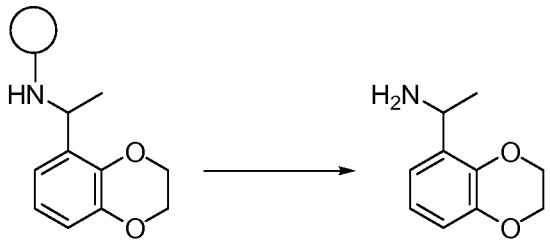
To a suspension of amine bound on a rink resin (1 eq) in trimethylorthoformate was added 2,3-dihydro-benzo[1,4]dioxine-5-carbaldehyde (2 eq). This mixture was shaken overnight, filtered and the solid dried.

Step 2. Synthesis of 1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamine



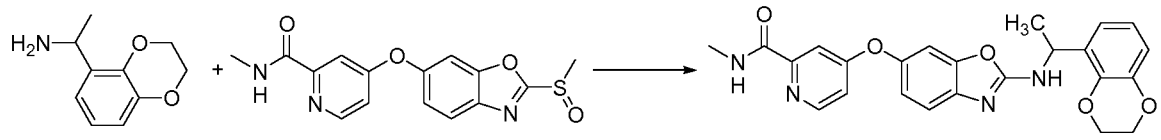
The dried resin to which the C-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-methyleneamine (1 eq) was bound was suspended in dry toluene. Under a nitrogen atmosphere methyl magnesium bromide (150 eq) in a 3 M solution in ethyl ether was added. This mixture was shaken for 24 hours at 60°C then filtered and washed with toluene, water, then methanol and dichloromethane alternately three times. The final wash was with methanol. The solid was dried under vacuum.

Step 3. Cleavage of 1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamine from resin



To the resin bound 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine suspended in dichloromethane was added trifluoroacetic acid (20% by volume). The mixture was shaken overnight then the mixture was made basic by the addition of 3 M sodium hydroxide. The solution was filtered to remove the resin, then diluted with dichloromethane and water. The water layer was extracted three times with dichloromethane. The combined organic extracts were washed once with brine, dried with anhydrous sodium sulfate, filtered and concentrated. The material recovered was clean enough to carry forward with no purification. MH+ = 180.1.

Step 4. Synthesis of 4-{2-[1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

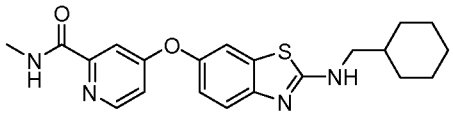


To a solution of 1-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-ethylamine (3 eq) in THF was added 4-(2-methanesulfinyl-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (1 eq). This was stirred at room temperature for 8 hours, concentrated and the residue was purified by preparatory reverse phase HPLC. MH+ = 447.1.

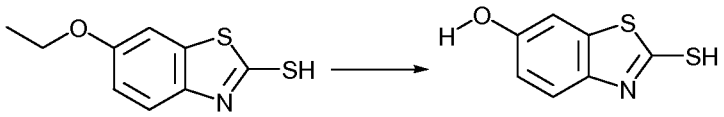
Compounds **41**, **42, 57**, **59**, **65**, **90**, **94**, **113**, and **122** in Table 2, below, were synthesized following the similar procedures as in Example 14.

Example 15 (Scheme 8)

Preparation of 4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide (Table 2, Compound 128)

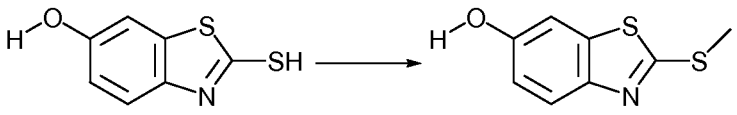


Step 1. Preparation of 2-Mercapto-benzothiazol-6-ol



As per the United States Patent **4,873,346**, hereby incorporated by reference in its entirety – Substituted Benzothiazoles, Benzimidazoles and benzoxazoles; Anderson, David J.; The Upjohn Company, Kalamazoo, Michigan; Oct.10th,1989. M+H = 184.0

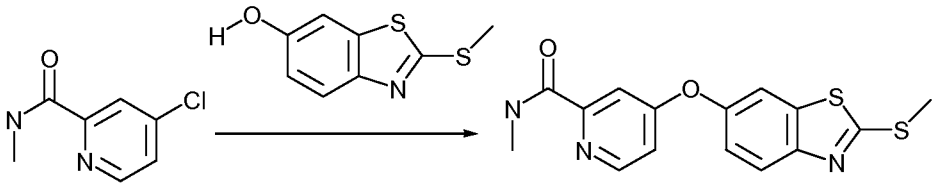
Step 2. Preparation of 2-Methylsulfanyl-benzothiazol-6-ol



To the ice cooled solution of 2-mercapto-benzothiazol-6-ol from step 1 (3.80g, 20.76 mmol, 1.0 eq) in DCM (40mL, 0.5M) at 0°C, was added triethylamine (7.29mL,

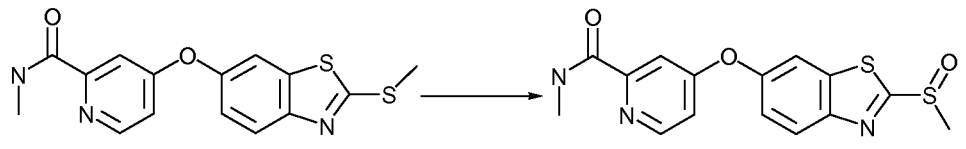
51.91 mmol, 2.5 eq) followed by iodomethane (1.93mL, 31.14mmol, 1.5eq). The reaction was stirred from 0°C to –10°C for 3 hours. The solvent was removed *in vacuo*. Water (ca.200mL) was added and the aqueous layer was extracted with ethyl acetate (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield 2-methylsulfanyl-benzothiazol-6-ol as light green powder (3.76g, 92%). The crude product was used in the next step without purification. M+H = 198.0

Step 3. Preparation of 4-(2-Methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide



To the solution of 2-methylsulfanyl-benzothiazol-6-ol (3.76g, 19.08mmol, 1.0eq) in DMF (25mL), was added $CsCO_3$ (15.54g, 47.70 mmol, 2.5 eq) at room temperature. After stirring for a while, 4-chloro-pyridine-2-carboxylic acid methylamide (4.86g, 28.62mmol, 1.5eq) was added to the mixture and the mixture was stirred at 70°C under reflux condenser overnight. After cooling the reaction mixture in ice bath, water (100mL) was added and the aqueous layer was extracted with ethyl acetate (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified using 20g of ISCO Silica Gel column (0%-50%-80%-100% ethyl acetate-hexane mixture over 45 min 40mL/min run) to yield 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (3.88g, 62%) as a white solid. M+H = 332.1

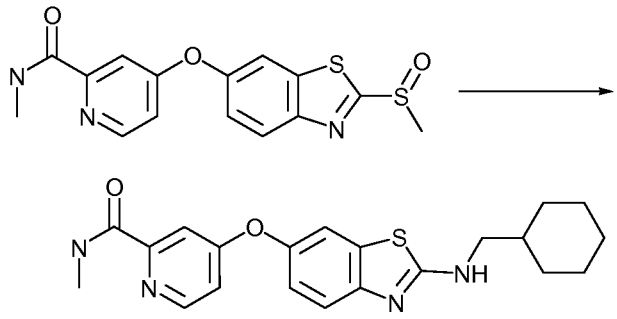
Step 4. Preparation of 4-(2-Methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide



To the solution of 4-(2-methylsulfanyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide from step 3 (3.88g, 11.72mmol, 1.0eq) in DCM (20mL) at 0°C, was added MCPBA (77%, 2.88g, 1.1eq). The mixture was stirred at this temperature for one

hour. Saturated sodium bicarbonate solution (100mL) was added. The aqueous layer was extracted with DCM (3X150mL). The organic layer was dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide as white powder in quantitative yields. The crude product was used in the next step without purification. M+H = 348.0.

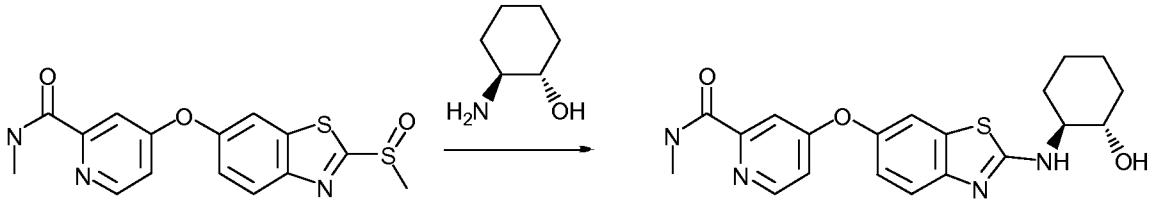
Step 5. Preparation of 4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide



To the solution of 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (25mg, 0.072 mmol, 1.0eq) in DMF (500µL), was added cyclohexylmethylamine (18.7µL, 0.144 mmol, 2.0eq) and reaction was stirred at 70°C overnight. The neat reaction mixture was purified on reverse phase preparatory HPLC. Pure fractions were lyophilized as TFA salts. M+H = 397.1

Example 16

Preparation of 4-(2-((1S,2S)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (Table 2, Compound 137)



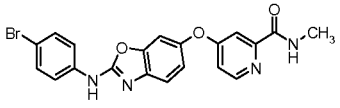
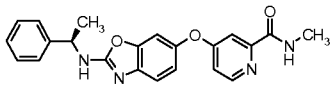
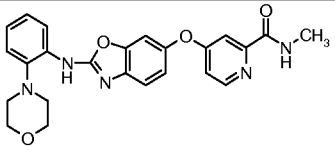
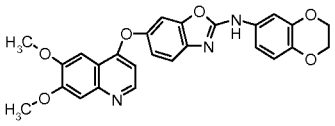
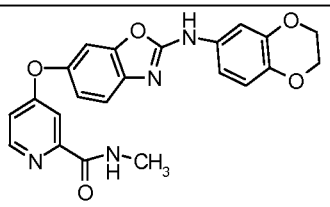
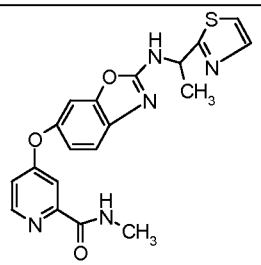
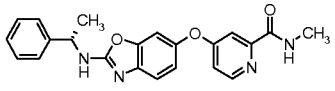
To the solution of 4-(2-methanesulfinyl-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide (70mg, 0.202 mmol, 1.0eq) in DMA (600µL), was added (1S,2S)-2-aminocyclohexanol hydrochloride (92 mg, 0.606 mmol, 3.0eq) followed by diisopropylethylamine (0.21 mL, 1.21 mmol). The reaction was heated at 110 °C for 24-

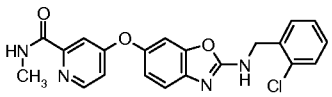
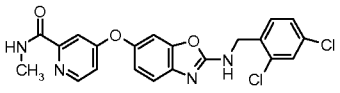
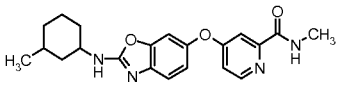
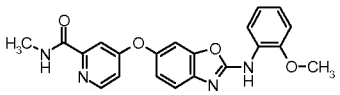
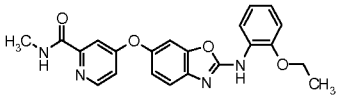
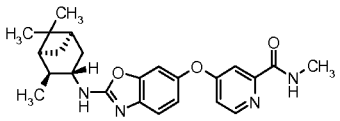
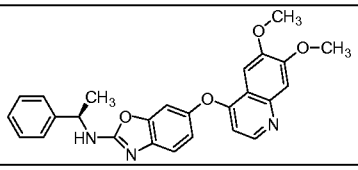
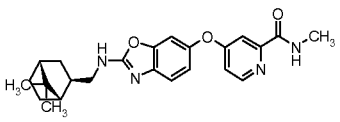
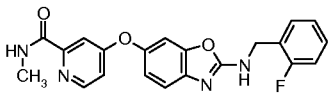
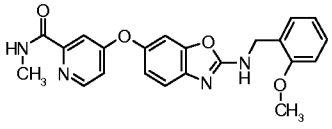
hours. The neat reaction mixture was purified on reverse phase preparatory HPLC. Pure fractions were lyophilized as TFA salts. M+H = 398

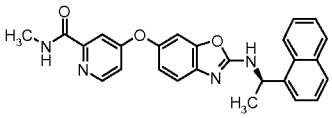
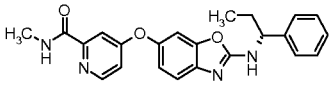
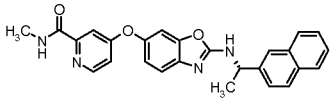
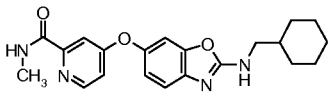
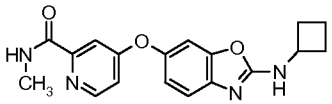
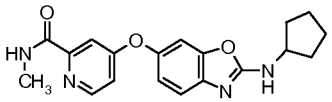
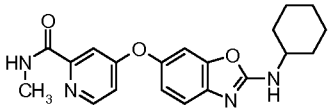
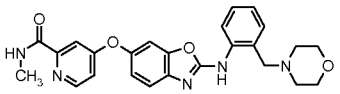
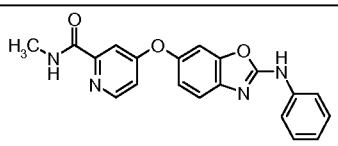
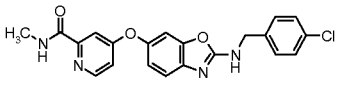
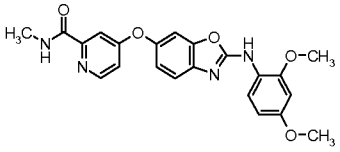
Example 17

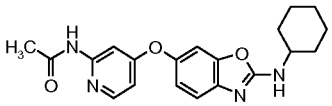
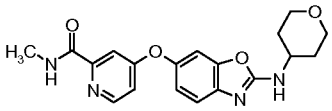
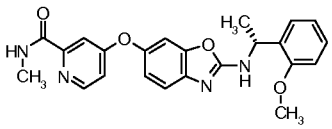
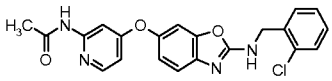
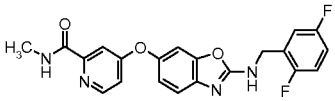
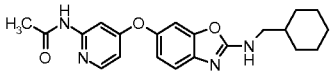
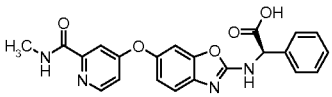
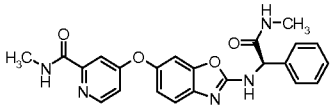
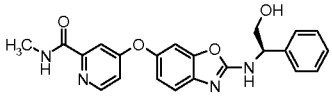
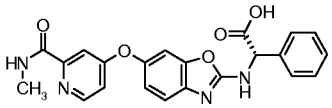
The compounds in the following Table 2 were made by the general procedures described above.

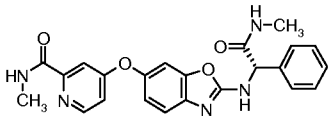
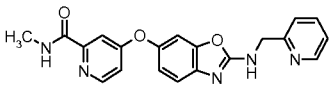
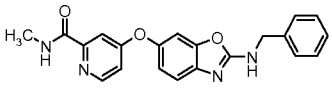
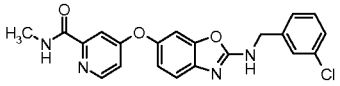
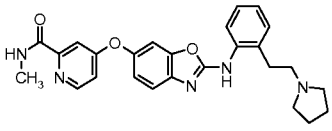
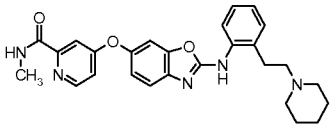
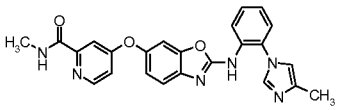
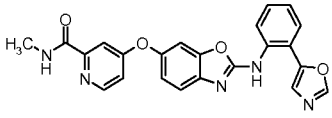
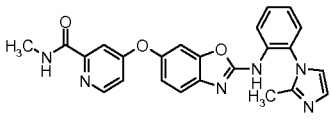
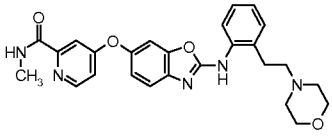
Table 2

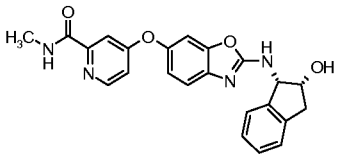
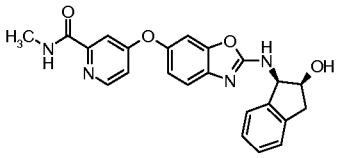
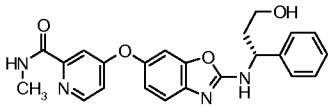
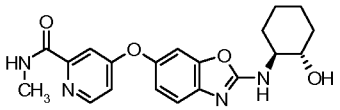
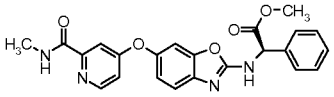
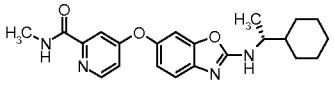
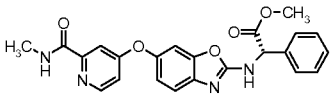
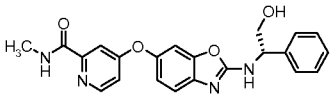
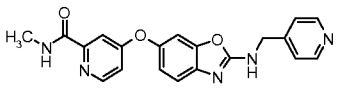
Compound	Structure	M+H; Rt(min)	Compound Name
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2		389.2	4-[2-((R)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
3		446.1; 2.74	4-[2-(2-Morpholin-4-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
4		472.1; 2.46	(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-[6-(6,7-dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-amine
5		419.1; 2.53	4-[2-(2,3-Dihydro-benzo-[1,4]dioxin-6-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
6		396.1; 2.07	4-[2-(1-Thiazol-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
7		389.2; 2.48	4-[2-((S)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

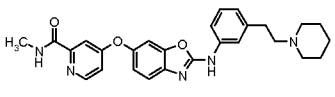
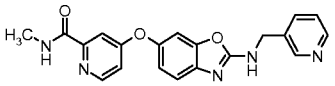
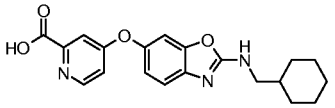
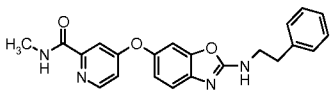
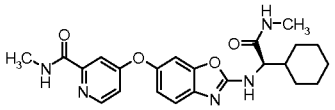
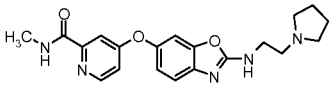
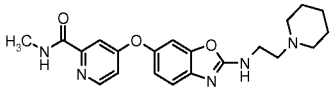
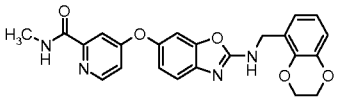
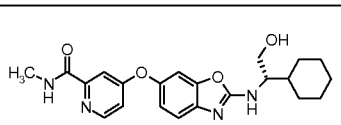
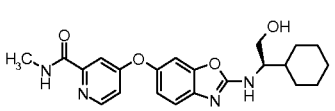
Compound	Structure	M+H; Rt(min)	Compound Name
8		409.1; 2.62	4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
9		443.0; 2.92	4-[2-(2,4-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
10		381.1; 2.53	4-[2-(3-Methyl-cyclohexyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
11		391.1; 2.77	4-[2-(2-Methoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
12		405.2; 2.98	4-[2-(2-Ethoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
13		421.2; 2.98	4-[2-((1S,2S,3S,5R)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-3-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
14		442.2; 2.50	[6-(6,7-Dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-((R)-1-phenyl-ethyl)-amine
15		421.3; 2.96	4-{2-[((1S,2R,4R)-7,7-Dimethyl-bicyclo[2.2.1]hept-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
16		393.0; 2.46	4-[2-(2-Fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
17		405.1; 2.44	4-[2-(2-Methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

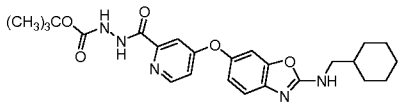
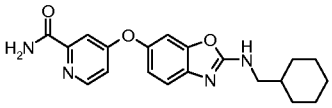
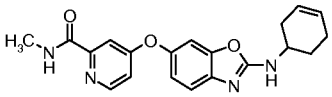
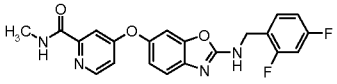
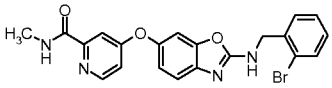
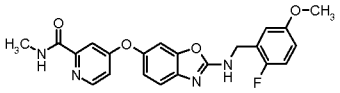
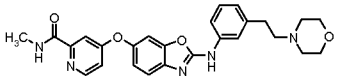
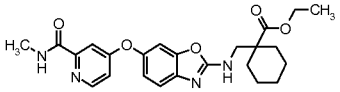
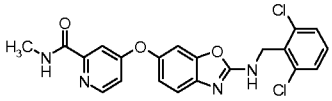
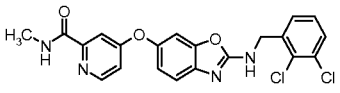
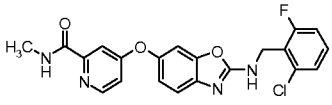
Compound	Structure	M+H; Rt(min)	Compound Name
18		439.1; 2.83	4-[2-((R)-1-Naphthalen-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
19		403.1; 2.62	4-[2-((R)-1-Phenyl-propyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
20		439.2; 2.83	4-[2-((S)-1-Naphthalen-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
21		381.1; 2.55	4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
22		339.0; 2.09	4-(2-Cyclobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
23		353.1; 2.18	4-(2-Cyclopentylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
24		367.1; 2.33	4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
25		460.1; 2.02	4-[2-(2-Morpholin-4-ylmethyl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
26		361.0; 2.61	4-(2-Phenylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
27		409.0; 2.61	4-[2-(4-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
28		421.0; 2.57	4-[2-(2,4-Dimethoxy-phenyl-amino)-benzooxazol-6-yl-oxy]-pyridine-2-carboxylic acid methylamide

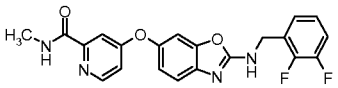
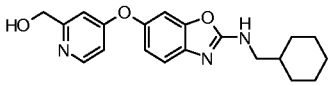
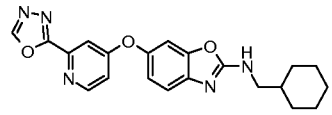
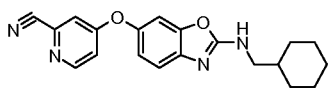
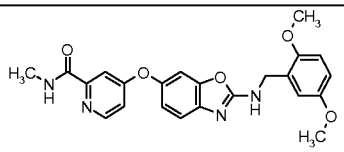
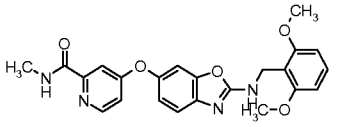
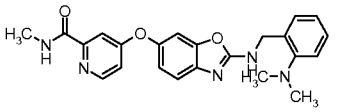
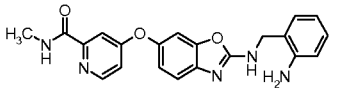
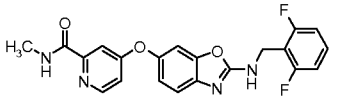
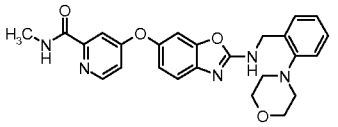
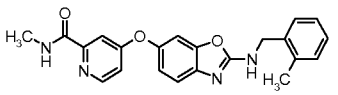
Compound	Structure	M+H; Rt(min)	Compound Name
29		367.0; 2.11	N-[4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridin-2-yl]-acetamide
30		369.1; 1.90	4-[2-(Tetrahydro-pyran-4-yl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
31		419.0; 2.55	4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
32		409.1; 2.31	N-{4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide
33		411.0; 2.53	4-[2-(2,5-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
34		381.1; 2.33	N-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide
35		419.1; 2.26	(R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid
36		432.1; 2.16	4-{2-[((R)-Methylcarbamoyl-phenyl-methyl)-amino]-benzo-oxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
37		405.1; 2.07	4-[2-((R)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
38		419.1; 2.26	(S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid

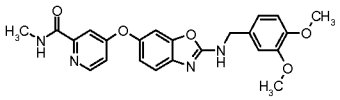
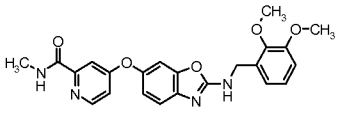
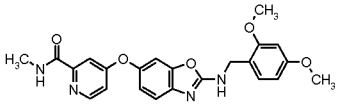
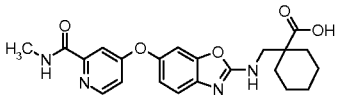
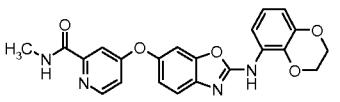
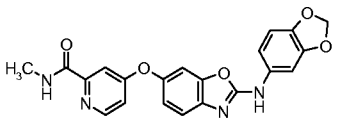
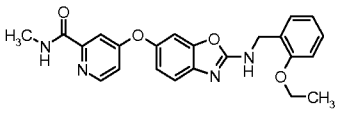
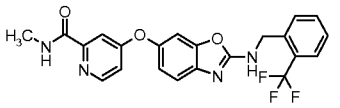
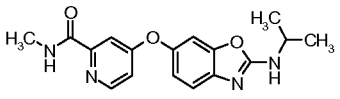
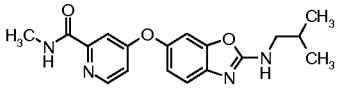
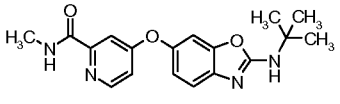
Compound	Structure	M+H; Rt(min)	Compound Name
39		432.1; 2.16	4-{2-[((S)-Methylcarbamoyl-phenyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
40		376.1; 1.76	4-{2-[(Pyridin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
41		375.1; 2.38	4-(2-Benzylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
42		409.0; 2.62	4-[2-(3-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
43		458.2; 2.13	4-{2-[2-(2-Pyrrolidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
44		472.2; 2.16	4-{2-[2-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
45		441.0; 2.11	4-{2-[2-(4-Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
46		428.1; 2.42	4-[2-(2-Oxazol-5-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
47		441.2; 2.29	4-{2-[2-(2-Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
48		474.1; 2.09	4-{2-[2-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzo-oxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

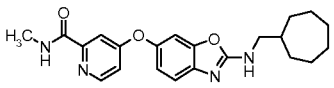
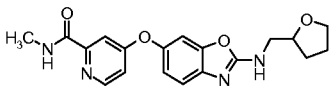
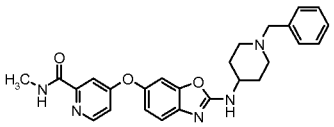
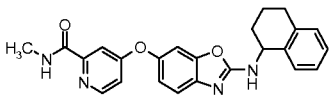
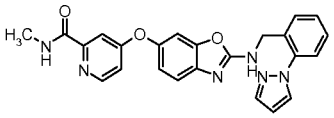
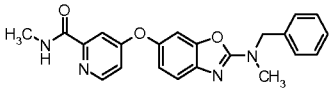
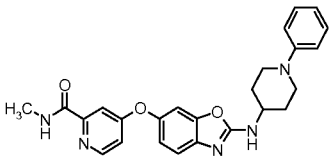
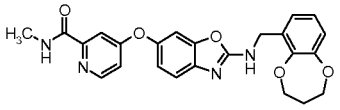
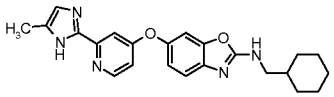
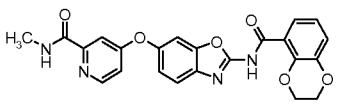
Compound	Structure	M+H; Rt(min)	Compound Name
49		417.0; 2.05	4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
50		417.0; 2.05	4-[2-((1R,2S)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
51		419.0; 2.18	4-[2-((R)-3-Hydroxy-1-phenyl-propylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
52		383.0; 1.94	4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
53		433.0; 2.51	(R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester
54		395.1; 2.68	4-[2-((R)-1-Cyclohexyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
55		433.0; 2.53	(S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester
56		405.0; 2.01	4-[2-((S)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
57		376.1; 1.72	4-{2-[(Pyridin-4-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

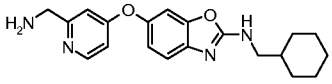
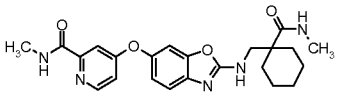
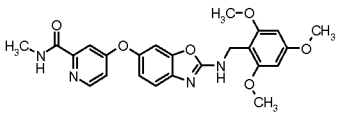
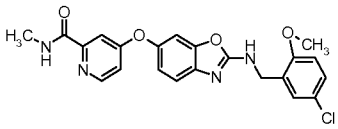
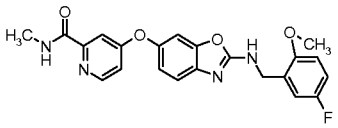
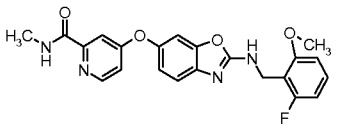
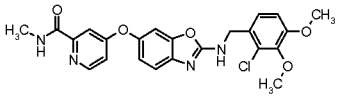
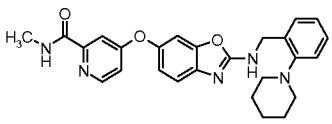
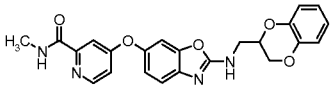
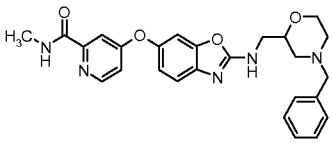
Compound	Structure	M+H; Rt(min)	Compound Name
58		472.1; 2.16	4-{2-[3-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
59		376.1; 1.76	4-{2-[(Pyridin-3-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
60		368.0; 2.13	4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid
61		389.1; 2.40	4-(2-Phenethylamino-benzo-oxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
62		438.0; 2.33	4-{2-[((R)-Cyclohexyl-methylcarbamoyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
63		382.2; 1.74	4-[2-(2-Pyrrolidin-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
64		396.2; 1.83	4-[2-(2-Piperidin-1-yl-ethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
65		433.0; 2.40	4-{2-[(2,3-Dihydro-benzo-[1,4]dioxin-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
66		411.1; 2.31	4-[2-((S)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzo-oxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
67		411.1; 2.33	4-[2-((R)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzo-oxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

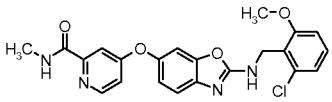
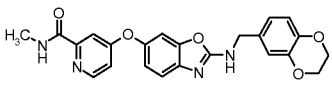
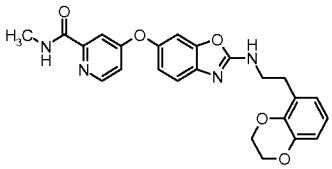
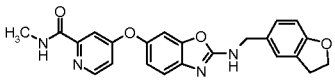
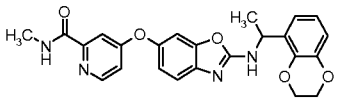
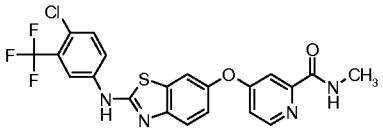
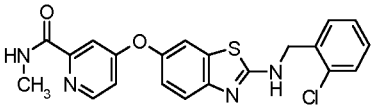
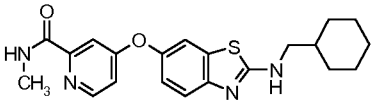
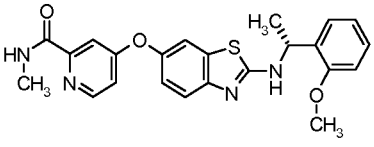
Compound	Structure	M+H; Rt(min)	Compound Name
68		482.1; 2.92	N'-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonyl}-hydrazinecarboxylic acid tert-butyl ester
69		367.1; 2.46	4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid amide
70		365.1; 2.29	4-[2-(Cyclohex-3-enylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
71		411.1; 2.53	4-[2-(2,4-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
72		455.0; 2.66	4-[2-(2-Bromo-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
73		423.0; 2.48	4-[2-(2-Fluoro-5-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
74		474.2; 2.03	4-{2-[3-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzo-oxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
75		453.1; 2.79	1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexane-carboxylic acid ethyl ester
76		443.0; 2.72	4-[2-(2,6-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
77		443.0; 2.83	4-[2-(2,3-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
78		427.0; 2.59	4-[2-(2-Chloro-6-fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

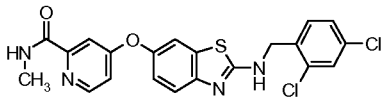
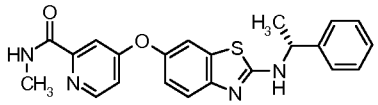
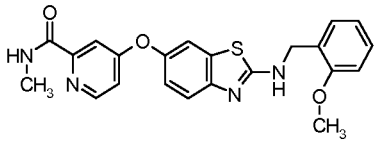
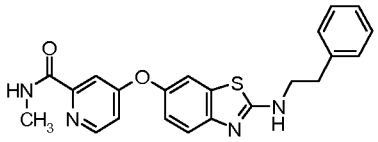
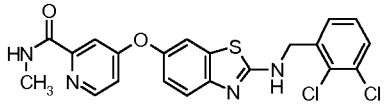
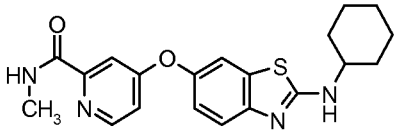
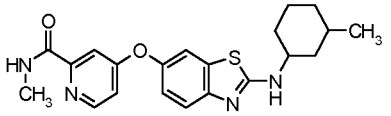
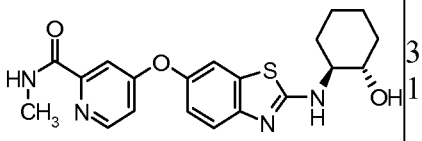
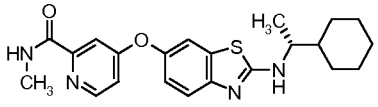
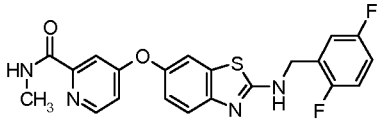
Compound	Structure	M+H; Rt(min)	Compound Name
79		411.1; 2.53	4-[2-(2,3-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
80		354.1; 2.22	{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-methanol
81		392.1; 2.59	Cyclohexylmethyl-[6-(2-[1,3,4]oxadiazol-2-yl-pyridin-4-yloxy)-benzooxazol-2-yl]-amine
82		349.1; 2.93	4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonitrile
83		435.1; 2.46	4-[2-(2,5-Dimethoxy-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
84		435.1; 2.44	4-[2-(2,6-Dimethoxy-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
85		419.1; 2.55	4-[2-(2-Dimethylamino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
86		390.1; 1.98	4-[2-(2-Amino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
87		411.1; 2.48	4-[2-(2,6-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
88		460.1; 2.40	4-[2-(2-Morpholin-4-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
89		389.1; 2.53	4-[2-(2-Methyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

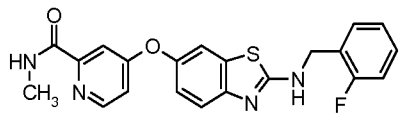
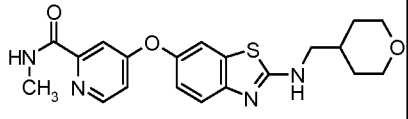
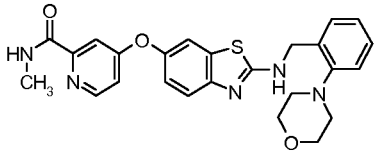
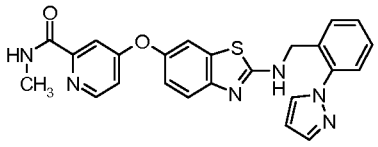
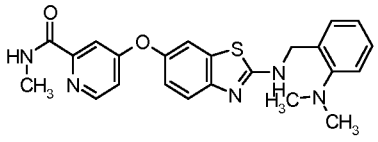
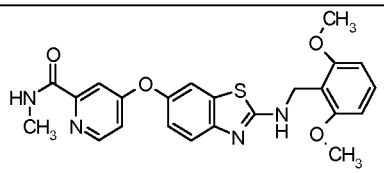
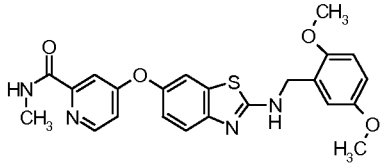
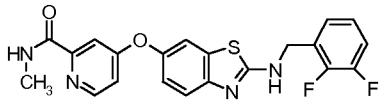
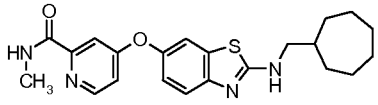
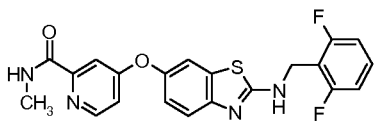
Compound	Structure	M+H; Rt(min)	Compound Name
90		435.1; 2.29	4-[2-(3,4-Dimethoxy-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
91		435.1; 2.42	4-[2-(2,3-Dimethoxy-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
92		435.1; 2.44	4-[2-(2,4-Dimethoxy-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
93		425.1; 2.29	1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexane-carboxylic acid
94		419.1; 2.62	4-[2-(2,3-Dihydro-benzo-[1,4]dioxin-5-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
95		405.0; 2.57	4-[2-(Benzo[1,3]dioxol-5-yl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
96		419.1; 2.62	4-[2-(2-Ethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
97		443.1; 2.77	4-[2-(2-Trifluoromethyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
98		327.1; 1.94	4-(2-Isopropylamino-benzo-oxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
99		341.1; 2.18	4-(2-Isobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
100		341.1; 2.24	4-(2-tert-Butylamino-benzo-oxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide

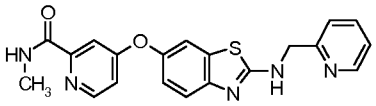
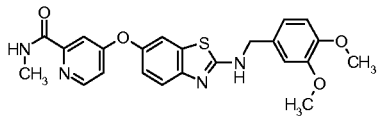
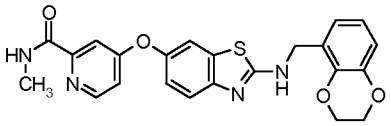
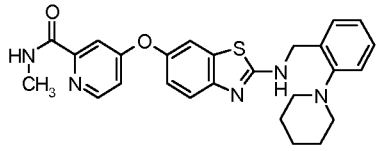
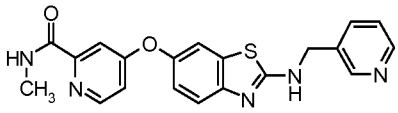
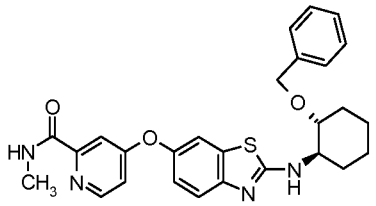
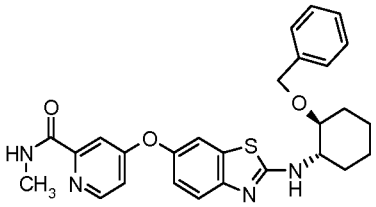
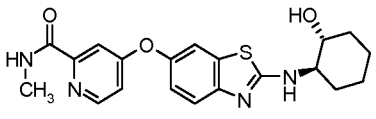
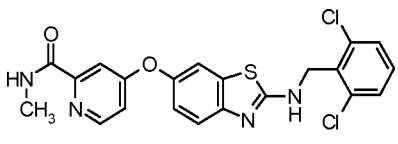
Compound	Structure	M+H; Rt(min)	Compound Name
101		395.2; 2.74	4-[2-(Cycloheptylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
102		369.1; 1.98	4-{2-[(Tetrahydro-furan-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
103		458.1; 2.05	4-[2-(1-Benzyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
104		415.1; 2.70	4-[2-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
105		441.1; 2.40	4-[2-(2-Pyrazol-1-yl-benzyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
106		389.1; 2.66	4-[2-(Benzyl-methyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
107		444.1; 2.02	4-[2-(1-Phenyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
108		447.1; 2.42	4-{2-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
109		404.1; 2.38	Cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine
110		447.0; 2.42	4-{2-[(2,3-Dihydro-benzo-[1,4]dioxine-5-carbonyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

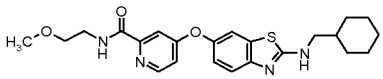
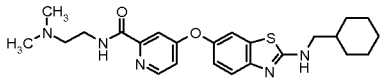
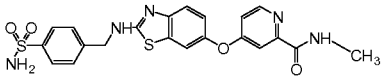
Compound	Structure	M+H; Rt(min)	Compound Name
111		353.1; 2.18	[6-(2-Aminomethyl-pyridin-4-yloxy)-benzooxazol-2-yl]-cyclohexylmethyl-amine
112		438.1; 2.16	4-{2-[(1-Methylcarbamoyl-cyclohexylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
113		465.1; 2.46	4-[2-(2,4,6-Trimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
114		439.1; 2.68	4-[2-(5-Chloro-2-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
115		423.1; 2.53	4-[2-(5-Fluoro-2-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
116		423.1; 2.48	4-[2-(2-Fluoro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
117		469.1; 2.57	4-[2-(2-Chloro-3,4-dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
118		458.1; 2.20	4-[2-(2-Piperidin-1-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
119		433.1; 2.55	4-{2-[(2,3-Dihydro-benzo-[1,4]dioxin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
120		474.1; 2.01	4-{2-[(4-Benzyl-morpholin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

Compound	Structure	M+H; Rt(min)	Compound Name
121		439.0; 2.63	4-[2-(2-Chloro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
122		433.1; 2.37	4-{2-[(2,3-Dihydro-benzo-[1,4]dioxin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
123		447.1; 2.44	4-{2-[2-(2,3-Dihydro-benzo-[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
124		417.1; 2.37	4-{2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
125		447.1; 2.50	4-{2-[1-(2,3-Dihydro-benzo-[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
126		479.9; 5.1	4-[2-(4-Chloro-3-trifluoromethyl-phenylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
127		425.0; 2.57	4-[2-(2-Chloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
128		397.1; 2.48	4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
129		435.1; 2.48	4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide

Compound	Structure	M+H; Rt(min)	Compound Name
130		459.0; 2.88	4-[2-(2,4-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
131		405.1; 2.42	4-[2-((R)-1-Phenyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
132		421.1; 2.37	4-[2-(2-Methoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
133		405.0; 2.35	4-(2-Phenethylamino-benzo-thiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
134		458.9; 2.81	4-[2-(2,3-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
135		383.1; 2.27	4-(2-Cyclohexylamino-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide
136		397.1; 2.46	4-[2-(3-Methyl-cyclohexyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
137		399.1; 1.94	4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
138		411.1; 2.59	4-[2-((R)-1-Cyclohexyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
139		427.0; 2.53	4-[2-(2,5-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

Compound	Structure	M+H; Rt(min)	Compound Name
140		409.0; 2.40	4-[2-(2-Fluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
141		399.1; 1.94	4-{2-[(Tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
142		476.1; 2.38	4-[2-(2-Morpholin-4-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
143		457.1; 2.33	4-[2-(2-Pyrazol-1-yl-benzyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
144		434.1; 2.05	4-[2-(2-Dimethylamino-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
145		451.1; 2.38	4-[2-(2,6-Dimethoxy-benzyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
146		451.1; 2.39	4-[2-(2,5-Dimethoxy-benzyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
147		427.0; 2.53	4-[2-(2,3-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
148		411.1; 2.62	4-[2-(Cycloheptylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
149		427.0; 2.46	4-[2-(2,6-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

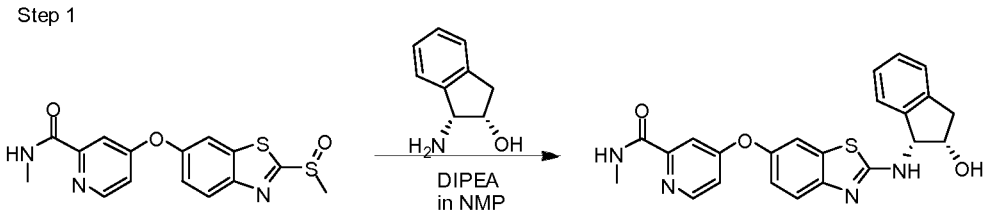
Compound	Structure	M+H; Rt(min)	Compound Name
150		392.1; 1.83	4-{2-[(Pyridin-2-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
151		451.0; 2.22	4-[2-(3,4-Dimethoxy-benzyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
152		449.0; 2.35	4-{2-[(2,3-Dihydro-benzo-[1,4]dioxin-5-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
153		474.1; 2.31	4-[2-(2-Piperidin-1-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
154		392.0; 1.78	4-{2-[(Pyridin-3-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide
155		489.2; 2.57	4-[2-((1R,2R)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
156		489.1; 2.57	4-[2-((1S,2S)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
157		399.1; 1.94	4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide
158		459.0; 2.68	4-[2-(2,6-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

Compound	Structure	M+H; Rt(min)	Compound Name
159		441.1; 2.59	4-(2-(cyclohexylmethyl-amino)benzothiazol-6-yloxy)-N-(2-methoxyethyl)-pyridine-2-carboxamide
160		454.2; 2.26	4-(2-(cyclohexylmethyl-amino)benzothiazol-6-yloxy)-N-(2-(dimethylamino)-ethyl)pyridine-2-carboxamide
161		470.0; 2.00	4-[2-(4-Sulfonamido-benzyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide

Example 162

Preparation of 4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below

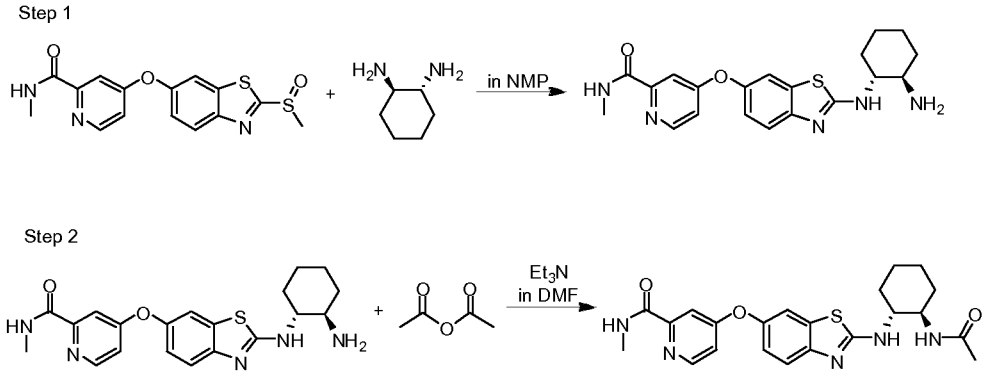


To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (300 mg, 0.86 mmol) in 5 ml of NMP was added (1R,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (597 mg, 4 mmol) and DIPEA (300 μL, 1.73 mmol). The reaction solution was stirred at 105°c for 24 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give 4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (347 mg, 0.63 mmol) as TFA salt. ES/MS *m/z* 433.1(MH^+).

Example 163

Preparation of 4-(2-((1R,2R)-2-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 4-(2-((1R,2R)-2-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (15 mg, 43 μmole) in 400 μL of NMP was added (1R,2R)-cyclohexane-1,2-diamine (17 mg, 150 μmole). The reaction solution was stirred at 105°c for 24 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give 4-(2-((1R,2R)-2-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (12 mg, 30 μmole) as white powder. ES/MS *m/z* 398.1(MH^+).

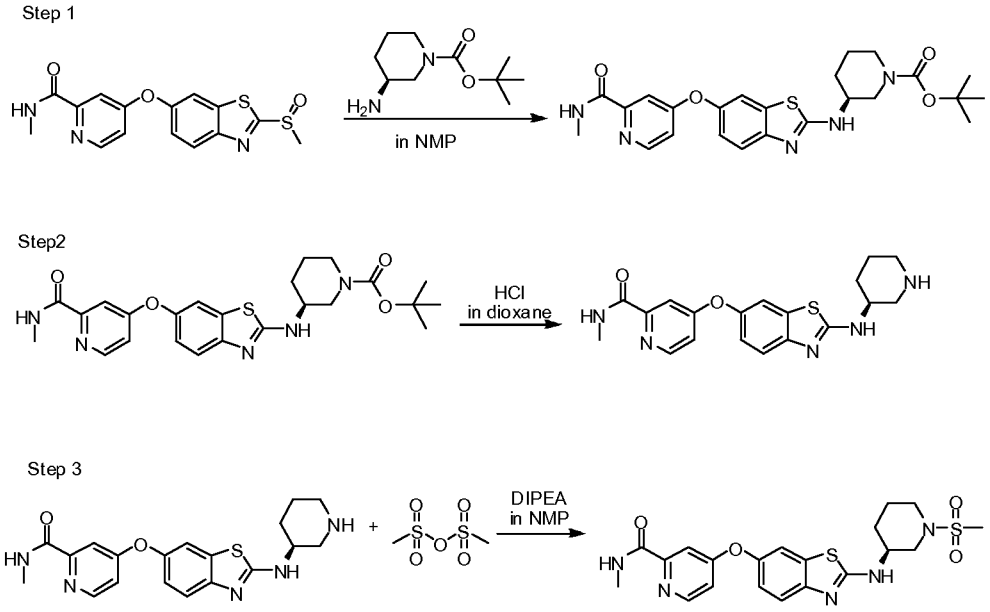
Step 2. Preparation of 4-(2-((1R,2R)-2-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

To the solution of 4-(2-((1R,2R)-2-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (9 mg, 22 μmole) and triethylamine (11 μL, 80 μmole) in 300 μL of DMF was added acetic anhydride (5 μL, 50 μmole). The reaction solution was stirred at room temperature for 1.5 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give 4-(2-((1R,2R)-2-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (5.1 mg, 12 μmole) as white powder. ES/MS *m/z* 440.2(MH^+).

Example 164

Preparation of (S)-N-methyl-4-(2-(1-(methylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (104 mg, 0.3 mmol) in 2 ml of NMP was added (S)-tert-butyl 3-aminopiperidine-1-carboxylate (240 mg, 1.2 mmol). The reaction solution was stirred at 105°c for 5 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) as white powder. ES/MS *m/z* 484.2 (MH^+).

Step 2. Preparation of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

(S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) was dissolved in 4 ml of 4M HCl in dioxane (16 mmol). The reaction solution was stirred at room temperature for 1 hour. The crude reaction solution was evaporated *in vaccuo* to give (S)-N-methyl-4-(2-(piperidin-3-

ylamino)benzo[d]thiazol-6-yloxy)picolinamide (46 mg, 0.12 mmol) as white solid. ES/MS *m/z* 384.0 (MH^+).

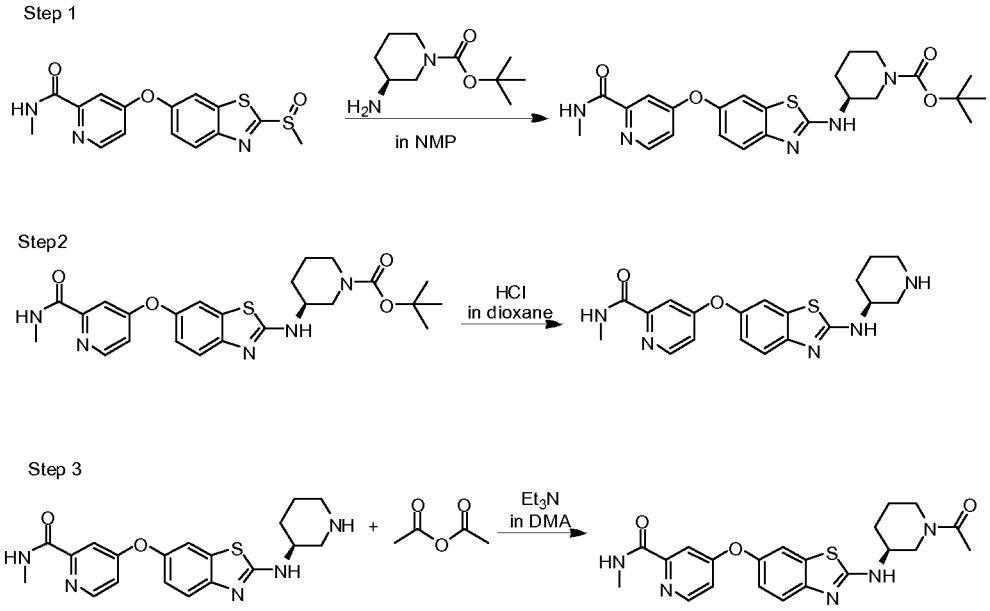
Step 3. Preparation of (S)-N-methyl-4-(2-(1-(methylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

To the solution of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide hydrochloride (12.5 mg, 30 μmol) and DIPEA (28 μL, 160 μmol) in 300 μL of NMP was added methanesulfonic anhydride (17 mg, 100 μmol). The reaction solution was stirred at 105°c for 46 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-N-methyl-4-(2-(1-(methylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (4.5 mg, 9.8 μmol) as white powder. ES/MS *m/z* 462.1 (MH^+).

Example 165

Preparation of (S)-4-(2-(1-acetylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (104 mg, 0.3 mmol) in 2 ml of NMP was added (S)-tert-butyl 3-aminopiperidine-1-carboxylate (240 mg, 1.2 mmol). The reaction solution was stirred at

105°c for 5 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) as white powder. ES/MS *m/z* 484.2 (MH^+).

Step 2. Preparation of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

(S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) was dissolved in 4 ml of 4M HCl in dioxane (16 mmol). The reaction solution was stirred at room temperature for 1 hour. The crude reaction solution was evaporated *in vaccuo* to give (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (46 mg, 0.12 mmol) as white solid. ES/MS *m/z* 384.0 (MH^+).

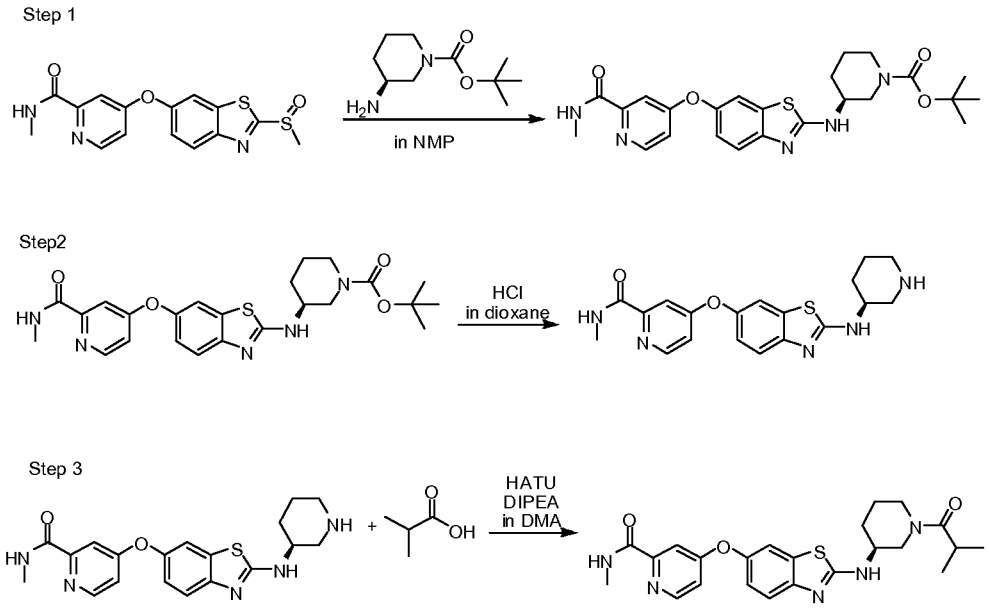
Step 3. Preparation of (S)-4-(2-(1-acetylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

To the solution of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (13 mg, 30 μmol) and triethylamine (13 μL, 90 μmol) in 300 μL of DMA was added acetic anhydride (6 μl, 60 μmol). The reaction solution was stirred at room temperature for 1.5 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-4-(2-(1-acetylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (4.8mg, 11 μmol) as white powder. ES/MS *m/z* 426.2 (MH^+).

Example 166

Preparation of (S)-4-(2-(1-isobutyrylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (104 mg, 0.3 mmol) in 2 ml of NMP was added (S)-tert-butyl 3-aminopiperidine-1-carboxylate (240 mg, 1.2 mmol). The reaction solution was stirred at 105°c for 5 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) as white powder. ES/MS *m/z* 484.2(MH^+).

Step 2. Preparation of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

(S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) was dissolved in 4 ml of 4M HCl in dioxane (16 mmol). The reaction solution was stirred at room temperature for 1 hour. The crude reaction solution was evaporated *in vaccuo* to give (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (46 mg, 0.12 mmol) as white solid. ES/MS *m/z* 384.0(MH^+).

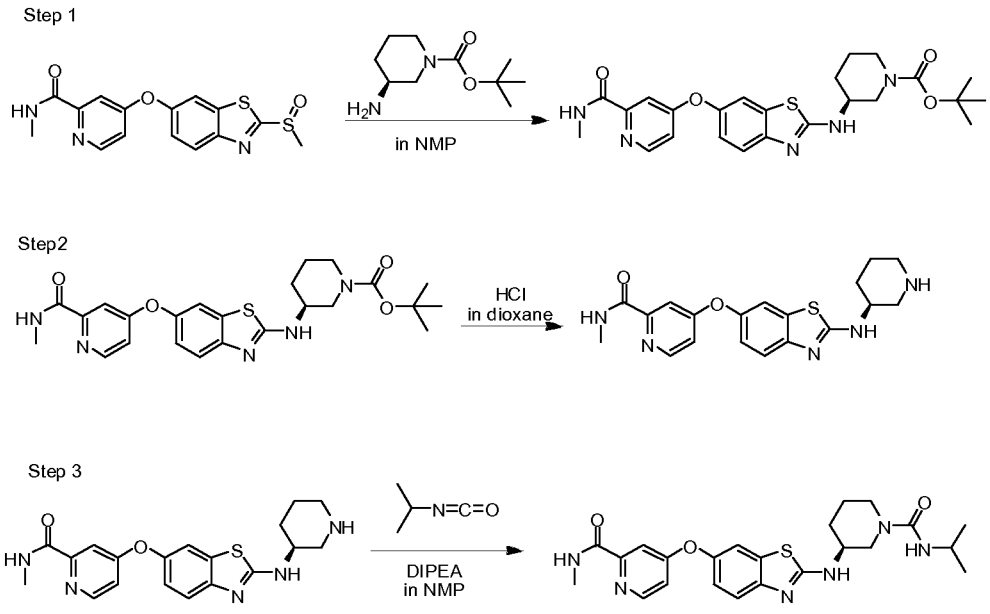
Step 3. Preparation of (S)-4-(2-(1-isobutyrylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

To the reaction solution of isobutyric acid (4 µl, 40 µmol), HATU (15 mg, 40 µmol) and DIEA (14 µL, 80 µmol) in 400 µL of DMA was added (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (13 mg, 30 µmol) and DIPEA (6 µL, 30 µmol). The reaction solution was stirred at room temperature for 16 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-4-(2-(1-isobutyrylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (6.8mg, 15 µmol) as white powder. ES/MS *m/z* 454.2(MH^+).

Example 167

Preparation of (S)-4-(2-(1-isobutyrylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (104 mg, 0.3 mmol) in 2 ml of NMP was added (S)-tert-butyl 3-aminopiperidine-1-carboxylate (240 mg, 1.2 mmol). The reaction solution was stirred at 105°c for 5 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-

ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) as white powder. ES/MS *m/z* 484.2(MH^+).

Step 2. Preparation of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

(S)-tert-butyl 3-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (56 mg, 0.12 mmol) was dissolved in 4 ml of 4M HCl in dioxane (16 mmol). The reaction solution was stirred at room temperature for 1 hour. The crude reaction solution was evaporated *in vaccuo* to give (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (46 mg, 0.12 mmol) as white solid. ES/MS *m/z* 384.0(MH^+).

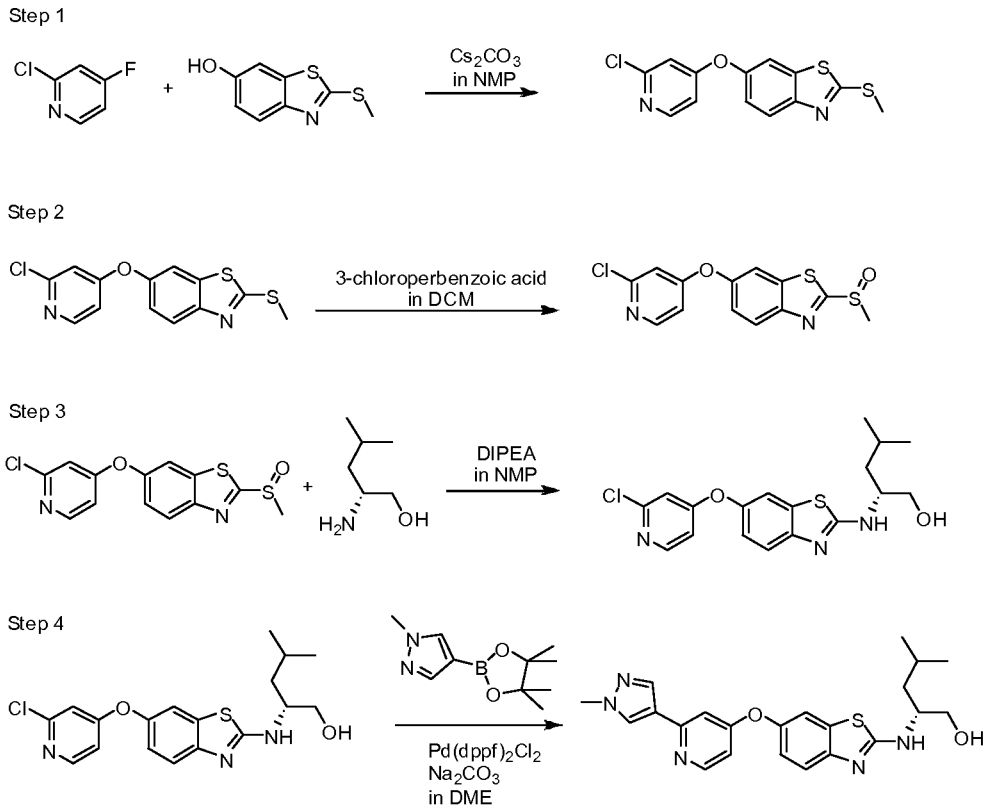
Step 3. Preparation of (S)-4-(2-(1-(isopropylcarbamoyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

To the solution of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide (13 mg, 30 μmol) and DIPEA (17 μL, 100 μmol) in 300 μL of NMP was added 2-isocyanatopropane (5 μL, 50 μmol). The reaction solution was stirred at room temperature for 18 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-4-(2-(1-(isopropylcarbamoyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (5.9 mg, 12 μmol) as white powder. ES/MS *m/z* 469.2(MH^+).

Example 168

Preparation of (R)-4-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole

To the mixture of 2-(methylthio)benzo[d]thiazol-6-ol (1 g, 5.08 mmol) and cesium carbonate (4.55 g, 14 mmol) in 15 ml of NMP was added 2-chloro-4-fluoropyridine(1.32 mg, 10 mmol). The reaction mixture was stirred at 55°c for overnight. The reaction mixture was poured into 80 ml of aq. saturated $NaHCO_3$ and extracted with ethyl acetate (2x150 ml). The combined organic layers were washed with aq. 0.1M $NaHSO_4$ (60ml), water (2x60 ml) and brine (60 ml), then dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole (1.72 g) as brown oil that carried on to next step without purification. ES/MS *m/z* 308.9(MH^+).

Step 2. Preparation of 6-(2-chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole

To the solution of 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole (1.72g, 5.08 mmol) in 32 ml of DCM was added 3-chloroperbenzoic acid (77%, 1.3 g, 5 mmol) portion-wise at 0°c. After being stirred at room temperature for 2 hours, the mixture was diluted with 80 ml of DCM. The resulting mixture was washed with aq. 0.2M $Na_2S_2O_3$ (25ml), aq. saturated $NaHCO_3$ (25ml), water (25ml) and brine, then dried over Na_2SO_4, filtered and evaporated *in vaccuo* to give a yellow brown solid (1.72 g). The residue was purified by flash column chromatography and evaporated *in vaccuo* to give 6-(2-

chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole (970 mg, 3 mmol) as ivory powder. ES/MS *m/z* 325.0(MH^+).

Step 3. Preparation of (R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol

To the solution of 6-(2-chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole (26 mg, 80 μmol) in 400 μL of NMP was added (R)-2-amino-4-methylpentan-1-ol (33 μL, 250 μmol) and DIPEA (17 μL, 100 μmol). The reaction solution was stirred at 100°c for 18 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol (12 mg, 31 μmol) as powder. ES/MS *m/z* 378.1(MH^+).

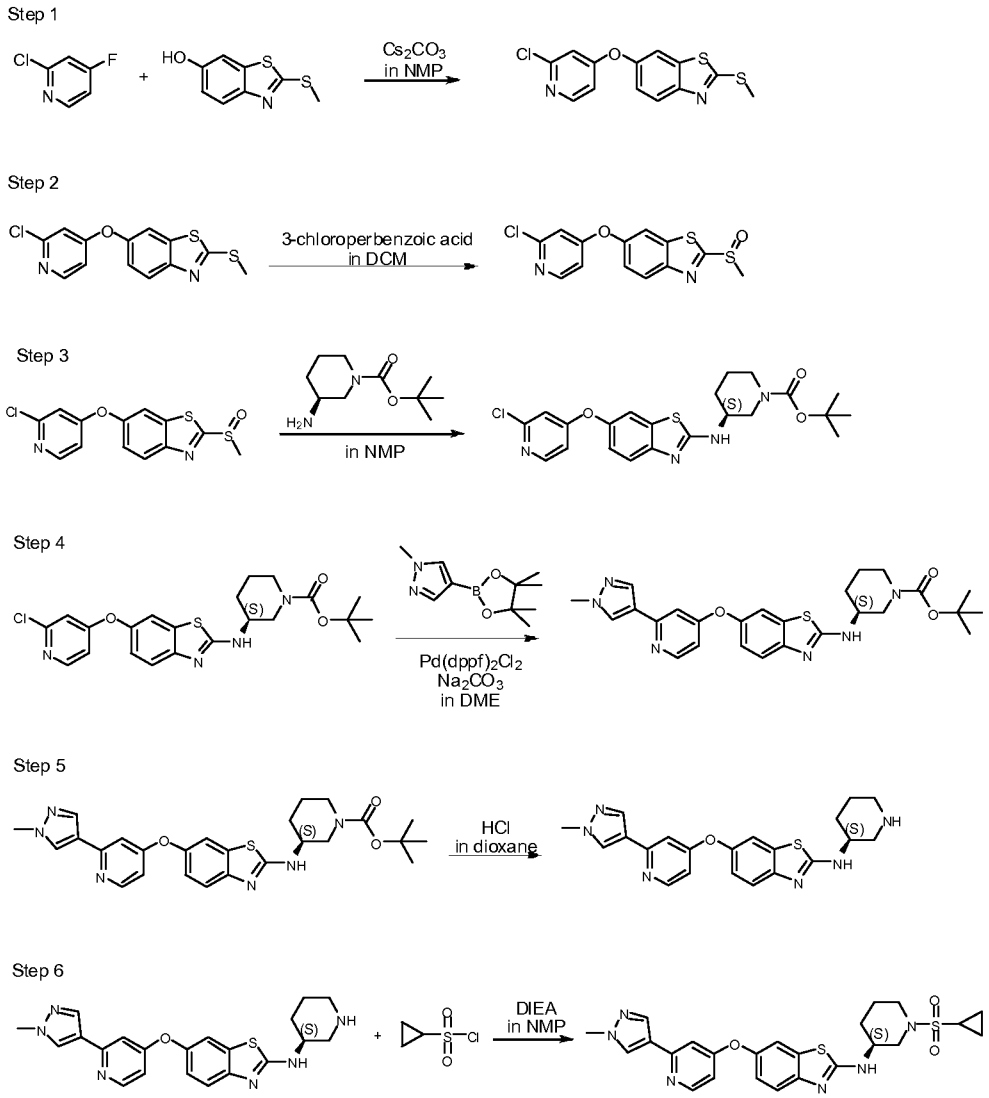
Step 4. Preparation of (R)-4-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol

To the reaction mixture of (R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol (12 mg, 31 μmol) in 400 μL of DME, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (21 mg, 100 μmol), $Pd(dppf)_2Cl_2$ (7 mg, 8 μmol) and aq. 2M Na_2CO_3 (100 μL, 200 μmol) were added. The reaction mixture was stirred at 90°c for 24 hours. The reaction mixture filtered, purified on prep HPLC and evaporated *in vaccuo* to give (R)-4-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol as powder (4.2 mg). ES/MS *m/z* 424.1 (MH^+).

Example 169

Preparation of (S)-N-(1-(cyclopropylsulfonyl)piperidin-3-yl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole

To the mixture of 2-(methylthio)benzo[d]thiazol-6-ol (1 g, 5.08 mmol) and cesium carbonate (4.55 g, 14 mmol) in 15 ml of NMP was added 2-chloro-4-fluoropyridine(1.32 mg, 10 mmol). The reaction mixture was stirred at 55°c for overnight. The reaction mixture was poured into 80 ml of aq. saturated $NaHCO_3$ and extracted with ethyl acetate (2x150 ml). The combined organic layers were washed with aq. 0.1M $NaHSO_4$ (60ml), water (2x60 ml) and brine (60 ml), then dried over $MgSO_4$, filtered and evaporated *in vaccuo* to give 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole (1.72 g) as brown oil that carried on to next step without purification. ES/MS *m/z* 308.9(MH^+).

Step 2. Preparation of 6-(2-chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole

To the solution of 6-(2-chloropyridin-4-yloxy)-2-(methylthio)benzo[d]thiazole (1.72g, 5.08 mmol) in 32 ml of DCM was added 3-chloroperbenzoic acid (77%, 1.3 g, 5

mmol) portion-wise at 0°c. After being stirred at room temperature for 2 hours, the mixture was diluted with 80 ml of DCM. The resulting mixture was washed with aq. 0.2M $Na_2S_2O_3$ (25ml), aq. saturated $NaHCO_3$ (25ml), water (25ml) and brine, then dried over Na_2SO_4, filtered and evaporated *in vaccuo* to give a yellow brown solid (1.72 g). The residue was purified by flash column chromatography and evaporated *in vaccuo* to give 6-(2-chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole (970 mg, 3 mmol) as ivory powder. ES/MS *m/z* 325.0(MH^+).

Step 3. Preparation of (S)-tert-butyl 3-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of 6-(2-chloropyridin-4-yloxy)-2-(methylsulfinyl)benzo[d]thiazole (100 mg, 0.31 mmol) in 1.6 ml of NMP was added (S)-tert-butyl 3-aminopiperidine-1-carboxylate (200 mg, 1 mmol) and DIPEA (70 µL, 0.4 mmol). The reaction solution was stirred at 95°c for 5 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-tert-butyl 3-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (160 mg) as TFA salt. ES/MS *m/z* 461.1(MH^+).

Step 4. Preparation of (S)-tert-butyl 3-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the reaction mixture of (S)-tert-butyl 3-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (68 mg, 148 µmol) in 1.2 m of DME, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (40 mg, 192 µmol), $Pd(dppf)_2Cl_2$ (18 mg, 22 µmol) and aq. 2M Na_2CO_3 (400 µL, 800 µmol) were added. The reaction mixture was stirred at 85°c for 72 hours or until done by LC. The reaction mixture was poured into 40 ml of saturated $NaHCO_3$ solution and extracted with ethyl acetate (2x80ml). The combined organic layers were washed with water (2x20ml) and brine (20 ml), then dried over Na_2SO_4, filtered and evaporated *in vaccuo* to give a brown glue (77 mg) that was purified on prep HPLC to give (S)-tert-butyl 3-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate as powder (9.6 mg). ES/MS *m/z* 507.1(MH^+).

Step 5. Preparation of (S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide

(S)-tert-butyl 3-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (9.6 mg, 19 µmol) was dissolved in 1 ml of 4M HCl in

dioxane (4 mmol). The reaction solution was stirred at room temperature for 1 hour. The crude reaction solution was evaporated *in vaccuo* to give (S)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(piperidin-3-yl)benzo[d]thiazol-2-amine (7.6 mg, 18 μmol) as white solid. ES/MS *m/z* 407.1(MH^+).

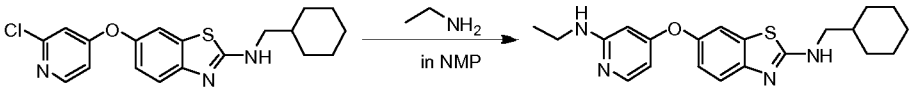
Step 6. Preparation of (S)-N-(1-(cyclopropylsulfonyl)piperidin-3-yl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

To the solution of (S)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(piperidin-3-yl)benzo[d]thiazol-2-amine (7.6 mg, 18 μmol) and DIPEA (35 μL, 200 μmol) in 400 μL of NMP was added cyclopropanesulfonyl chloride (10 mg, 98 μmol). The reaction solution was stirred at 55 for 16 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give (S)-N-(1-(cyclopropylsulfonyl)piperidin-3-yl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine (6.2mg, 12 μmol) as white powder. ES/MS *m/z* 511.2(MH^+).

Example 170

Preparation of N-(cyclohexylmethyl)-6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine

Step 1

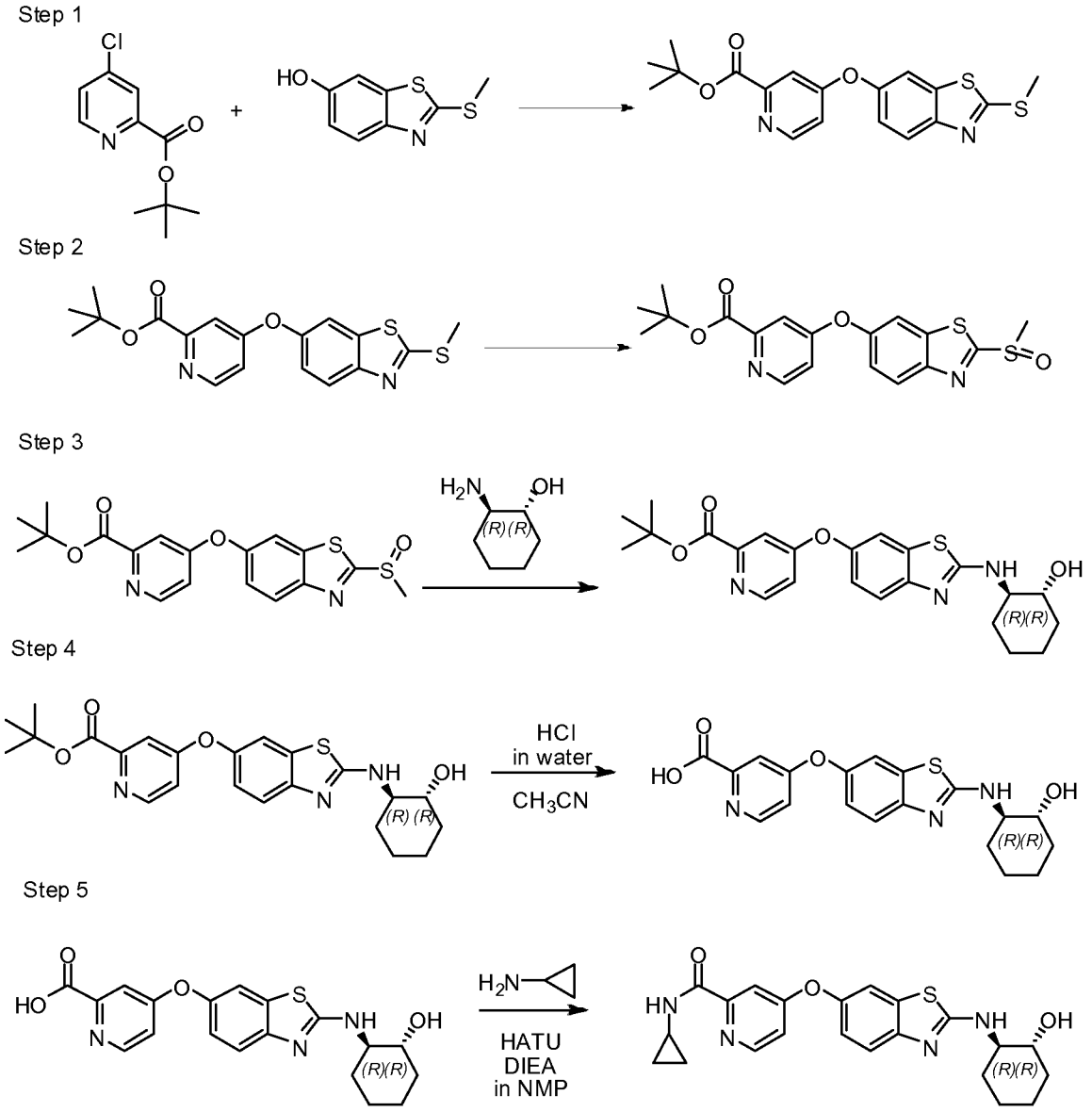


To the reaction solution of 6-(2-chloropyridin-4-yloxy)-N-(cyclohexylmethyl) benzo[d]thiazol-2-amine (12 mg, 0.03 mmol) in 400 μL of NMP was added DIPEA (9 μL, 0.05 mmol) and 70% ethylamine in water (200 μL , 2.51 mmol). The reaction mixture was stirred at 110 °C for 96 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and evaporated *in vaccuo* to give N-(cyclohexylmethyl)-6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine as TFA salt (1.8 mg). ES/MS *m/z* 383.1 (MH^+).

Example 171

N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide

The subject compound was prepared according to the general Scheme below:



Step 1 . Synthesis of tert-butyl 4-(2-(methylthio)benzo[d]thiazol-6-yloxy)picolinate

To a solution of 2-(methylthio)benzo[d]thiazol-6-ol (5.0 g, 25.38 mmol, 1.0 eq) in 25 mL of *N*,*N*-dimethylformamide was added tert-butyl 4-chloropicolinate (8.13 g, 38.07 mmol, 1.5 eq) and cesium carbonate (20.67 g, 63.45 mmol, 2.5 eq). The reaction mixture was stirred at 75°C for 6 hours. After the mixture was cooled to room temperature, the mixture was added 120 mL of water and aqueous phase extracted with ethyl acetate (3X150mL), combined organic layers were dried over sodium sulfate. After filtration, the solid was purified by silica gel column eluted with ethyl acetate-hexane 0%-50% mixture to give 5.84g of the titled compound as brown powder (62%). MH+ = 375.

Step 2. Synthesis of tert-butyl 4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy) picoli- nate

To a solution of the tert-butyl 4-(2-(methylthio)benzo[d]thiazol-6-yloxy)picolinate (5.84 g, 15.61 mmol, 1.0 eq) in 25 mL of methylene chloride was added 3-chloroperoxybenzoic acid (77%, 3.84 g, 17.17 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 1.5 hours and then was diluted with 200 mL of methylene chloride. The resulting mixture was washed with aqueous sodium bicarbonate and brine then dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give crude product, which was used to next step without further purification. MH+ = 391.0.

Step 3. Preparation of tert-butyl 4-(2-((1R,2R)-2 hydroxycyclohexylamino)-benzo[d]thiazol-6-yloxy)picolinate

To the solution of tert-butyl 4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinate (500 mg, 1.25 mmol) in 10 ml of NMP was added (1R,2R)-cyclohexane-1,2-diamine (581 mg, 3.84 mmol) and DIPEA (0.995 ml, 5.76 mmol). The reaction solution was stirred at 100°c for 3 days. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give tert-butyl 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinate (240 mg, 0.544 mmol) as white powder. ES/MS *m/z* 442.5(MH^+).

Step 4. Preparation of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinic acid

To the solution of tert-butyl 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinate (250 mg, 0566 mmol) in 10 ml of acetonitrile was added 6 M of hydrochloric acid (1 ml, 6 mmol). The reaction solution was stirred at room temperature for 1 hour and then at 60°c for 2 hours. The crude reaction solution was concentrated and re-dissolved with 10 ml of acetonitrile. The resulting solution was evaporated *in vaccuo* to give light brown oily product 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinic acid (215 mg, 0.56 mmol). ES/MS *m/z* 386.5(MH^+).

Step 5. Preparation of N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)-benzo[d]thiazol-6-yloxy)picolinamide

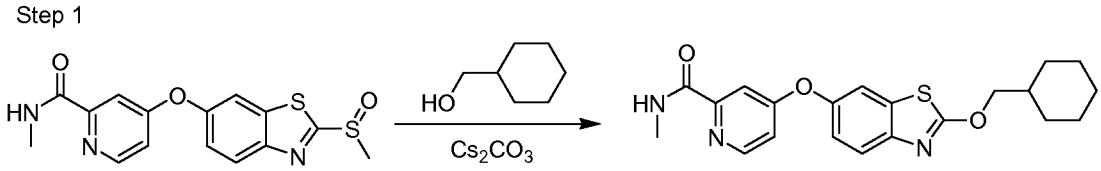
To the reaction solution of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinic acid (5 mg, 39 μmol), HATU (15 mg, 39 μmol) and DIPEA (14 μL, 78 μmol) in 1 ml of NMP was added cyclopropylamine (7ul mg, 30 μmol). The reaction solution was stirred at room temperature

for 12 hours. The crude reaction solution was purified on prep HPLC and evaporated *in vaccuo* to give N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide (1 mg, 2.3 μmol) as white powder. ES/MS *m/z* 425.2(MH^+).

Example 172

Preparation of 4-(2-(cyclohexylmethoxy)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 4-(2-(cyclohexylmethoxy)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

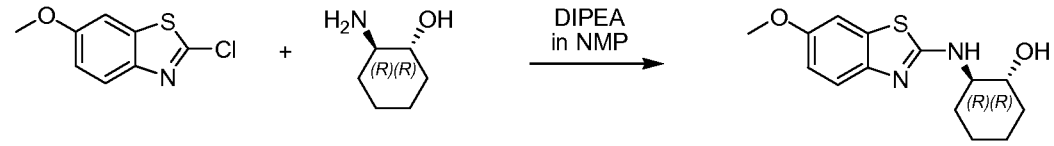
N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (15 mg, 43 μmol) was mixed with 500 μL of cyclohexylmethanol and cesium carbonate (42 mg, 0.13 mmol). The resulting reaction mixture was stirred at 90°c for 12 hours. The crude reaction mixture was filtered and purified on prep HPLC and then evaporated *in vaccuo* to give 4-(2-(cyclohexylmethoxy)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (7 mg, 17.6 μmol) as powder. ES/MS *m/z* 398.1(MH^+).

Example 173

Preparation of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:

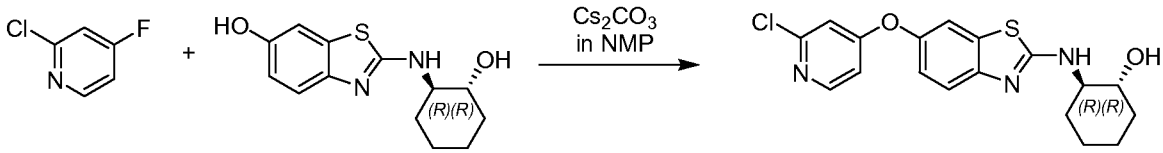
Step 1



Step 2



Step 3



Step 1. Preparation of (1R,2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol.

To the solution of 2-chloro-6-methoxybenzo[d]thiazole (1.0 g, 5 mmol) in 5.5 ml of NMP was added (1R, 2R)-2-aminocyclohexanol hydrochloride (910 mg, 6 mmol) and DIPEA (2.44 ml, 14 mmol). The reaction solution was stirred at 115°c for 96 hours. The crude reaction solution was purified by prep HPLC to give purified fractions that was combined and neutralized with solid $NaHCO_3$. The resulting solution was extracted with ethyl acetate (2x300ml). The combined organic layers were washed with water (60 ml) and brine (60 ml), then dried over Na_2SO_4 and evaporated *in vaccuo* to give (1R,2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol (1.06 g, 3.81 mmol) as an ivory solid. ES/MS *m/z* 279.1(MH^+).

Step 2. Preparation of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol.

To the solution of (1R, 2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol (1.06 g, 3.81 mmol) in 16 ml of DCM was added 1 M boron tribromide in DCM (8 ml, 8 mmol) slowly at 0°c. The reaction solution was stirred at room temperature for 2 hours. Removal of all solvent *in vaccuo*, followed by quenching with water (ca. 30ml) and diluted $NaHCO_3$ solution, and extraction of aqueous phase with ethyl acetate (3x100ml) and drying of combined organic extracts over Na_2SO_4 and subsequent removal of ethyl acetate *in vaccuo* yielded the desired product (1.16 g) as pink solid. The residue was purified by flash

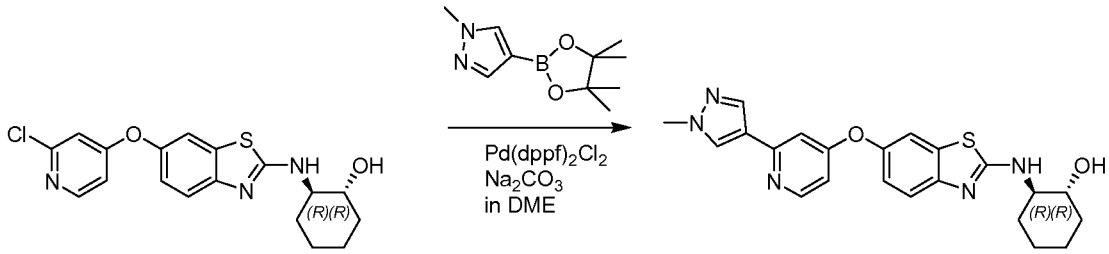
column chromatography to give 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (1.0 g, 3.78 mmol) as brown solid. ES/MS *m/z* 265.1(MH^+).

Step 3. Preparation of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (265 mg, 1 mmol) and cesium carbonate (651 mg, 2 mmol) in 3 ml of NMP was added 2-chloro-4-fluoropyridine(263 mg, 2 mmol). The reaction mixture was stirred at 60°c for 20 hours. The crude reaction mixture was filtered and then purified on prep HPLC to give (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as powder (341 mg, 0.9 mmol). ES/MS *m/z* 376.0(MH^+).

Example 174

Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol



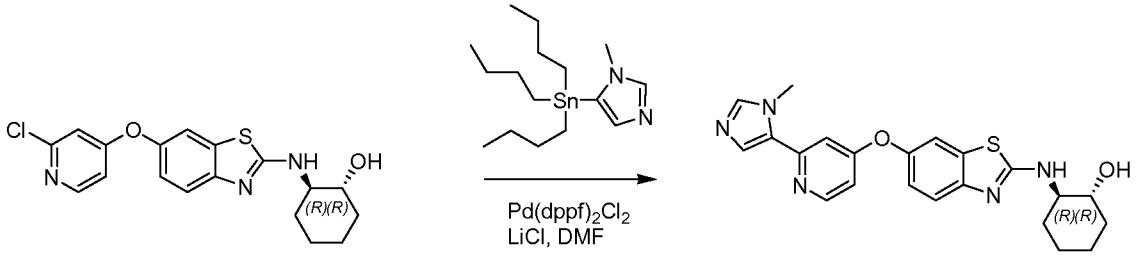
Step 4. Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (20 mg, 40 μmol) in 400 μL of DME, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (21 mg, 100 μmol), $Pd(dppf)_2Cl_2$ (4 mg, 5 μmol) and 2M Na_2CO_3 (100 μL, 200 μmol) were added. The reaction mixture was stirred at 90°c for 24hours. The reaction mixture was poured into 10 ml of saturated $NaHCO_3$ solution and extracted with ethyl acetate (2x30ml). The combined organic layers were washed with water (2x10ml) and brine (20 ml), then dried over Na_2SO_4 and evaporated *in vaccuo* to give a brown solid (65 mg) that was purified on prep HPLC to give (1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as powder (6.4 mg). ES/MS *m/z* 422.2(MH^+).

Example 175

Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:



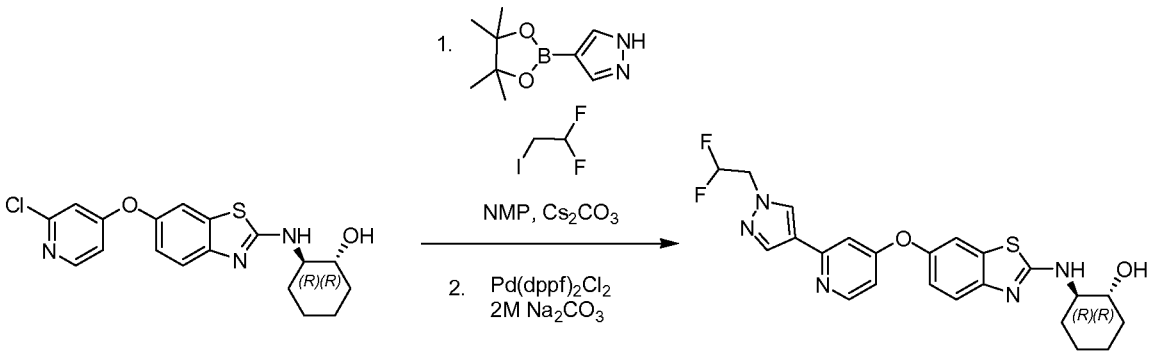
Preparation of (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (11 mg, 0.029 mmol) in 0.5 ml of DMF was added $Pd(dppf)_2Cl_2$ (7.2 mg, 0.0088 mmol), LiCl (19 mg, 0.44 mmol) and then 1-methyl-5-(tributylstannyl)-1H-imidazole (44 mg, 0.117 mmol). The reaction solution was stirred at 105-110 °C for 18 hours or done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.5 mg). ES/MS *m/z* 422.1(MH^+).

Example 176

Preparation of (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:



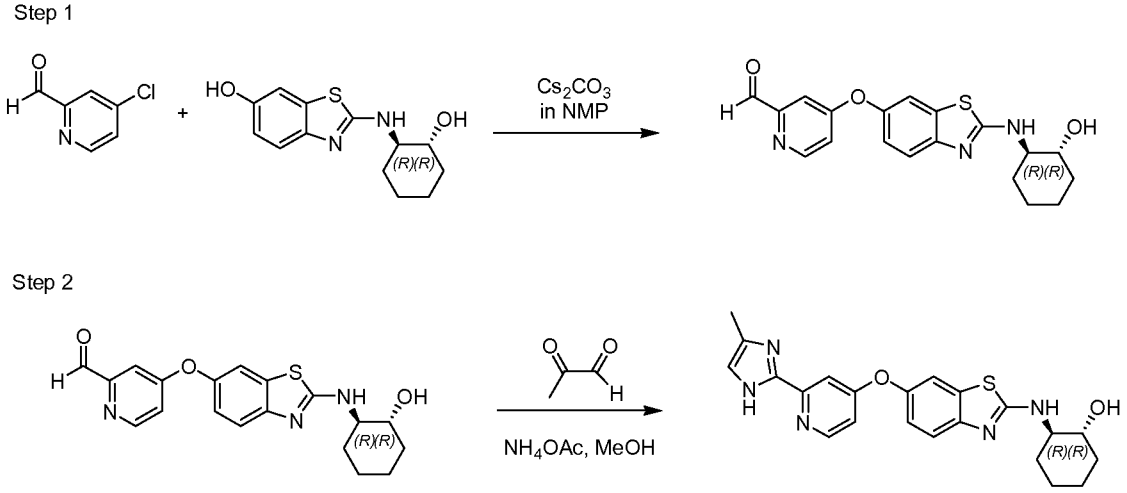
Preparation of (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (210 mg, 1.08 mmol) in 2.0 ml of NMP was added Cesium Carbonate (672 mg, 2.06mmol). The reaction mixture was stirred for 5 minutes and then 1,1-difluoro-2-iodoethane (197 mg, 1.03 mmol) was added and stirred at RT for 40hours. From the above crude reaction mixture remove (0.8 ml, 0.432 mol) and use. (The remaining 1.2 ml was stored in freezer). To the 0.8 ml reaction mixture add (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (20 mg, 0.053 mmol), $Pd(dppf)_2Cl_2$ (15.2 mg, 0.019 mmol) and 2M Na_2CO_3 (0.150 ml, 0.3 mmol). The reaction mixture was microwaved at 140 °C for 720 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (4.6 mg). ES/MS *m/z* 472.0 (MH^+).

Example 177

Preparation of (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde.

To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (90 mg, 0.34 mmol) in 1.9 ml of NMP was added Cesium Carbonate (232 mg,

0.71mmol) and 4-chloropicolinaldehyde (125 mg, 0.883 mmol). The reaction mixture was stirred at RT. for 10 minutes and then microwaved at 150 °C for 750 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde as TFA salt (88 mg). ES/MS *m/z* 388.1(MH^+) as the hydrate (+18).

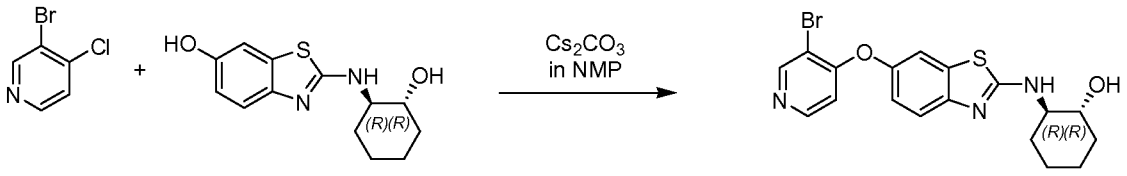
Step 2. Preparation of (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde (16 mg, 0.041 mmol) in 0.75 ml of MeOH was added ammonium acetate (32 mg, 0.41 mmol) and 2-oxopropanal 40% wt solution of in water (0.037 ml, 0.21 mmol). The reaction mixture was stirred at 70 °C for 2 hours. The crude reaction mixture was concentrated, re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.2 mg). ES/MS *m/z* 422.1 (MH^+).

EXAMPLE 178

Preparation of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:



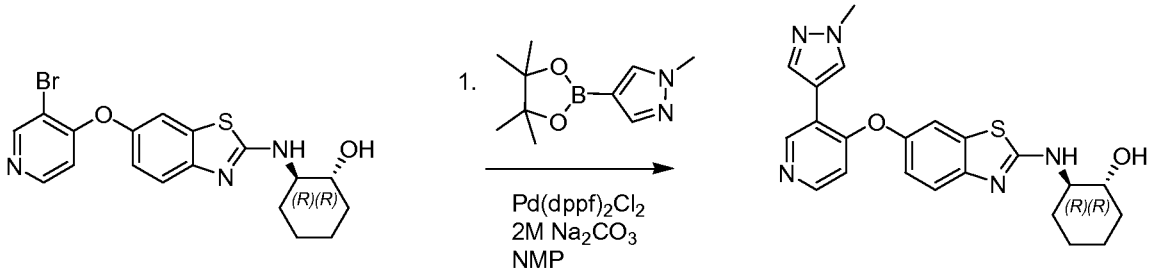
Preparation of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (12.5 mg, 0.047 mmol) in 0.4 ml of NMP was added Cesium Carbonate (39 mg, 0.118mmol) and stirred at RT for 1-3 minutes. To this mixture was added 3-bromo-4-chloropyridine (18.2 mg, 0.094 mmol). The reaction mixture was stirred at 90 °C for 4 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (9.2 mg). ES/MS *m/z* 420.1/422.0 (MH^+).

EXAMPLE 179

Preparation of (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:



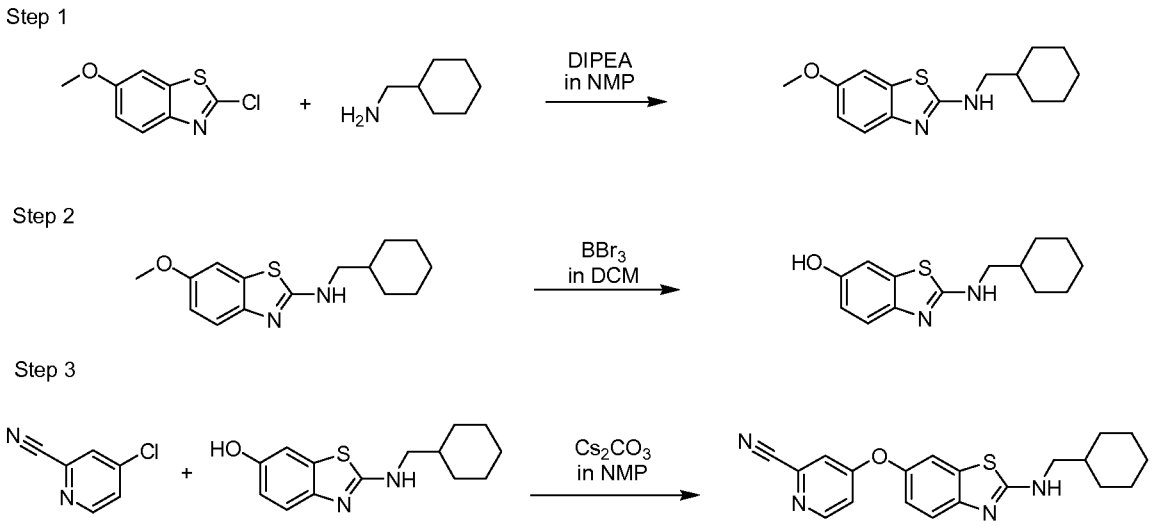
Preparation of (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (15 mg, 0.036 mmol) in 0.5 ml of NMP was added $Pd(dppf)_2Cl_2$ (8.8 mg, 0.0107 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (30 mg, 0.143 mmol) and 2M Na_2CO_3 (0.12 ml, 0.24 mmol). The reaction solution was stirred at 105-110 °C for 2 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (5.5 mg). ES/MS *m/z* 422.1(MH^+).

EXAMPLE 180

Preparation of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine.

To the solution of 2-chloro-6-methoxybenzo[d]thiazole (900 mg, 4.5 mmol) in 4.5 ml of NMP was added cyclohexylmethanamine (865 mg, 7.65 mmol) and DIPEA (1.57 ml, 9.0 mmol). The reaction solution was stirred at 105-110 °C for 66 hours. The reaction was worked up by adding 250 ml ethyl acetate and washed with 2 x 60 ml of saturated $NaHCO_3$, 3 x 60 ml water, 1 x 60 ml saturated NaCl, dried with sodium sulfate, filtered and concentrated *in vaccuo* to give N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine as solid (1.18 grams). ES/MS *m/z* 277.1(MH^+).

Step 2. Preparation of 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol.

To the solution of N-(cyclohexylmethyl)-6-methoxybenzo[d]thiazol-2-amine (1.40 g, 5.05 mmol) in 12 ml of DCM was added 1 M boron tribromide in DCM (10.6 ml, 10.6 mmol) slowly over about 3 minutes at 0 °C. The reaction solution was stirred at 0 °C for 20 min and then at RT. for 2 hr. The reaction mixture was concentrated to a solid. To the residual solids add 200 ml of ethyl acetate and 50 ml of water and stir at RT. for 10 minutes. With stirring, carefully add excess solid $NaHCO_3$ until basic. Stir at RT. about 1 hour to dissolve the solids. Remove the aqueous layer and extract with 100 ml of ethyl acetate. Combine organic layers and wash with 1 x 30 ml water, 1 x 25 ml saturated NaCl solution and dry with sodium sulfate. This mixture was filter through a silica gel plug (1.25 in. x 3 in.) and flushed with ethyl acetate. The filtrate was concentrated under reduced pressure to give 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol as solid (1.32 grams). ES/MS *m/z* 263.1(MH^+).

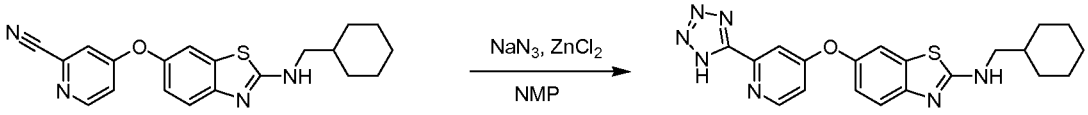
Step 3. Preparation of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile.

To the reaction mixture of 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol (18 mg, 0.068 mmol) in 0.4 ml of NMP was added Cesium Carbonate (56 mg, 0.171mmol) and stirred at RT for 1-3 minutes. To this mixture was added 4-chloropicolinonitrile (19 mg, 0.136 mmol). The reaction mixture was stirred at 60 °C for 5 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile as TFA salt (9.8 mg). ES/MS *m/z* 365.1(MH^+).

EXAMPLE 181

Preparation of 6-(2-(1H-tetrazol-5-yl)pyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



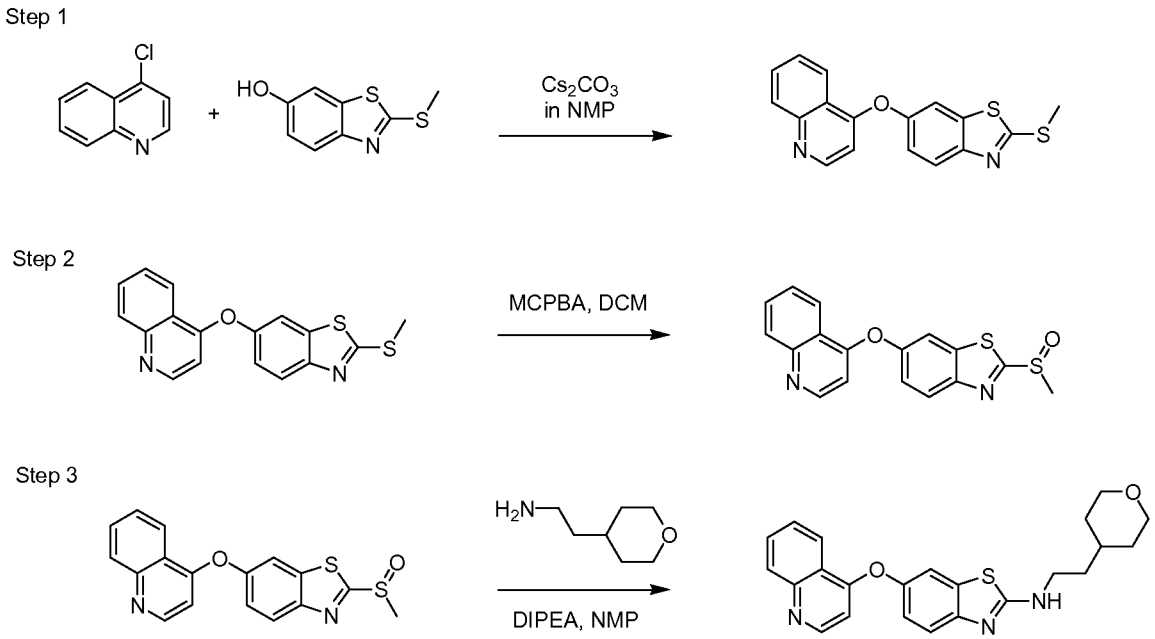
Preparation of 6-(2-(1H-tetrazol-5-yl)pyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine.

To the reaction mixture of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile (20 mg, 0.055 mmol) in 0.6 ml of NMP was added $ZnCl_2$ (37 mg, 0.274 mmol) and sodium azide (35.5mg, 0.55 mmol). The reaction solution was microwaved at 170 °C for 800 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 6-(2-(1H-tetrazol-5-yl)pyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine as TFA salt (6.6 mg). ES/MS *m/z* 408.2(MH^+).

EXAMPLE 182

Preparation of 6-(quinolin-4-yloxy)-N-(2-(tetrahydro-2H-pyran-4-yl)ethyl)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 2-(methylthio)-6-(quinolin-4-yloxy)benzo[d]thiazole.

To the reaction mixture of 2-(methylthio)benzo[d]thiazol-6-ol (750 mg, 3.79 mmol) in 10 ml of NMP was added Cesium Carbonate (3.2 g, 9.5 mmol) and stirred at RT for 3 minutes. To this mixture was added 4-chloroquinoline (682 mg, 4.17 mmol). The reaction mixture was stirred at 110 °C for 24 hours. The reaction was worked up by adding 250 ml ethyl acetate and washed with 75 ml of saturated $NaHCO_3$, 2 x 60 ml water, 1 x 50 ml saturated NaCl, dried with sodium sulfate, filtered and concentrated in vacuo. The resulting solid residue was purified by silica gel column chromatography, eluted with (40% EtOAc: 60% Hexanes) and concentrated *in vaccuo* to give 2-(methylthio)-6-(quinolin-4-yloxy)benzo[d]thiazole as solid (980 mg). ES/MS *m/z* 325.1(MH^+).

Step 2. Preparation of 2-(methylsulfinyl)-6-(quinolin-4-yloxy)benzo[d]thiazole.

The reaction mixture of 2-(methylthio)-6-(quinolin-4-yloxy)benzo[d]thiazole (460 mg, 1.415 mmol) was dissolved in 8 ml of DCM and cooled to –5°C. A solution was made of 77% MCPBA (333 mg, 1.486 mmol) and 6 ml of DCM. This solution was added to above cooled reaction mixture dropwise over 3-4 minutes. The reaction was stirred at –5 °C for 10 minutes, stirred at RT. for 90 minutes. The reaction followed by LC indicated 95% completed and stalled. A new solution was made of 77% MCPBA (25 mg, 0.1132 mmol) and 1 ml of DCM. This solution was added to above RT. reaction mixture dropwise. The reaction was stirred for 90 minutes more with LC indicating the reaction was complete. The reaction was worked up by adding 80 ml of DCM and 25 ml of a 10% sodium thiosulfate solution and stirred at RT. for 10 minutes. Aqueous layer was extracted and the DCM layer

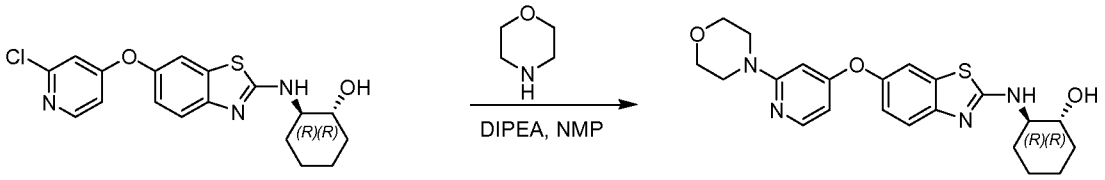
was washed with 25 ml of saturated $NaHCO_3$, 2 x 25 ml 5% $NaHCO_3$ solution, 1 x 25 ml water, 1 x 25 ml saturated NaCl, dried with sodium sulfate. About 1 gram of Silica gel was added and stirred for 10 minutes. The mixture was filtered and concentrated *in vaccuo* to give 2-(methylsulfinyl)-6-(quinolin-4-yloxy)benzo[d]thiazole as solid (357 mg). ES/MS *m/z* 341.0(MH^+).

Step 3. Preparation of 6-(quinolin-4-yloxy)-N-(2-(tetrahydro-2H-pyran-4-yl)ethyl)benzo[d]thiazol-2-amine.

To the reaction mixture of 2-(methylsulfinyl)-6-(quinolin-4-yloxy)benzo[d]thiazole (11.5 mg, 0.034 mmol) in 0.4 mL of NMP was added (DIPEA) diisopropylethylamine (15uL, 0.084 mmol) and 2-(tetrahydro-2H-pyran-4-yl)ethanamine (17.4 mg , 0.134 mmol). The reaction mixture was stirred at 100 °C for 20 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 6-(quinolin-4-yloxy)-N-(2-(tetrahydro-2H-pyran-4-yl)ethyl)benzo[d]thiazol-2-amine as TFA salt (5.1 mg). ES/MS *m/z* 406.1 (MH^+).

EXAMPLE 183

Preparation of (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol



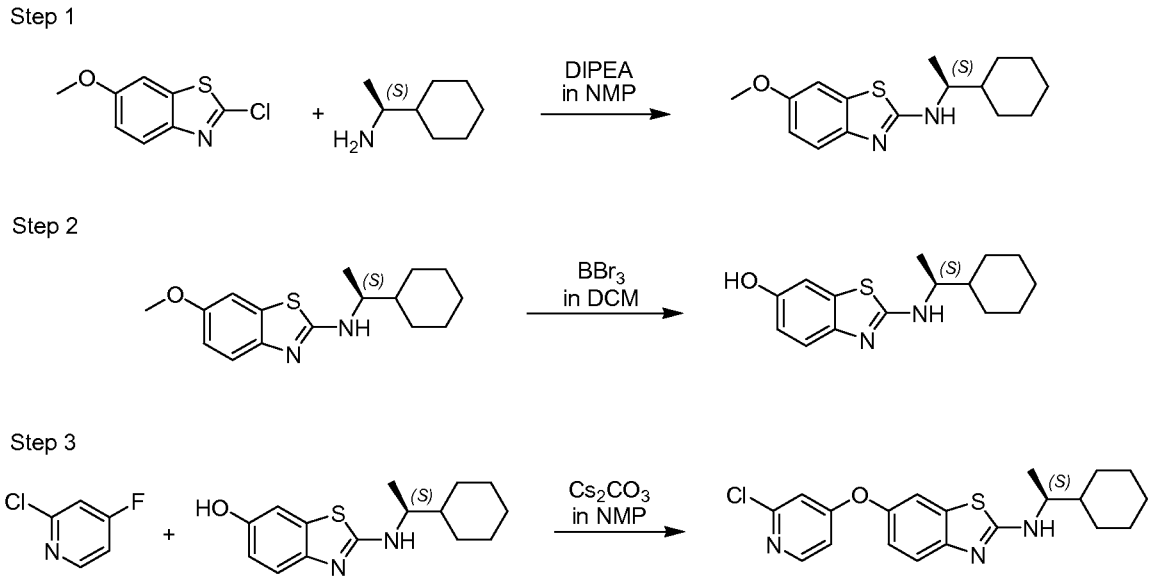
Preparation of (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (14 mg, 0.037 mmol) in 0.4 ml of NMP was added (DIPEA) diisopropylethylamine (13ul, 0.074 mmol) and morpholine (49 mg , 0.558 mmol). The reaction mixture was stirred at 110 °C for 48 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (3.7 mg). ES/MS *m/z* 427.1(MH^+).

Example 184

(S)-6-(2-chloropyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-N-(1-cyclohexylethyl)-6-methoxybenzo[d]thiazol-2-amine.

To the solution of 2-chloro-6-methoxybenzo[d]thiazole (2.0 g, 10 mmol) in 10 ml of NMP was added (S)-1-cyclohexylethanamine (2.3 g, 18 mmol) and DIPEA (3.5 ml, 20 mmol). The reaction solution was stirred at 110°C for 96 hr. The reaction was worked up by adding 170 ml ethyl acetate and washed with 1 x 60 ml of saturated $NaHCO_3$, 1 x 60 ml 5% $NaHCO_3$ solution, 1 x 60 ml water, 1 x 60 ml saturated NaCl, dried with sodium sulfate, filtered and concentrated *in vaccuo* to give (S)-N-(1-cyclohexylethyl)-6-methoxybenzo[d]thiazol-2-amine as crude solid (3.39 grams). ES/MS *m/z* 291.1(MH^+).

Step 2. Preparation of (S)-2-(1-cyclohexylethylamino)benzo[d]thiazol-6-ol.

To the solution of (S)-N-(1-cyclohexylethyl)-6-methoxybenzo[d]thiazol-2-amine (3.39 g, 10 mmol) in 30 ml of DCM was added 1 M boron tribromide in DCM (20 ml, 20 mmol) slowly at 0 °C. The reaction solution was stirred at 0 °C then at RT for 2 hr. The reaction mixture was concentrated to a solid. To the residual solids add 400 ml of ethyl acetate and 90 ml of water and stir at RT. for 10 minutes. With stirring, carefully add excess solid $NaHCO_3$ until basic. Stir at RT about 1 hour to dissolve the solids. Remove the aqueous layer and extract with 100 ml of ethyl acetate. Combine organic layers and wash with 1 x 50 ml water, 1 x 50 ml saturated NaCl solution, dry with sodium sulfate, filter and concentrate under reduced pressure. The resulting solid was purified by silica gel

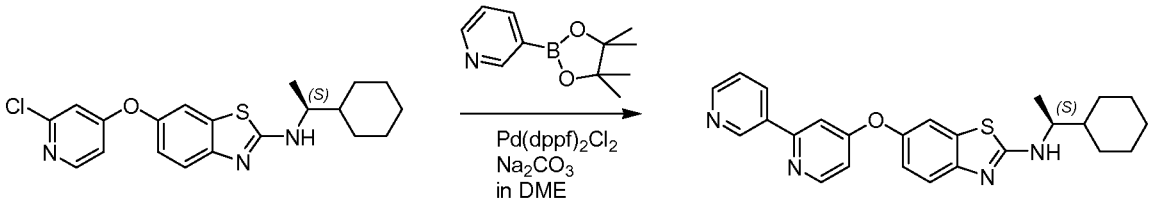
column chromatography, eluted with (30% EtOAc: 70% Hexanes) and concentrated *in vaccuo* to give (S)-2-(1-cyclohexylethylamino)benzo[d]thiazol-6-ol as solid (2.0 grams). ES/MS *m/z* 277.1(MH^+).

Step 3. Preparation of (S)-6-(2-chloropyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine.

To the mixture (S)-2-(1-cyclohexylethylamino)benzo[d]thiazol-6-ol (270 mg, 0.974mmol) and cesium carbonate (794 mg, 2.44 mmol) in 3.6 ml of NMP was added 2-chloro-4-fluoropyridine(254 mg, 1.95 mmol). The reaction mixture was stirred at 60°c for 18 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (S)-6-(2-chloropyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine as TFA salt (298 mg). ES/MS *m/z* 388.1(MH^+).

Example 185

Preparation of (S)-6-(2,3'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine



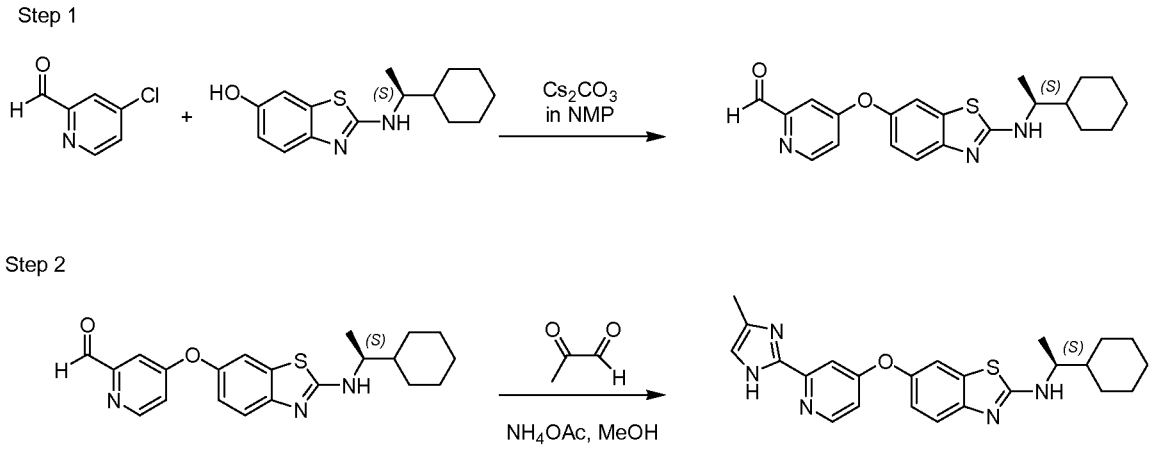
Preparation of (S)-6-(2,3'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine.

To the reaction mixture of (S)-6-(2-chloropyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine (15 mg, 0.039 mmol) in 0.6 ml of DME, 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (32 mg, 0.155 mmol), $Pd(dppf)_2Cl_2$ (7.9 mg, 0.0096 mmol) and 2M Na_2CO_3 (0.18 ml, 0.36 mmol) were added. The reaction solution was stirred at 100-105 °C for 90 minutes or until done by LC. The crude reaction mixture was concentrated to solid, re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give (S)-6-(2,3'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine as TFA salt (5.2 mg). ES/MS *m/z* 431.2(MH^+).

Example 186

(S)-N-(1-cyclohexylethyl)-6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde.

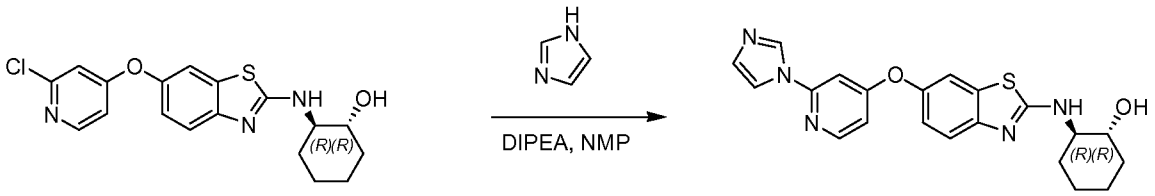
To the reaction mixture of (S)-2-(1-cyclohexylethylamino)benzo[d]thiazol-6-ol (110 mg, 0.40 mmol) in 2.0 ml of NMP was added Cesium Carbonate (272 mg, 0.834 mmol) and 4-chloropicolinaldehyde (146 mg, 1.03 mmol). The reaction mixture was stirred at RT. for 20 minutes and then microwaved at 150 °C for 750 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde as TFA salt (105 mg). ES/MS *m/z* 400.2(MH^+) as the hydrate (+18).

Step 2. Preparation of (S)-N-(1-cyclohexylethyl)-6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine.

To the reaction mixture of (S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde (15 mg, 0.038 mmol) in 0.6 ml of methanol was added ammonium acetate (29 mg, 0.38 mmol) and 2-oxopropanal 40% wt solution of in water (0.034 ml, 0.19 mmol). The reaction mixture was stirred at 70 °C for 2 hours. The crude reaction mixture was concentrated to solid, re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give (S)-N-(1-cyclohexylethyl)-6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine as TFA salt (6.5 mg). ES/MS *m/z* 434.2(MH^+).

EXAMPLE 187

Preparation of (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

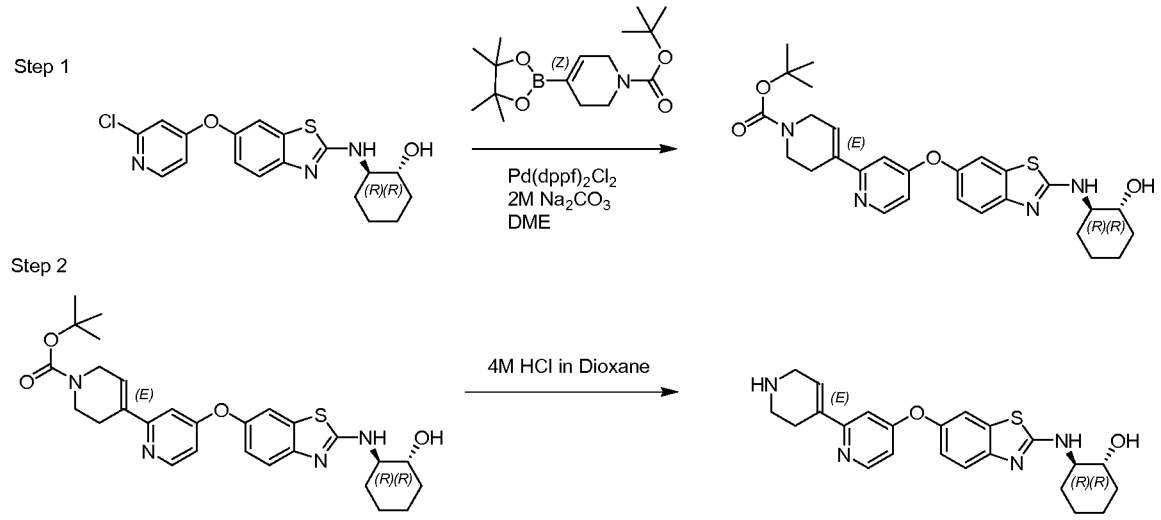


Preparation of (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (12 mg, 0.032 mmol) in 0.55 ml of NMP was added (DIPEA) diisopropylethylamine (17ul, 0.096 mmol) and 1H-imidazole (180 mg , 2.64 mmol). The reaction mixture was followed by LC, LCMS and microwaved as follows: (150 °C for 750 seconds, 230 °C for 750 seconds, 250 °C for 1000 seconds, again at 250 °C for 1000 seconds). The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (1.4 mg). ES/MS *m/z* 408.2(MH^+).

Example 188

Preparation of (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol



Step 1. Preparation of tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (11 mg, 0.029 mmol) in 0.5 ml of DME, tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (36 mg, 0.117 mmol), $Pd(dppf)_2Cl_2$ (7.2 mg, 0.0088 mmol) and 2M Na_2CO_3 (0.125 ml, 0.25 mmol) were added. The reaction solution was stirred at 105-110 °C for 24 hours or until done by LC. The crude reaction mixture was concentrated to solid re-dissolved in 0.8 ml DMF, filtered, purified on prep HPLC and lyophilized to give tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate as TFA salt (2.5 mg). ES/MS *m/z* 523.1(MH^+).

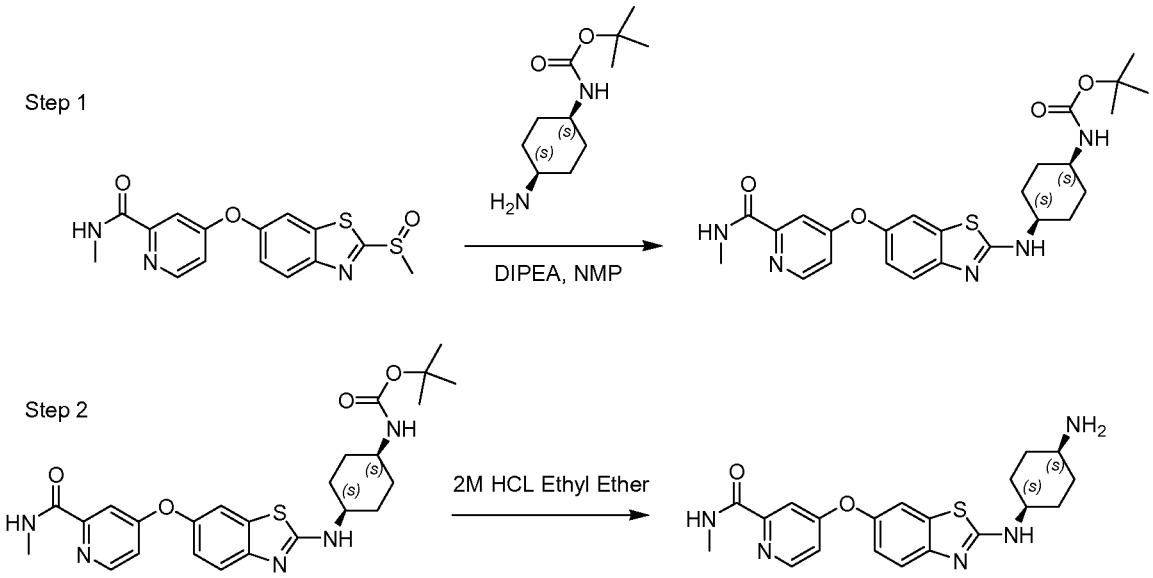
Step 2. Preparation of (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the solid of tert-butyl 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.5 mg, 0.0039 mmol) was added 4M HCL in Dioxane (1 ml, 4.0 mmol). The reaction mixture was stirred at RT for 45 minutes. The crude reaction mixture was concentrated to solid and lyophilized to give (1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as HCl salt (1.4 mg). ES/MS *m/z* 423.1(MH^+).

Example 189

Preparation of 4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below



Step 1. Preparation of tert-butyl (1s,4s)-4-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexylcarbamate.

To the reaction mixture of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (15 mg, 0.043 mmol) in 0.4 ml of NMP was added tert-butyl (1s,4s)-4-aminocyclohexylcarbamate (47 mg, 0.215 mmol) and (DIPEA) diisopropylethylamine (22ul, 0.129 mmol). The reaction mixture was stirred at 105-100 °C for 20 hr or until done by LC. The crude reaction solution was purified by prep HPLC and lyophilized to give tert-butyl (1s,4s)-4-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexylcarbamate (16 mg) as TFA salt. ES/MS *m/z* 498.2(MH^+).

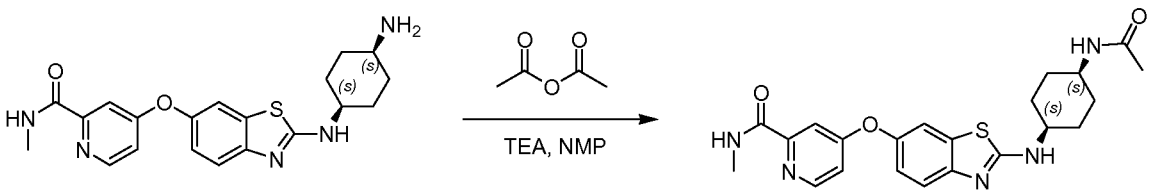
Step 2. Preparation of 4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide.

To the solid of tert-butyl (1s,4s)-4-(6-(2-(methylcarbamoyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexylcarbamate (16mg, 0.032 mmol) was added 2M HCL in Ethyl Ether (2 ml, 4.0 mmol). The reaction mixture was stirred at RT for 60 minutes. The crude reaction mixture was concentrated to solid and lyophilized to give 4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide as HCl salt (12.0 mg). ES/MS *m/z* 398.1(MH^+).

Example 190

Preparation of 4-(2-((1s,4s)-4-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below



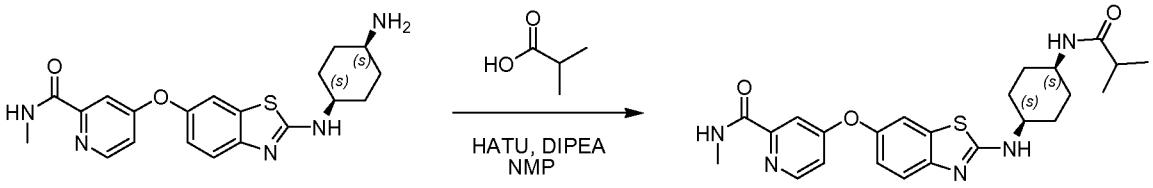
Preparation 4-(2-((1s,4s)-4-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide.

To the reaction mixture of 4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (9.0 mg, 0.0226 mmol) in 0.6 ml of NMP was added (TEA) triethylamine (19ul, 0.136 mmol) and then acetic anhydride (7.0 mg, 0.0678 mmol). The reaction mixture was stirred at RT. for 90 minutes. The crude reaction solution was purified by prep HPLC and lyophilized to give 4-(2-((1s,4s)-4-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (8.7 mg) as TFA salt. ES/MS *m/z* 440.2(MH^+).

Example 191

Preparation of 4-(2-((1s,4s)-4-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

The subject compound was prepared according to the general Scheme below:



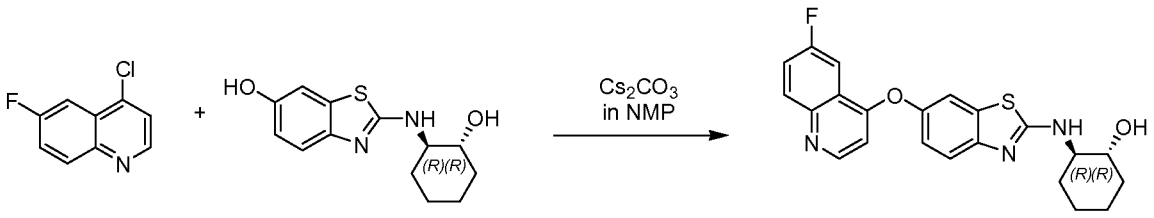
Preparation 4-(2-((1s,4s)-4-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide.

To the reaction mixture of isobutyric acid (4.4 mg, 0.050 mmol) in 0.3 ml of NMP was added HATU (17.1 mg, 0.045 mmol) and then (DIPEA) diisopropylethylamine (11ul, 0.0625 mmol). The reaction mixture was stirred at RT. for 10-15 minutes. To the above reaction mixture was added a solution of 4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (10 mg, 0.025 mmol) and (DIPEA) diisopropylethylamine (13ul, 0.075 mmol) in 0.3 ml of NMP. The reaction solution was stirred at RT. for 18 hours. The crude reaction solution was purified by prep HPLC and lyophilized to give 4-(2-((1s,4s)-4-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (4.0 mg) as TFA salt. ES/MS *m/z* 468.3(MH^+).

Example 192

Preparation of (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol

The subject compound was prepared according to the general Scheme below:

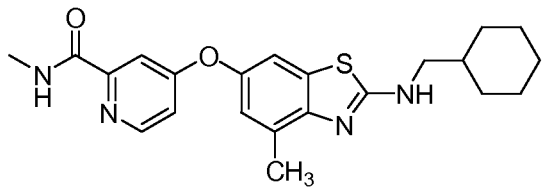


Preparation of (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

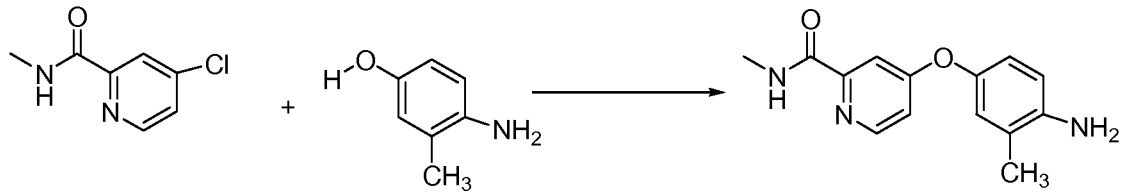
To the reaction mixture of2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (15.1 mg, 0.057 mmol) in 0.4 ml of NMP was added Cesium Carbonate (47 mg, 0.143 mmol) and stirred at RT for 1-3 minutes. To this mixture was added 4-chloro-6-fluoroquinoline (21 mg, 0.114 mmol). The reaction mixture was stirred at 105-110 °C for 18 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (9.2 mg). ES/MS *m/z* 410.1(MH^+).

Example 193

4-(2-(cyclohexylmethylamino)-4-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide

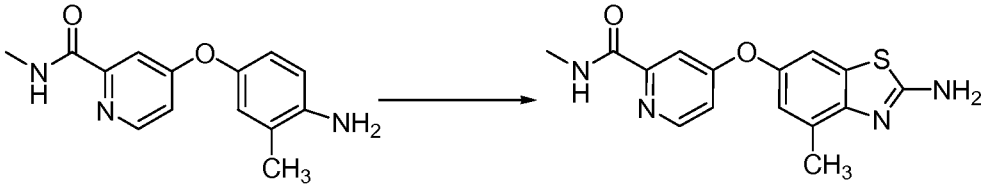


Step 1. Synthesis of 4-(4-amino-3-methylphenoxy)-N-methylpicolinamide



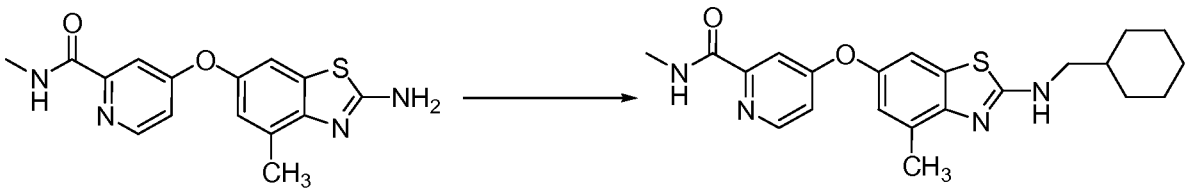
To the solution of 4-amino-m-cresol (125mg, 1.01mmol, 1.0eq) in 1mL of NMP was added 4-chloro-N-methylpicolinamide (189mg, 1.11mmol, 1.1eq) and cesium carbonate (658mg, 2.02mmol, 2.0eq) at room temperature. The reaction mixture was stirred at 75^{0}C for 12 hours, thereafter the mixture was diluted with water (ca. 50mL) and aqueous layer extracted with ethyl acetate (ca.50mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give sufficiently pure crude product which was carried to next step without further purification. LC/MS (m/z) [258.1] (MH^+).

Step 2. Synthesis of 4-(2-amino-4-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide



To the solution of 4-(4-amino-3-methylphenoxy)-N-methylpicolinamide (25mg, 0.097mmol, 1.0eq) in 1mL of cold acetic acid was added ammonium thiocyanate (11mg, 0.145mmol, 1.5eq). After stirring for a few minutes, bromine (6µL, 0.116mmol, 1.2eq) was injected dropwise and reaction stirred at room temperature for 3 hours. Thereafter, reaction was quenched with $NaHCO_3$ saturated solution (ca.10mL) and extracted with ethyl acetate (ca. 25mL X3), combined organic extracts were dried over sodium sulfate and condensed under reduced pressure to give sufficiently pure crude product which was carried to next step without further purification. LC/MS (m/z) [315.1] (MH^+).

Step 3. Synthesis of 4-(2-(cyclohexylmethylamino)-4-methylbenzo[d]thiazol-6-yloxy) methyl picolinamide

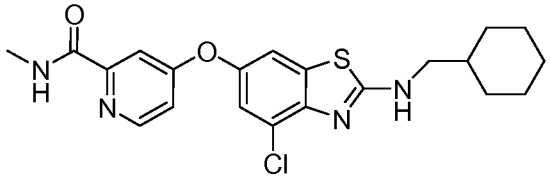


To the solution of 4-(2-amino-4-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide (30mg, 0.095mmol, 1.0eq) in 1mL of NMP was added bromomethyl

cyclohexane (20μL, 0.142mmol, 1.5eq) and potassium carbonate (40mg, 0.285mmol, 3.0eq) at room temperature. The reaction mixture was stirred at 80^0C for 12 hours and thereafter purified via reverse phase HPLC. LC/MS (m/z) [411.1] (MH^+)

Example 194

4-(4-chloro-2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



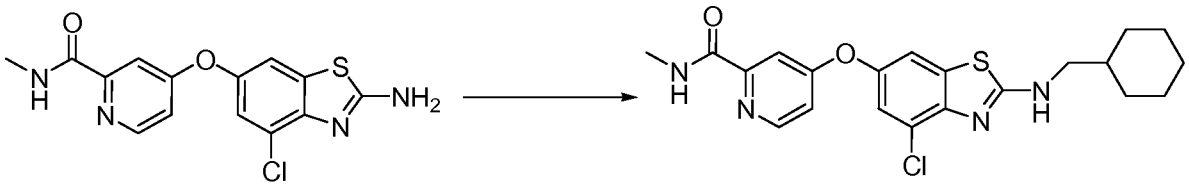
Step 1. Synthesis of 4-(4-amino-3-chlorophenoxy)-N-methylpicolinamide

Prepared following the procedure outlined in Step 1 of Example 1. LC/MS (m/z) [278.1] (MH^+)

Step 2. Synthesis of 4-(2-amino-4-chlorobenzo[d]thiazol-6-yloxy)-N-methylpicolinamide

Prepared following the procedure outlined in Step 2 of Example 1. LC/MS (m/z) [335.0] (MH^+)

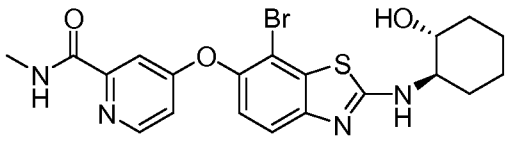
Step 3. Synthesis of 4-(4-chloro-2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



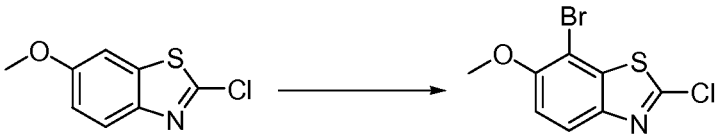
To the solution of 4-(2-amino-4-chlorobenzo[d]thiazol-6-yloxy)-N-methylpicolinamide (30mg, 0.089mmol, 1.0eq) in 2mL of NMP was added bromomethyl cyclohexane (18μL, 0.134mmol, 1.5eq) and potassium carbonate (36mg, 0.267mmol, 3.0eq) at room temperature. The reaction mixture was stirred at 80^0C for 2 hours and thereafter purified via reverse phase HPLC. LC/MS (m/z) [431.0] (MH+)

Example 195

4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

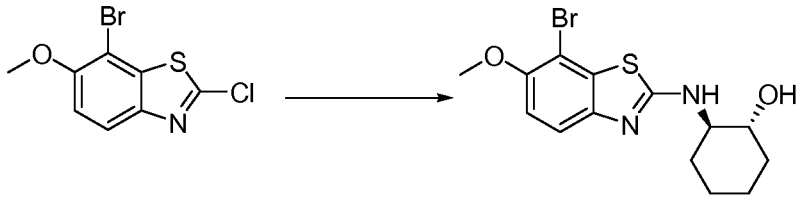


Step 1. Synthesis of 7-bromo-2-chloro-6-methoxybenzo[d]thiazole



To the solution of 2-chloro-6-methoxy-benzothiazole (200mg, 1.0mmol, 1.0eq) in 5mL of NMP was added N-bromosuccinimide (213mg, 1.20mmol, 1.2eq) at room temperature. The reaction mixture was stirred at 75^{0}C for >24 hours with subsequent addition of NBS in small batches for reaction progress, thereafter the mixture was diluted with water (ca. 100mL) and aqueous layer extracted with ethyl acetate (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure. Purification on ISCO using gradient 0%-50% ethyl acetate-hexane gave 336 mg of product as off white fluffy powder in 60% yields structure of which was confirmed by H^+NMR. LC/MS (m/z) [279.9] (MH^+)

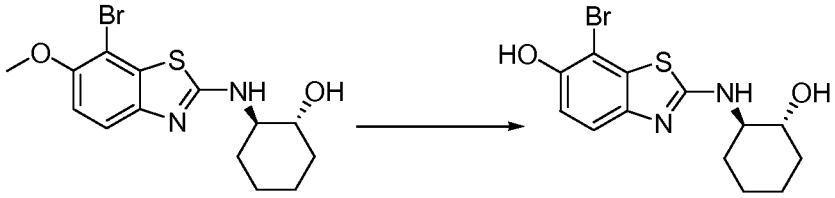
Step 2. Synthesis of (1R,2R)-2-(7-bromo-6-methoxybenzo[d]thiazol-2ylamino)cyclohexanol



To the solution of 7-bromo-2-chloro-6-methoxybenzo[d]thiazole (150mg, 0.539mmol, 1.0eq) in 1mL of NMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (0.123mg, 0.809mmol, 1.5eq) and DIPEA (263µL, 1.503 mmol, 2.8 eq) at room temperature. The reaction mixture was stirred at 125^{0}C for 12 hours, thereafter the mixture was diluted with saturated sodium bicarbonate solution (ca. 100mL) and aqueous

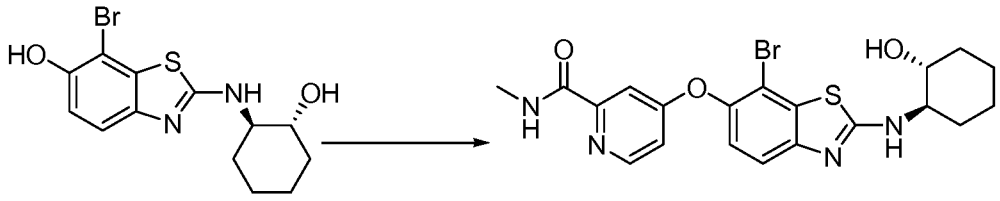
layer extracted with ethyl acetate (ca. 200mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give crude product as brown oil which was sufficiently pure and was carried to next step without further purification. LC/MS (m/z) [359.0] (MH^+)

Step 3. Synthesis of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)-benzo[d]thiazol-6-ol



To the solution of (1R,2R)-2-(7-bromo-6-methoxybenzo[d]thiazol-2-ylamino) cyclohexanol (191mg, 0.537mmol, 1.0eq) in 10mL of DCM was added 1 M solution of boron tribromide (ca.3.0mL, 2.68 mmol, 5.0eq) at room temperature. The reaction mixture was refluxed for 12 hours, thereafter the mixture was diluted with saturated sodium bicarbonate (ca. 100mL) till PH=7 and aqueous layer extracted with ethyl acetate (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give sufficiently pure crude product which was carried to next step without further purification LC/MS (m/z) [345.0] (MH^+).

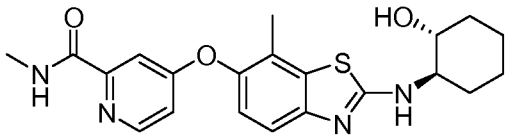
Step 4. Synthesis of 4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



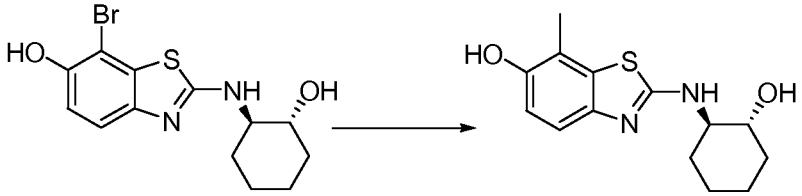
To the solution of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (50mg, 0.145mmol, 1.0eq) in 1mL of NMP was added 4-chloro-N-methylpicolinamide (29mg, 0.174mmol, 1.2eq) and cesium carbonate (165mg, 0.507mmol, 3.5eq) at room temperature. The reaction mixture was stirred at 80^0C for ca.12 hours, thereafter the mixture was purified on the reverse phase HPLC. LC/MS (m/z) [479.0] (MH^+)

Example 196

4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide

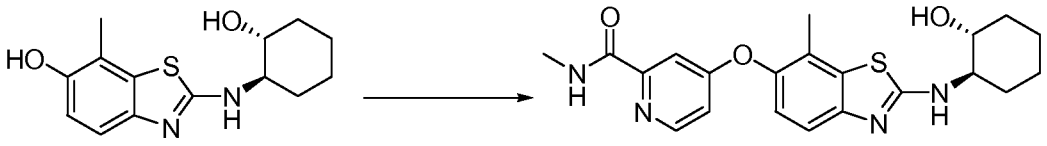


Step 1. Synthesis of 2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-ol



To the solution of 7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (117mg, 0.34 mmol, 1.0eq) in 1mL DMF in a microwave vial was added trimethylboraxine (128mg, 1.02 mmol, 3.0eq) , $Pd(Cl_2)dPPf$ (27mg, 0.034mmol, 0.1eq) and 1mL of 2M Na_2CO_3 solution at room temperature. Thereafter, the reaction mixture was heated in the microwave at 120^0C for 15 minutes. The reaction was quenched with saturated $NaHCO_3$ solution (25ml) and the aqueous phase extracted with ethyl acetate (50mLX3), combined organic layers dried over Na_2SO_4, filtered and condensed under reduced pressure. Purification over ISCO using a gradient of 0%-18% methanol-DCM gave 17 mg of product as brownish powder in 17% yield. LC/MS (m/z) [279.1] (MH^+)

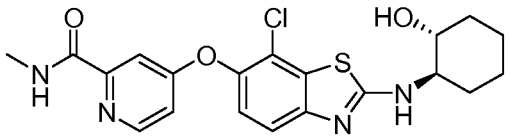
Step 2. Synthesis of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo-[d]thiazol-6-yloxy)-N-methylpicolinamide



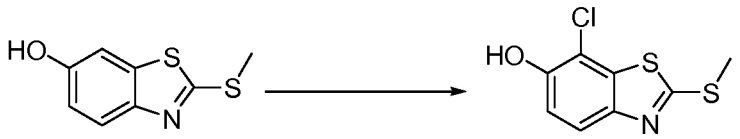
Prepared following the procedure in example 543 step 4. LC/MS (m/z) [413.1] (MH^+)

Example 197

4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide

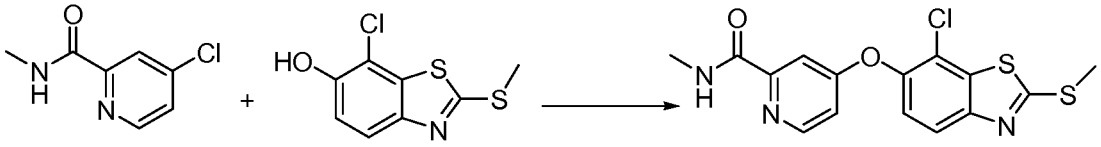


Step 1. Synthesis of 7-chloro-2-(methylthio)benzo[d]thiazol-6-ol



To the solution of 2-(methylthio)benzo[d]thiazol-6-ol (500mg, 2.53mmol, 1.0eq) in 10mL of NMP was added N-chlorosuccinimide (507mg, 3.80mmol, 1.5eq) at room temperature. The reaction mixture was stirred at room temperature for 1 hour thereafter the mixture was diluted with saturated sodium bicarbonate solution (ca. 100mL) and aqueous layer extracted with DCM (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure. Purification on ISCO using gradient 0%-100% ethyl acetate-hexane gave 283.39 mg of product in 48% yields structure of which was confirmed by H^+NMR. LC/MS (m/z) [232.0] (MH^+)

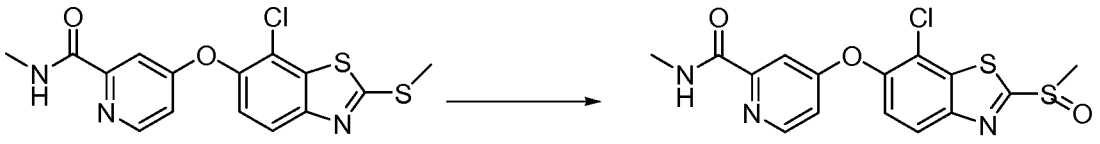
[0001] Step 2. Synthesis of 4-(7-chloro-2-(methylthio)benzo[d]thiazol-6-yloxy)-N methyl picolinamide



To the solution of 7-chloro-2-(methylthio)benzo[d]thiazol-6-ol (80mg, 0.346mmol, 1.0eq) in 1mL of NMP was added 4-chloro-N-methylpicolinamide (88mg, 0.519mmol, 1.5eq) and cesium carbonate (281mg, 0.865mmol, 2.5eq) at room temperature. The reaction mixture was stirred at 85^0C for >48 hours till ca. 75%-80% completion, thereafter the mixture was diluted with water (ca. 50mL) and aqueous layer extracted with ethyl acetate (ca. 50mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give crude product which was purified on ISCO using

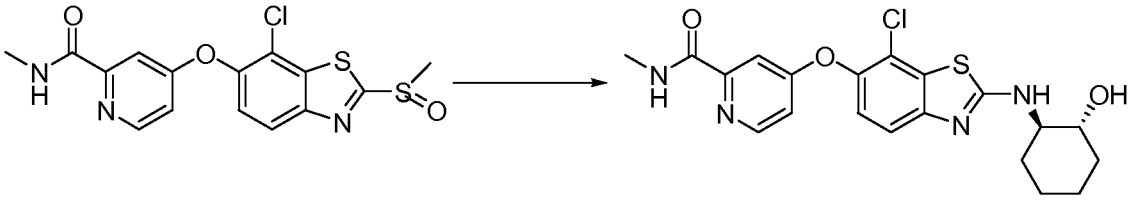
gradient 0%-100% ethyl acetate-hexane mixture to give 64 mg of product in 50% yield. LC/MS (m/z) [366.0] (MH^+)

Step 3. Synthesis of 4-(7-chloro-2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



To the solution of 4-(7-chloro-2-(methylthio)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (64mg, 0.175mmol, 1.0eq) in 5 mL of DCM was added MCPBA (33mg, 0.192 mmol, 1.1eq) at 0^0C and reaction stirred for 30-45min. Thereafter, it was quenched with water (10mL) and aqueous phase extracted with ethyl acetate (25mLX5), combined organic layers dried over sodium sulfate, filtered and condensed under reduced pressure to yield crude product which was sufficiently pure and was carried to next step without further purification. LC/MS (m/z) [382.0] (MH^+)

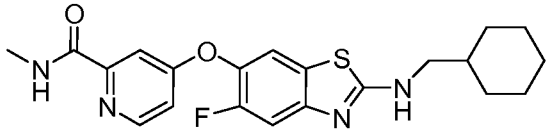
Step 4. Synthesis of 4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



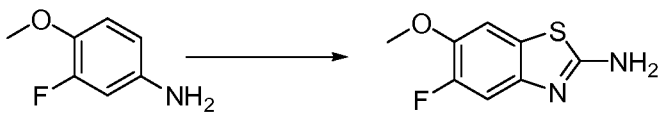
To the solution of 4-(7-chloro-2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)-Nmethylpicolinamide (10mg, 0.026mmol, 1.0eq) in NMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (6mg, 0.039mmol, 1.5eq) and DIPEA (13µL, 0.078mmol, 3.0eq) and reaction mixture heated at 160^0C in microwave for 15 min. Thereafter, the product was purified via reverse phase HPLC. LC/MS (m/z) [433.1] (MH^+)

Example 198

4-(2-(cyclohexylmethylamino)-5-fluorobenzo[d]thiazol-6-yloxy)-N-methylpicolinamide



Step 1. Synthesis of 5-fluoro-6-methoxybenzo[d]thiazol-2-amine



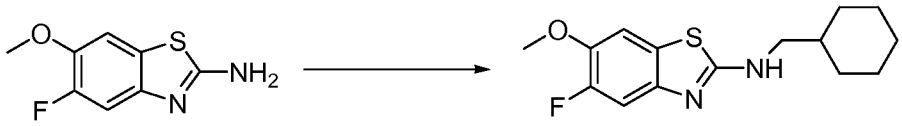
Reference used – "Synthesis and biological activity of α -[(6-chloro-5-fluoro-2 benzothiazolyl)amino]acetanilides". Pattan, S. R.; Narendra, Babu S. N.; Angadi, J. S. Dept. of Mechanical Chemistry, K.L.E.S's College of Pharmacy, Belg. Indian Drugs (2002), 39(10), 515-517.

To the solution of 3-fluoro-p-anisidine (1.00g, 7.09mmol, 1.0eq) in 30 mL of cold acetic acid was added ammonium thiocyanate (1.07g, 14.18 mmol, 2.0eq). After stirring for a few minutes, bromine (437µL, 8.50mmol, 1.2eq) in 6mL acetic acid was injected slowly dropwise through addition funnel and reaction stirred at room temperature for 3 hours. Thereafter, acetic acid was removed under reduced pressure and $NaHCO_3$ saturated solution (100mL) added to the residue which was extracted with ethyl acetate (125mLX3), combined organic extracts were dried over sodium sulfate and condensed under reduced pressure to give crude which was sufficiently pure and was carried to next step without further purification.

NMR (H^+) (DMSO)1H(d) 7.51, 7.48, 2H (s) 7.34, 1H (d) 7.17, 7.13, 3H (s) 3.78.

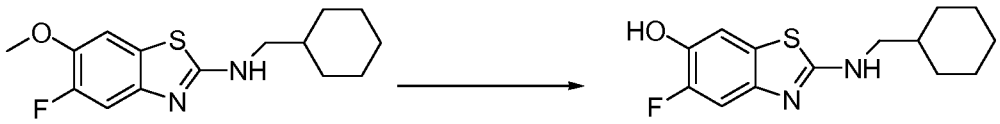
LC/MS (m/z) [199.0] (MH^+)

Step 2. Synthesis of N-(cyclohexylmethyl)-5-fluoro-6-methoxybenzo[d]thiazol-2-amine



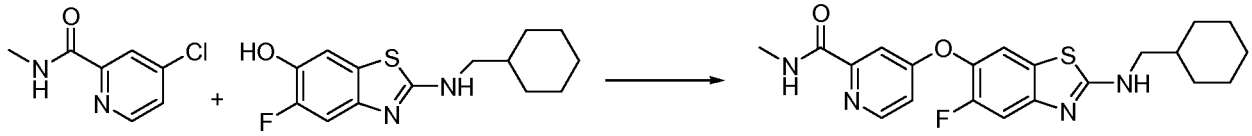
To the solution of 5-fluoro-6-methoxybenzo[d]thiazol-2-amine (350mg, 1.76mmol, 1.0 eq) in 2mL of NMP was added bromomethyl cyclohexane (370µL, 2.65mmol, 1.5eq) and potassium carbonate (366 mg, 2.65 mmol, 1.5eq) at room temperature. The reaction mixture was stirred at 80^0C for 24 hours with subsequent addition of reagents till reaction completion and thereafter quenched with saturated sodium bicarbonate solution (100mL) which was then extracted with ethyl acetate (125mLX3), combined organic layers dried over sodium sulfate, filtered and condensed under reduced pressure. Purification of the crude over ISCO using slow gradient of 0%-50% ethyl acetate-hexane gave 310 mg of product in 60%yield. LC/MS (m/z) [295.1] (MH+)

Step 3. Synthesis of 2-(cyclohexylmethylamino)-5-fluorobenzo[d]thiazol-6-ol



To the solution of N-(cyclohexylmethyl)-5-fluoro-6-methoxybenzo[d]thiazol-2-amine (114mg, 0.387mmol, 1.0eq) in 10mL of DCM was added 1M solution of boron tribromide (ca.1.0mL, 0.775 mmol, 2.0eq) at room temperature. The reaction mixture was stirred for 2 hours, thereafter the mixture was diluted with saturated sodium bicarbonate solution (ca. 100mL) till PH=7 and aqueous layer extracted with ethyl acetate (ca. 150mLX3). Combined organic layers were dried over sodium sulfate, filtered and condensed under reduced pressure to give crude product which was sufficiently pure and was carried to next step without further purification. LC/MS (m/z) [281.1] (MH^+)

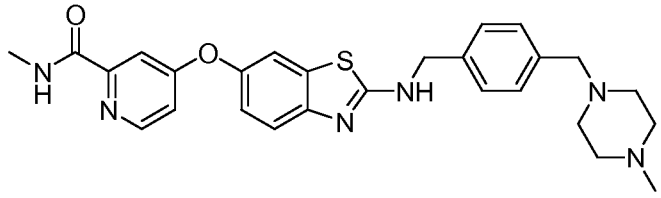
Step 4. Synthesis of 4-(2-(cyclohexylmethylamino)-5-fluorobenzo[d]thiazol-6-yloxy)-N-methylpicolinamide



To the solution of 2-(cyclohexylmethylamino)-5-fluorobenzo[d]thiazol-6-ol (25mg, 0.089mmol, 1.0eq) in 2mL of NMP was added 4-chloro-N-methylpicolinamide (18mg, 0.107mmol, 1.2eq) and cesium carbonate (86mg, 0.267mmol, 3.0eq) at room temperature. The reaction mixture was stirred at 85^0C for 12 hours, thereafter the mixture was purified on reverse phase HPLC giving 1.6mg of product as TFA salt in ca. 3.5% yield. LC/MS (m/z) [415.1] (MH^+)

Example 199

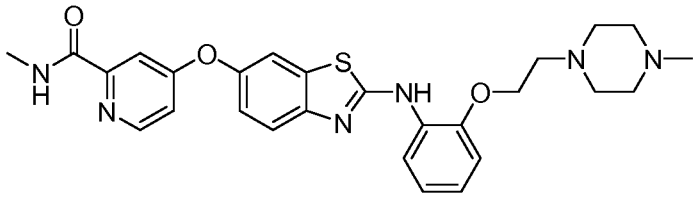
N-methyl-4-(2-(4-((4-methylpiperazin-1-yl)methyl)benzylamino)benzo[d]thiazol-6-yloxy)picolinamide



[0002] To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (25mg, 0.072 mmol, 1.0eq) in 2 mL of NMP was added (4-((4-methylpiperazin-1-yl)methyl) phenyl) methanamine (23mg, 0.108mmol, 1.5eq) and DIPEA (37µL, 0.216mmol, 3.0eq) and reaction mixture heated at 80^{0}C in oil bath for 12 hours. Thereafter, the product was purified via reverse phase HPLC. LC/MS (m/z) [503.1] (MH^+).

Example 200

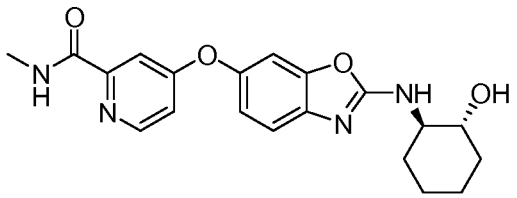
N-methyl-4-(2-(2-(2-(4-methylpiperazin-1-yl)ethoxy)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide



To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinamide (25mg, 0.072mmol,1.0eq) in 1 mL of IPA and 1 mL conc. HCl was added 2-(2-(4-methylpiperazin-1-yl)ethoxy) aniline (25mg, 0.108 mmol, 1.5eq) and reaction mixture heated at 80^{0}C in oil bath for 2 hours. Thereafter, the product was purified via reverse phase HPLC. This procedure was generalized for other analogues for which progress of the reaction was monitored by LC-MS and amount of aniline and reaction time adjusted as needed. LC/MS (m/z) [519.1] (MH^+)

Example 201

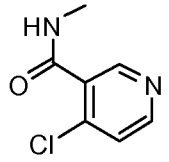
4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide



To the solution of N-methyl-4-(2-(methylsulfinyl)benzo[d]oxazol-6-yloxy)picolinamide (25mg, 0.075 mmol, 1.0eq) in 1 mL of NMP was added (1R,2R)-2-aminocyclohexanol hydrochloride (17mg, 0.112mmol, 1.5eq) and DIPEA (40µL, 0.225mmol, 3.0eq) and reaction mixture stirred at room temperature for 48 hours. Thereafter, the product was purified via reverse phase HPLC. LC/MS (m/z) [383.1] (MH^+)

Intermediates

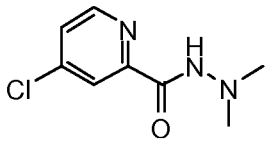
Synthesis of 4-chloro-*N*-methylpyridine-3-carboxamide



Step 1. To a suspension of 4-chloronicotinic acid (1.57 g, 10.0 mmol, 1.0 eq) in 25 mL of toluene was added thionyl chloride (1.8 mL, 25.0 mmol, 2.5 eq) at room temperature. The reaction mixture was stirred at 100°C for 3 hours. The mixture was concentrated under reduced pressure, dissolved in 25mL of toluene and concentrated again to give crude 4-chloronicotinoyl chloride hydrochloride salt, which was used in the next step without further purification.

Step 2. To a suspension of crude 4-chloronicotinoyl chloride hydrochloride in 25 mL of THF was added methylamine solution (2M in THF, 20 mL, 40 mmol, 4.0 eq) at 0°C. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The crude material was dissolved in ethylacetate (75 mL) and water/brine/saturated sodium bicarbonate solution (1/1/1, 75 mL). The separated aqueous layer was extracted with EtOAc. The combined organic layers were washed with water/brine/saturated sodium bicarbonate solution (1/1/1, 25 mL) and brine (25 mL) and dried over sodium sulfate. Removal of the solvent under reduced pressure afforded the title compound as orange solid (400 mg, 24%), which was used without further purification. MH+ = 171.0, Rt = 0.55min.

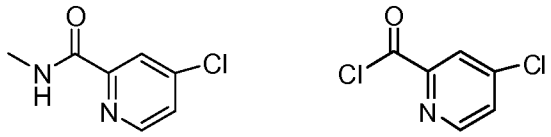
Synthesis of 4-chloro-*N*',*N*'-dimethylpyridine-2-carboxhydrazide



To a suspension of 4-chloropicolinoyl chloride hydrochloride (352 mg, 2.0 mmol, 1,0 eq) in 10 mL of THF were added *N*,*N*-dimethylhydrazine (120 mg, 2.0 mmol, 1.0 eq) and *N*,*N*-diisopropylethylamine (383 µL, 2.2 mmol, 1.1 eq) at room temperature. The reaction mixture was stirred for 15 min and diluted with water (25 mL) and EtOAc (50 mL). The separated organic layer was washed with brine (25mL), saturated sodium bicarbonate solution (25 mL) and dried over sodium sulfate. Concentration under reduced pressure gave

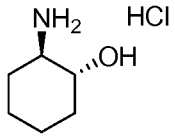
the title compound as colorless solid (223 mg, 56%), which was used without further purification. MH+ = 200, Rt = 1.42min.

Synthesis of 4-chloro-N-methylpicolinamide and 4-chloropicolinoyl chloride



Prepared following the method described in "A Scaleable Synthesis of BAY 43-9006: A Potent Raf Kinase Inhibitor for the treatment of cancer". Donald Bankston, Jacques Dumas, Reina Natero, Bernd Riedl, Mary-Katherine Monahan, Robert Sibley.; Bayer Research Center. Pharmaceutical Division. Organic Process Research and Development 2002 (6) 777-781.

Synthesis of (1R,2R)-2-aminocyclohexanol hydrochloride

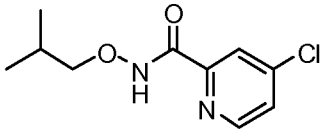


To an ice bath cooled solution of amine (1R,2R)-(-)-2-Benzyloxycyclohexylamine (20 g, 97.4 mmol) in dry MeOH (390 mL) was added 4.0 M HCl solution in dioxane (49 mL, 195 mmol) slowly via syringe. The ice bath was removed and resulting solution was sparged with N_2 for 10 min. 10 % Pd/C (3 g, 28 mmol) was added to the solution and the reaction was purged with H_2 and maintained under a H_2 atmosphere. After 4 h, an additional 10 mL of 4.0 M HCl solution in dioxane was added[2] and the reaction was maintained under a H_2 atmosphere overnight. Upon completion (followed by LCMS), the reaction was filtered through a thin, tightly packed pad of Celite and the collected solids were washed successively with MeOH and EtOAc. The combined organic filtrates were evaporated and dried under vacuum gave (1R,2R)-2-aminocyclohexanol hydrochloride as a pale-colored solid, (13.8 g, 91 mmol, 93%). LCMS *m/z* 116.0 (MH^+), t_R = 0.37 min.

(1S,2S)-2-aminocyclohexanol hydrochloride was prepared in the same manner.

Example 202

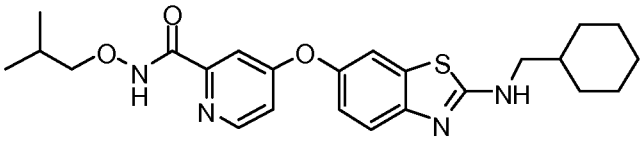
4-chloro-*N*-isobutoxypicolinamide



To a suspension of 4-chloropicolinoyl chloride hydrochloride (1.0 g, 5.68 mmol, 1.0 eq) in 25 ml of THF were added *O*-isobutylhydroxylamin hydrochloride (785 mg, 6.25 mmol, 1.1 eq) and *N*,*N*-diisopropylethylamine (2.97 ml, 17.0 mmol, 3.0 eq) at room temperature. The reaction mixture was stirred for 30 min and diluted with water (25 mL) and EtOAc (50 mL). The separated organic layer was washed with brine (25mL), saturated sodium bicarbonate solution (2x 25 mL) and dried over sodium sulfate. Concentration under reduced pressure gave the title compound as colorless solid (870 mg, 67%), which was used without further purification. ES/MS *m/z* 229.0 (MH^+), Rt = 2.61 min.

Example 203

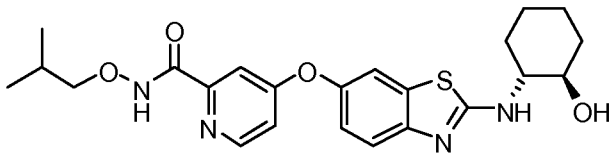
4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide



To the reaction mixture 2-(cyclohexylmethylamino)benzo[d]thiazol-6-ol (30 mg, 0.114 mmol)) and cesium carbonate (326 mg, 0.228 mmol) in 1.2 ml of DMF was added 4-chloro-*N*-isobutoxypicolinamide (40 mg, 0.171 mmol). The reaction mixture was stirred at rt for 10 min and then microwaved at 130 °C for 3x 20min. The crude reaction mixture was filtered, purified on preparative HPLC and lyophilized to give the title compound as its TFA salt as a white solid (15 mg, 23%). ES/MS *m/z* 455.1 (MH^+), Rt = 2.90 min.

Example 204

4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide

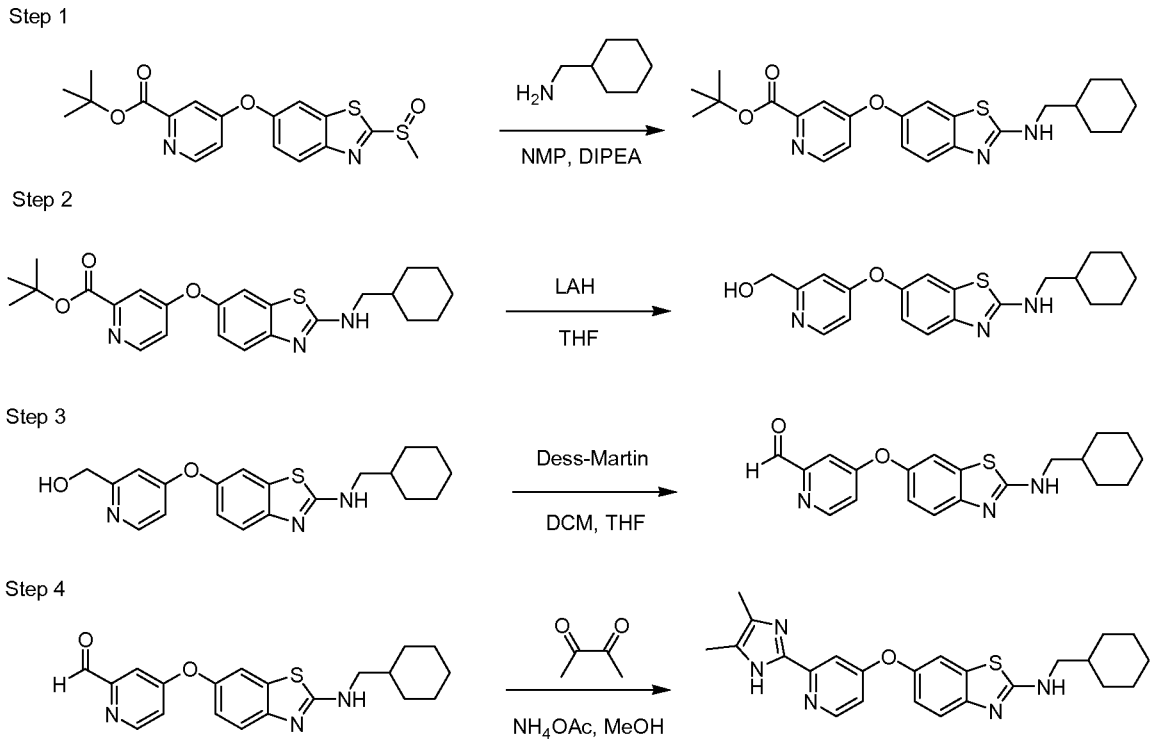


Prepared as in the preceeding example. ES/MS *m/z* 457.0 (MH^+), Rt = 2.35 min.

Example 205

N-(cyclohexylmethyl)-6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (1R,2R)-2-(6-methoxybenzo[d]thiazol-2-ylamino)cyclohexanol.

To the solution of tert-butyl 4-(2-(methylsulfinyl)benzo[d]thiazol-6-yloxy)picolinate (500 mg, 1.28 mmol) in 8.0 ml of NMP was added cyclohexylmethanamine (407 mg, 3.6 mmol) and DIPEA (0.887 ml, 5.12 mmol). The reaction solution was stirred at 110°C for 12 hours or until done by LCMS. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give tert-butyl 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinate as TFA salt (420 mg). ES/MS *m/z* 440.2 (MH^+).

Step 2. Preparation of (4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)methanol.

To the solution of tert-butyl 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinate (420 mg, 1.14 mmol) under argon in 50 ml of THF was added 1 M LAH solution in THF (3.41ml, 3.41 mmol) slowly at room temperature. The reaction mixture was stirred at room temperature for 30 minutes. The crude reaction mixture was worked up by carefully adding methanol (5 ml), then 6M NaOH (5 ml), and water (5 ml) with stirring at room temperature. The aluminum salts were allowed to precipitate out. Ethyl acetate (200 ml) was added and the organic layer was decanted off from salts. The salts were washed again with ethyl acetate (100 ml) and decanted. The organic layers were combined and washed with brine (2 x 50 ml), dried with Na_2SO_4, filtered and concentrated. The resulting solid residue was purified by silica gel column chromatography, eluted with (5%

methanol 95% DCM) and concentrated *in vaccuo* to give (4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)methanol as solid (157 mg). ES/MS *m/z* 370.2 (MH^+).

Step 3. Preparation of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde.

To the solution of (4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)methanol (30 mg, 0.081 mmol) in 2 ml of THF and 2 ml of DCM was added Dess-Martin Periodinane (38 mg, 0.089 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The crude reaction mixture diluted with ethyl acetate (60 ml), washed with saturated sodium bicarbonate (2 x 15ml), brine (1 x 15 ml), dried with Na_2SO_4, filter and concentrated *in vaccuo* to give 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde as solid (29 mg). ES/MS *m/z* 386.1(MH^+) as the hydrate (+18).

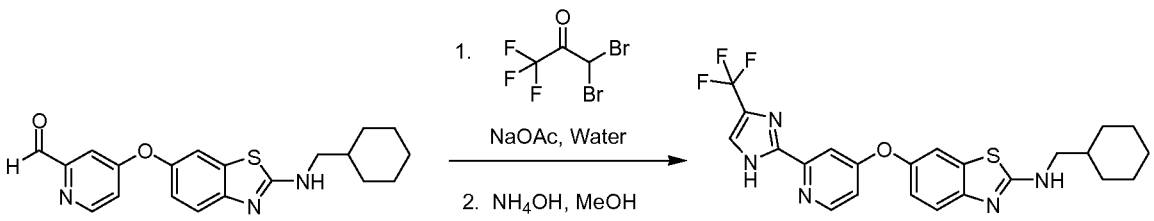
Step 4. Preparation of N-(cyclohexylmethyl)-6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine.

To the solution of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde (15 mg, 0.041 mmol) in 1.0 ml of methanol was added ammonium acetate (32 mg, 0.41 mmol) and biacetyl (14 mg, 0.163 mmol). The reaction mixture was stirred at 70 °C for 2 hours or until done by LCMS. The crude reaction mixture was concentrated to solid, re-dissolved in 0.8 ml NMP, filtered, purified on prep HPLC and lyophilized to give N-(cyclohexylmethyl)-6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine as TFA salt (3.0mg). ES/MS *m/z* 434.2 (MH^+).

Example 206

N-(cyclohexylmethyl)-6-(2-(4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

The subject compound was prepared according to the general Scheme below



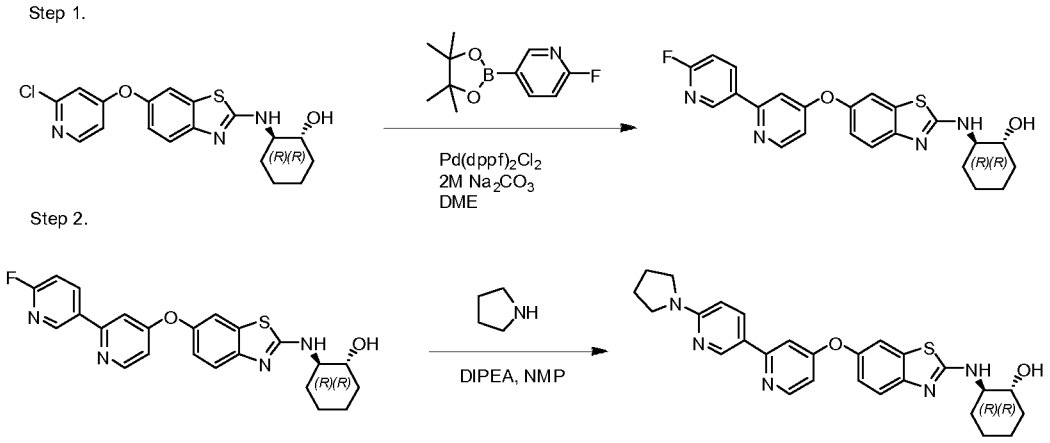
To the solution of sodium acetate (300 mg, 3.7 mmol) in 1.6 ml of water was added 3,3-dibromo-1,1,1-trifluoropropan-2-one (500 mg, 1.85 mmol). The reaction mixture was

stirred at 100 °C for 1 hour. From the above crude reaction mixture remove approximately (0.5 ml, 0.46 mol), cool to room temperature. This crude mixture was added to a solution of 4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinaldehyde (15 mg, 0.041 mmol) in 2 ml of methanol. To the crude reaction mixture was added ammonium hydroxide (28%-30%) solution (0.5 ml, 4 mmol). The reaction mixture was stirred at room temperature for 18 hours or until done by LCMS. The crude reaction mixture was concentrated to solid, re-dissolved in 0.8 ml NMP, filtered, purified on prep HPLC and lyophilized to give N-(cyclohexylmethyl)-6-(2-(4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine as TFA salt (3.0mg). ES/MS *m/z* 474.2 (MH^+).

Example 207

(1R,2R)-2-(6-(6'-(pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of (1R,2R)-2-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (130 mg, 0.345 mmol) in 5.0 ml of DME, 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (268 mg, 1.21 mmol), $Pd(dppf)_2Cl_2$ (56 mg, 0.069 mmol) and 2M Na_2CO_3 (1.05 ml, 2.1 mmol) were added. The reaction solution was stirred at 105 °C for 2 hours or until done by LC. The crude reaction mixture was

concentrated to solid, re-dissolved in 3 ml of DMF, filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (149 mg). ES/MS *m/z* 437.1 (MH^+).

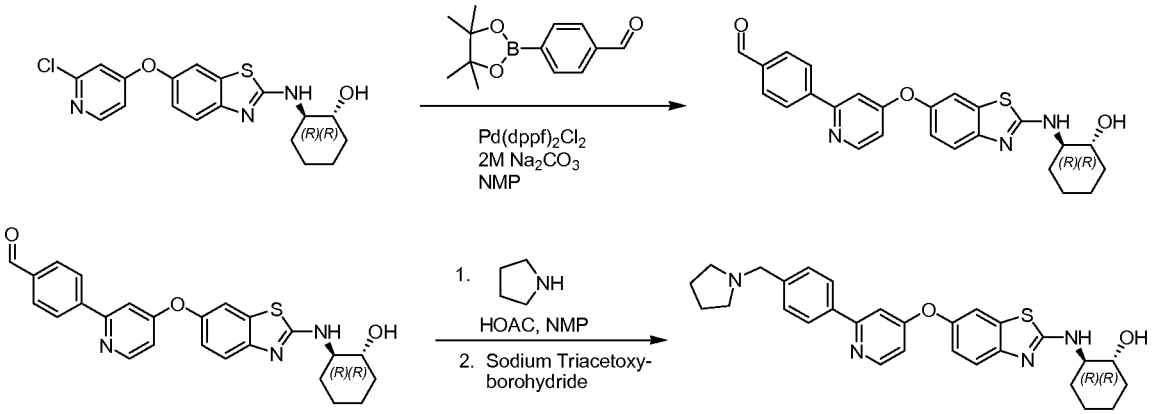
Step 2. Preparation of (1R,2R)-2-(6-(6'-(pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (11 mg, 0.0252 mmol) in 0.4 ml of NMP was added (DIPEA) diisopropylethylamine (13ul, 0.0756 mmol) and pyrrolidine (14.4 mg , 0.202 mmol). The reaction mixture was stirred at 105-110 °C for 20 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(6'-(pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (2.3 mg). ES/MS *m/z* 488.1 (MH^+).

Example 208

(1R,2R)-2-(6-(2-(4-(pyrrolidin-1-ylmethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)benzaldehyde.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (70 mg, 0.186 mmol) in 2.5 ml of NMP, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (130 mg, 0.558 mmol), $Pd(dppf)_2Cl_2$ (38 mg, 0.0465 mmol) and 2M Na_2CO_3 (0.56 ml, 1.12 mmol) were added. The reaction solution was stirred at 110 °C for 4 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(4-(2-((1R,2R)-2-

hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)benzaldehyde as TFA salt (61 mg). ES/MS *m/z* 446.0 (MH^+).

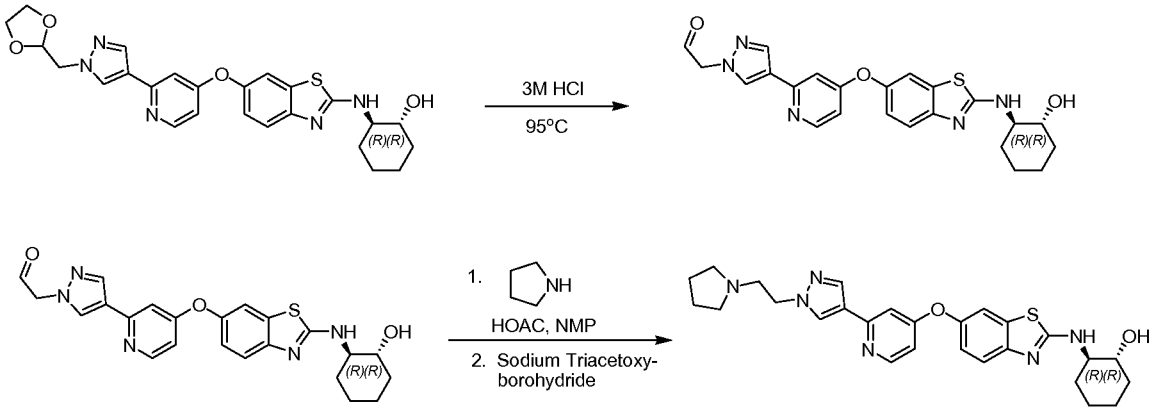
Step 2. Preparation of (1R,2R)-2-(6-(2-(4-(pyrrolidin-1-ylmethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of 4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)benzaldehyde (12 mg, 0.027 mmol) in 0.6 ml of NMP was added in order pyrrolidine (19.2 mg, 0.27 mmol), excess acetic acid (0.060 ml , 1.0 mmol) and triethyl orthoformate (20 mg, 0.135 mmol). The reaction mixture was stirred at room temperature for 20 minutes. To this reaction mixture was added sodium triacetoxyborohydride (14.3 mg, 0.0675 mmol). The reaction mixture was stirred at room temperature for 18 hours. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(4-(pyrrolidin-1-ylmethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (2.8 mg). ES/MS *m/z* 501.2 (MH^+).

Example 209

(1R,2R)-2-(6-(2-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 2-(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-1H-pyrazol-1-yl)acetaldehyde.

To the reaction solid of (1R,2R)-2-(6-(2-(1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (195 mg, 0.395 mmol) was added 3M HCl (6.0 ml, 18 mmol). The reaction solution was stirred at 95°C for 6 hours or until done by LC. The crude reaction mixture was lyophilized to solid and re-dissolved in 2

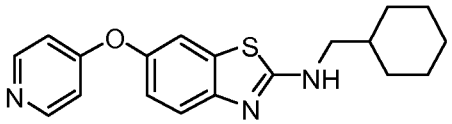
ml of water and 2ml of NMP, purified on prep HPLC and lyophilized to give 2-(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-1H-pyrazol-1-yl)acetaldehyde as TFA salt (50 mg). ES/MS *m/z* 468.2 (MH^+).

Step 2. Preparation of (1R,2R)-2-(6-(2-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of 2-(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-1H-pyrazol-1-yl)acetaldehyde (12.5 mg, 0.0267 mmol) in 0.5 ml of NMP was added pyrrolidine (19 mg, 0.267 mmol) and stirred for 10 minutes. To this reaction mixture was added excess acetic acid (0.070 ml , 1.16 mmol) and stirred for 20 minutes. To this reaction mixture was added sodium triacetoxyborohydride (13 mg, 0.0614 mmol). The reaction mixture was stirred at room temperature for 90 minutes. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (1.4 mg). ES/MS *m/z* 505.2 (MH^+).

Example 210

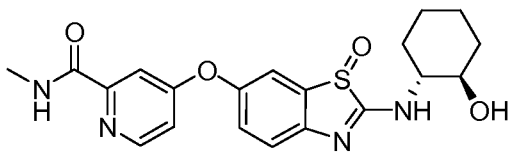
Preparation of N-(cyclohexylmethyl)-6-(pyridin-4-yloxy)benzo[d]thiazol-2-amine



To the solution of N-(cyclohexylmethyl)-6-(pyridin-4-yloxy)benzo[d]thiazol-2-amine (20 mg, 0.076 mmol, 1.0 eq) in NMP at room temperature was added cesium carbonate (61 mg, 0.190 mmol, 2.5 eq), 4-chloropyridine HCl (12.5 mg, 0.083 mmol, 1.1 eq) and DIPEA (33μL, 0.190 mmol, 2.5 eq) and reaction left stirring at 80°C for 72 hours. Thereafter, the product was isolated by preparative HPLC and pure fraction lyophilized to give the title compound as TFA salt (1.4 mg). ES/MS *m/z* 340.1 (MH^+).

Example 211

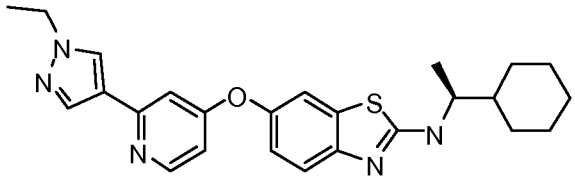
Preparation of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)-1-oxo-benzo[d]thiazol-6-yloxy)-N-methylpicolinamide



A solution of OXONE® ($KHSO_5$, 380 mg, mmol) in water (4 ml) was added dropwise to a solution of 4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide (25mg, mmol) in methanol (4 ml) at rt. After stirring for 23 hours the suspension is diluted with water (50 ml) and extracted with ethyl acetate (2x 10 ml). The combined organic layers were washed with brine, concentrated, and purified by prep HPLC to yield the title compound as white solid. Yield: 2.4 mg. ES/MS *m/z* 415.1 (MH^+), Rt = 1.81 min.

Example 212

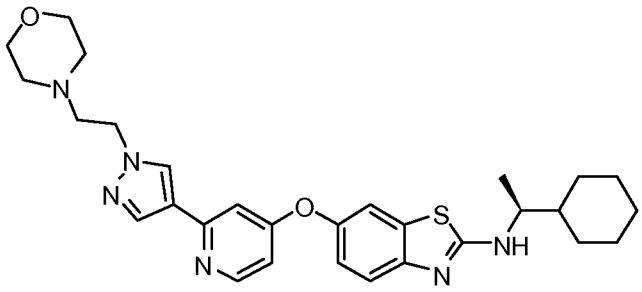
Preparation of (S)-N-(1-cyclohexylethyl)-6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine



Following the procedure for Example 176 (Table 3). The reaction mixture was heated at 110 °C for 3 hours and purified by prep HPLC to give the title compound. Yield: 13 mg. ES/MS *m/z* 448.1 (MH^+), Rt = 2.79 min.

Example 213

Preparation of (S)-N-(1-cyclohexylethyl)-6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine

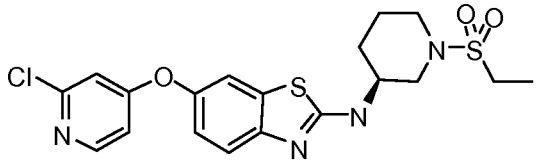


Following the procedure of Example 185 (Table 3), the crude material was firstly purified by prep HPLC and lyophilized. The residue was dissolved in ethyl acetate / saturated sodium bicarbonate solution (10 ml / 10 ml). The separated organic layer was dried over sodium sulfate, concentrated *in vacuo*, and purified by prep TLC using dichloromethane / methanol (95:5). The purified product was dissolved in acetonitrile (3 ml)

and 1N aqueous HCl (0.5 ml) and lyophilized to give the title compound as its HCl salt. Yield: 11 mg. ES/MS *m/z* 533.1 (MH^+), Rt = 2.14 min.

Example 214

Preparation of (S)-6-(2-chloropyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine



Step 1. Preparation of (S)-tert-butyl 3-(6-methoxybenzo[d]thiazol-2-ylamino)piperidine-1-carboxylate

To the solution of 2-chloro-6-methoxybenzo[d]thiazole (2.6 g, 13 mmol) in 25 ml of NMP was added (S)-tert-butyl 3-(6-methoxybenzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (5 g, 25 mmol) and DIPEA (2.6 ml, 15 mmol). The reaction solution was stirred at 100 °C for 7 days. The crude reaction solution was mixed with ethyl acetate (250ml) and diluted aqueous sodium bicarbonate solution (80 ml) and the organic phase was separated. The separated organic layer was washed with water (2x 60 ml) and brine (60 ml), then dried over sodium sulfate and evaporated *in vacuo* to give a brown oily product that was purified by flash chromatography over silica gel with ethyl acetate:hexane (35:65 – 50:50) to give (S)-tert-butyl 3-(6-methoxybenzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (3.33 g, 9.16 mmol) as an ivory solid. ES/MS *m/z* 364.2 (MH^+). Rt = 2.2 min.

Step 2. Preparation of (S)-6-methoxy-N-(piperidin-3-yl)benzo[d]thiazol-2-amine

To a solution of (S)-tert-butyl 3-(6-methoxybenzo[d]thiazol-2-ylamino)piperidine-1-carboxylate (3.35 g, 9.22 mmol) in methanol / dioxane (3 ml/ 3 ml) was added slowly 4M HCl in dioxane (60 ml, 240 mmol) [Caution: gas development!]. The reaction mixture was stirred 2.5 hours at ambient temperature and concentrated *in vacuo* in order to remove methanol and half of dioaxane. The residue was suspended in diethylether (50 ml). The solids were filtered off, washed with diethylether (50 ml) and dried *in vacuo* to give (S)-6-methoxy-N-(piperidin-3-yl)benzo[d]thiazol-2-amine as its hydrochloride salt as white solid. Yield: 4.29 g. ES/MS *m/z* 264.1 (MH^+), Rt = 1.62 min.

Step 3. Preparation of (S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-methoxybenzo[d]thiazol-2-amine

A mixture of (S)-6-methoxy-N-(piperidin-3-yl)benzo[d]thiazol-2-amine hydrochloride salt (2.0 g, 5.95 mmol), ethylsulfonyl chloride (1.13 ml, 11.91 mmol) and DIPEA (4.11 ml, 23.8 mmol) in NMP (25 ml) was heated at 55 °C for 16 hours 50 min. The reaction mixture was allowed to cool down to room temperature and diluted with water (150 ml) and ethyl acetate (150 ml). After stirring vigorously for 1 hour the separated organic layer was washed with water (3x 100 ml), saturated sodium bicarbonate solution (3x 100 ml), water (100 ml) and brine (100 ml) and dried over sodium sulfate. Concentration *in vacuo* and purification by flash chromatography over silica gel with ethyl acetate:hexane (20:80 – 100:0) provided (S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-methoxybenzo[d]thiazol-2-amine as tan solid. Yield: 1.22 g. ES/MS *m/z* 356.0 (MH^+), Rt = 2.12 min.

Step 4. Preparation of (S)-2-(1-(ethylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-ol

A solution of (S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-methoxybenzo[d]thiazol-2-amine (1.22 g, 3.43 mmol) in dichloromethane (25 ml) under nitrogen atmosphere was treated with boron tribromide (1M in dichloromethane, 7.5 ml) at 0 °C. Stirring was continued for 10 min at 0 °C and for ~135 min at ambient temperature. The reaction mixture was carefully diluted with water (50 ml), ethyl acetate (200 ml) and treated with solid sodium bicarbonate (until no further gas development was observed). The mixture was stirred until phases became clear. The separated organic phase was washed with saturated sodium bicarbonate solution (2x 75 ml), water (75 ml), brine (75 ml) and dried over sodium sulfate. Concentration *in vacuo* afforded crude (S)-2-(1-(ethylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-ol which was used in the next step without further purification. Yield: 1.15 g. ES/MS *m/z* 342.0 (MH^+), Rt = 1.86 min.

Step 5. Preparation of (S)-6-(2-chloropyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine

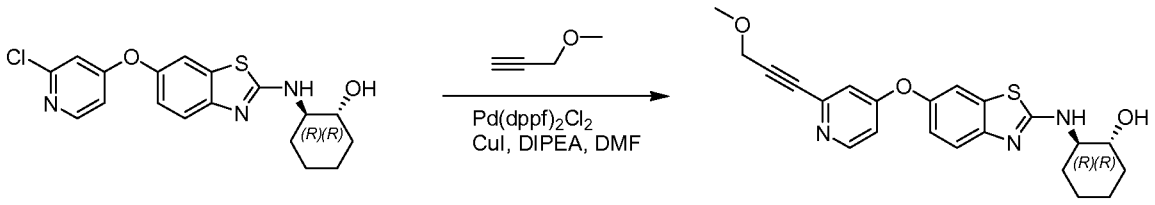
To a mixture of (S)-2-(1-(ethylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-ol (1.15 g, 3.37 mmol) and cesium carbonate (2.20 g, 6.74 mmole) in 12 ml of NMP was added 2-chloro-4-fluoropyridine (532 mg, 4.05 mmol). The reaction mixture was stirred at 60 °C for 17 hours. The reaction mixture was diluted with water (100 ml) and ethyl acetate (100 ml). The separated organic layer was washed with water (3x 50 ml), saturated sodium bicarbonate solution (3x 50 ml), water (50 ml), brine (100 ml) and dried over sodium

sulfate. Concentration *in vacuo* and purification by flash chromatography over silica gel with ethyl acetate:hexane (1:1 to 3:1) provided the title compound. Yield: 671 mg. ES/MS *m/z* 453.0 (MH^+), Rt = 2.59 min.

Example 215

(1R,2R)-2-(6-(2-(3-methoxyprop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

The subject compound was prepared according to the general Scheme below:



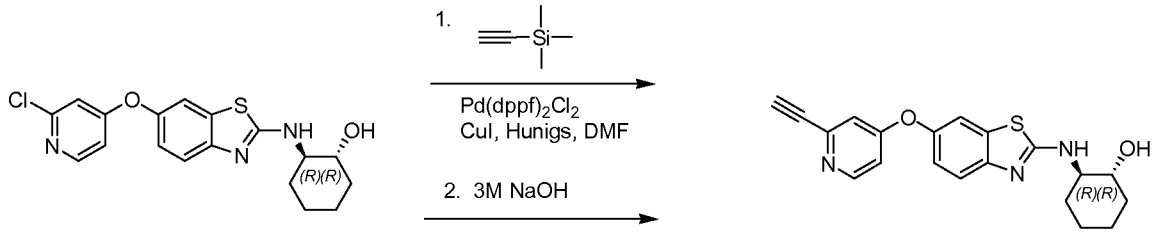
Preparation of (1R,2R)-2-(6-(2-(3-methoxyprop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (18.8 mg, 0.05 mmol) in 0.5 ml of DMF was added $Pd(dppf)_2Cl_2$ (8.2 mg, 0.01 mmol), CuI (4.3 mg, 0.0225 mmol), 3-methoxyprop-1-yne (15.8 mg, 0.225 mmol) and last add DIPEA (0.026 ml, 0.15 mmol). The reaction solution was stirred at 100 °C for 90 minutes or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-(3-methoxyprop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (9.2 mg). ES/MS *m/z* 410.1 (MH^+).

Example 216

(1R,2R)-2-(6-(2-ethynylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

The subject compound was prepared according to the general Scheme below:

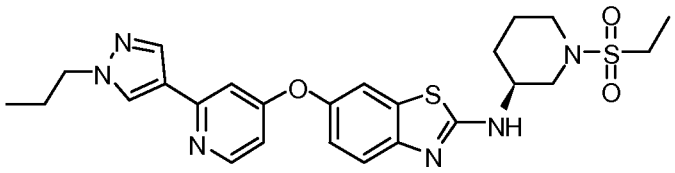


Preparation of (1R,2R)-2-(6-(2-ethynylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

To the reaction mixture of (1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol (16 mg, 0.043 mmol) in 0.5 ml of DMF was added $Pd(dppf)_2Cl_2$ (8.8 mg, 0.0108 mmol), CuI (4.5 mg, 0.024 mmol), ethynyltrimethylsilane (21.1 mg, 0.215 mmol) and last add DIPEA (0.023 ml, 0.129 mmol). The reaction solution was stirred at 100 °C for 90 minutes or until done by LC. To the crude reaction mixture a 3M NaOH solution (0.175 ml, 0.525mmol) was added. The crude reaction mixture was stirred at room temperature for 30 minutes or until done by LC. The thick crude reaction mixture was neutralize with excess acetic acid (0.085, 1.41 mmol) and 0.5 ml DMF was added. The mixture was stirred for 5 minutes, filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(2-ethynylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (4.6 mg). ES/MS *m/z* 366.1 (MH^+).

Example 217

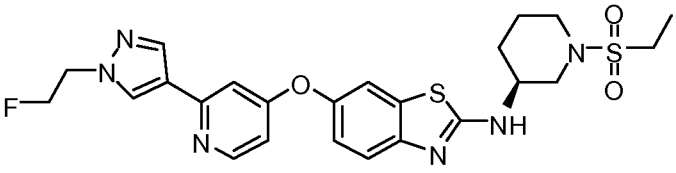
Preparation of (S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine



Following the procedure for Example 176. The reaction mixture was heated at 85 °C for 18 hours and at 90 °C for 24 hour. Purification by prep HPLC gave the title compound. Yield: 2.1 mg. ES/MS *m/z* 527.1 (MH^+), Rt = 2.24 min.

Example 218

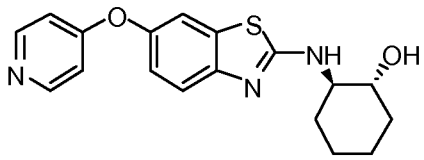
Preparation of (S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine



Following the procedure for Example 176. The reaction mixture was heated at 105 °C for 18 hours and purified by prep HPLC to give the title compound. Yield: 9.8 mg. ES/MS *m/z* 531.2 (MH^+), Rt = 1.89 min.

Example 219

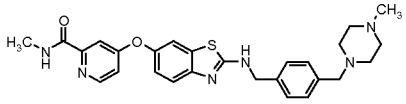
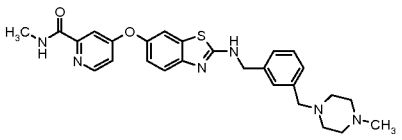
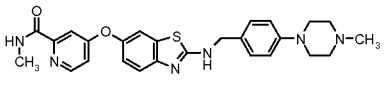
Preparation of (1R,2R)-2-(6-(pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol.

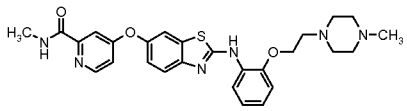
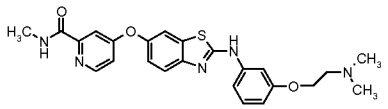
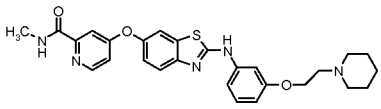
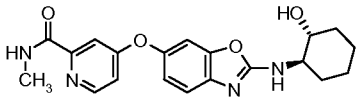
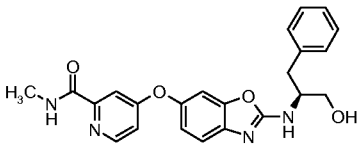
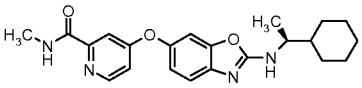
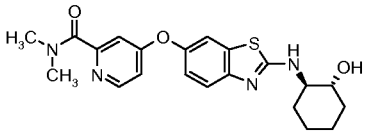
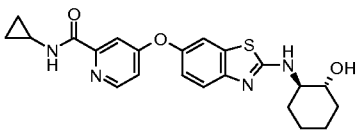
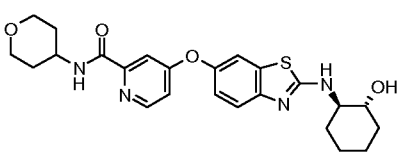


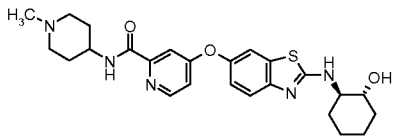
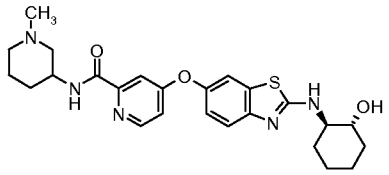
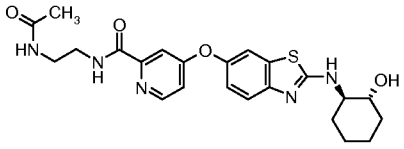
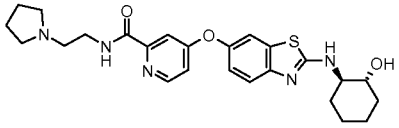
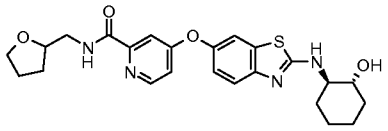
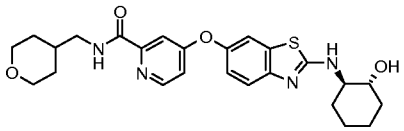
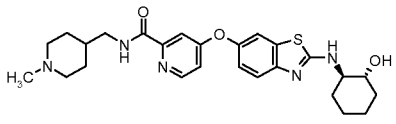
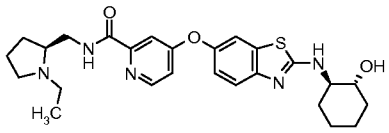
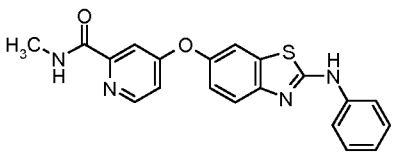
To the reaction mixture of 2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-ol (20 mg, 0.0755mmole) in 0.5 ml of NMP was added cesium carbonate (62 mg, 0.189 mmol) and stirred at room temperature for 1-3 minutes. To this mixture was added additional cesium carbonate (98.5 mg, 0.302 mmol) and 4-chloropyridine hydrochloride (45.3 mg, 0.302 mmol). The reaction mixture was stirred at 105-110 °C for 48 hours or until done by LC. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (1R,2R)-2-(6-(pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol as TFA salt (1.1 mg). ES/MS *m/z* 342.1 (MH^+).

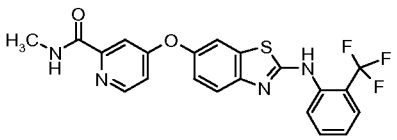
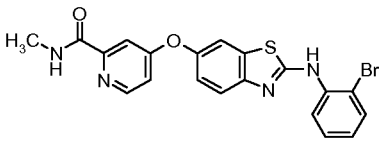
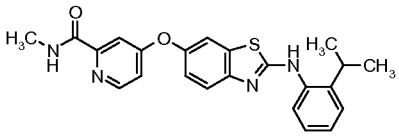
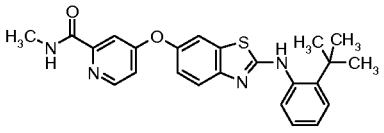
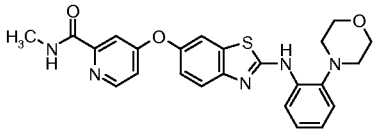
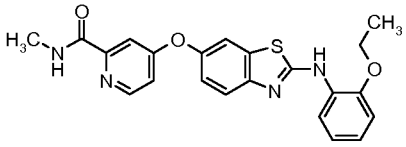
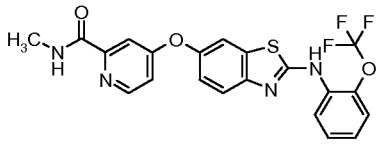
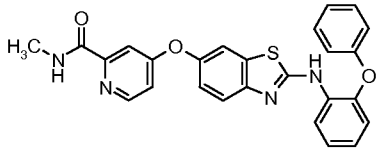
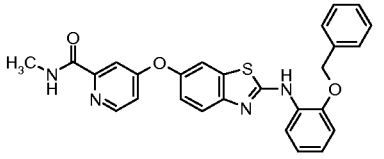
Compounds 1-381 in Table 3 and 1-102, 104-106, and 112-119 in Table 4 were made according to the examples above, and in particular according to the example noted in the Ex Prep (Example Preparation) column. Compounds 103 and 107-111 can be made according to the examples above.

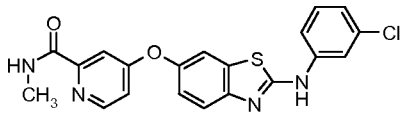
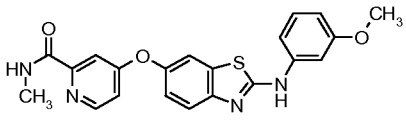
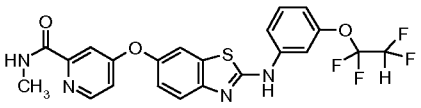
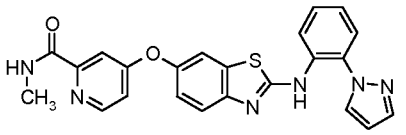
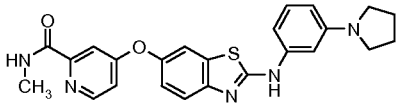
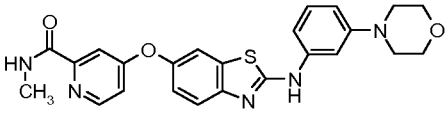
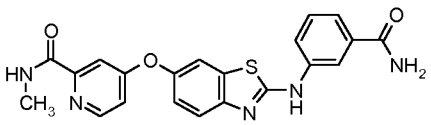
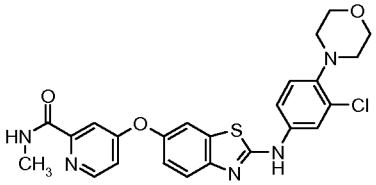
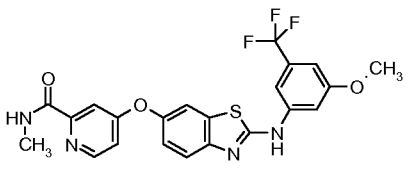
Table 3

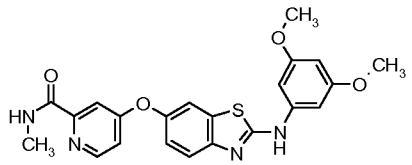
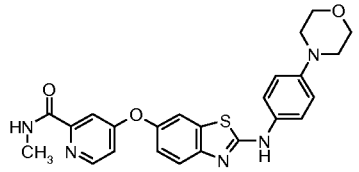
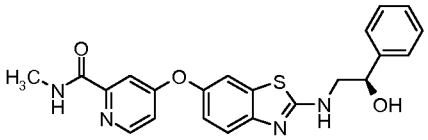
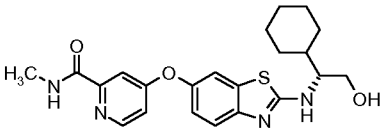
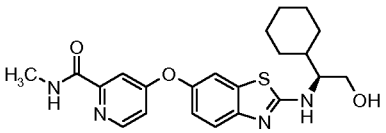
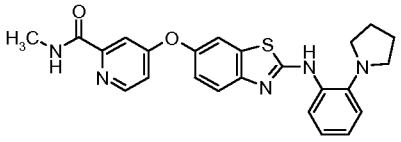
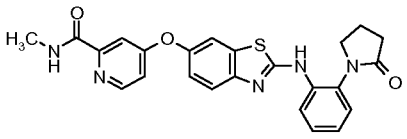
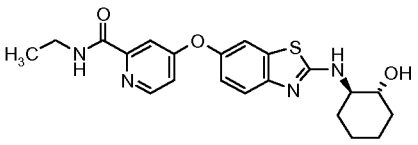
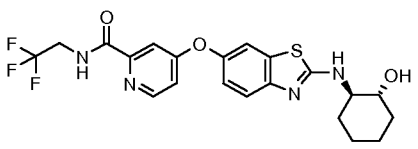
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
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2	199		N-methyl-4-(2-(3-((4-methylpiperazin-1-yl)methyl)benzylamino)benzo[d]thiazol-6-yloxy)picolinamide	503, 1.89
3	199		N-methyl-4-(2-(4-(4-methylpiperazin-1-yl)benzylamino)benzo[d]thiazol-6-yloxy)picolinamide	489, 1.98

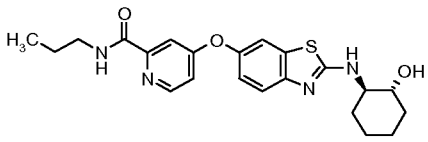
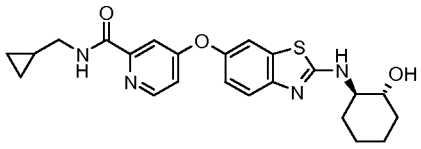
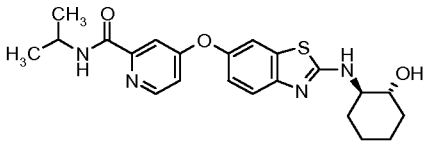
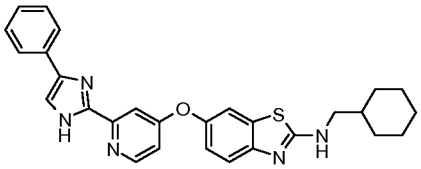
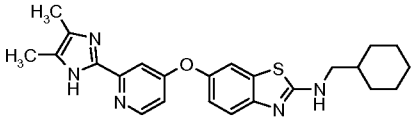
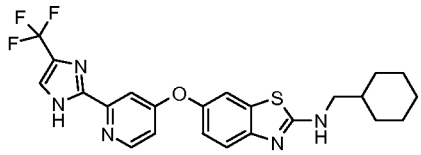
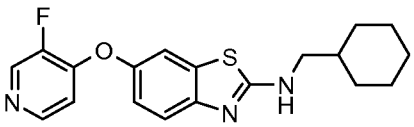
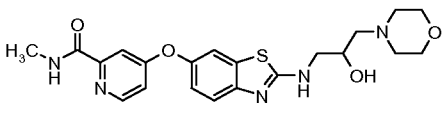
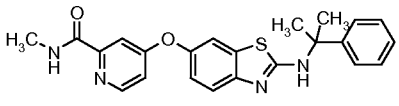
4	200		N-methyl-4-(2-(2-(2-(4-methylpiperazin-1-yl)ethoxy)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	519, 2.20
5	200		4-(2-(3-(2-(dimethylamino)ethoxy)phenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	464, 2.18
6	200		N-methyl-4-(2-(3-(2-(piperidin-1-yl)ethoxy)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	504, 2.29
7	201		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide	383, 1.96
8	201		(S)-4-(2-(1-hydroxy-3-phenylpropan-2-ylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide	419, 2.22
9	201		(S)-4-(2-(1-cyclohexylethylamino)benzo[d]oxazol-6-yloxy)-N-methylpicolinamide	395, 2.68
10	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N,N-dimethylpicolinamide	413.1, 1.87
11	171		N-cyclopropyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	425.2, 2.13
12	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(tetrahydro-2H-pyran-4-yl)picolinamide	469.2, 2.09

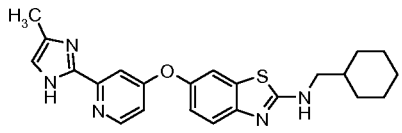
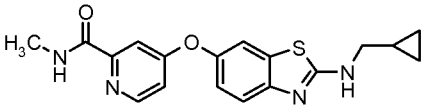
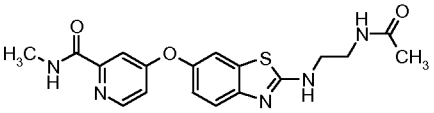
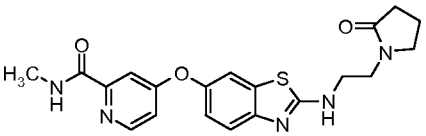
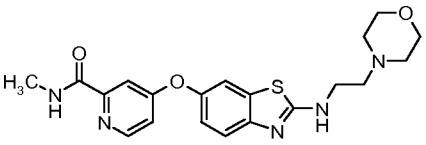
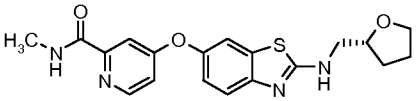
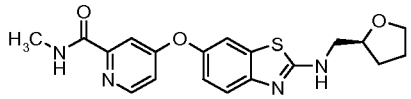
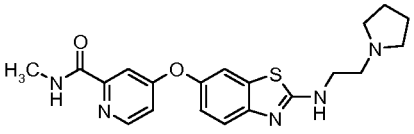
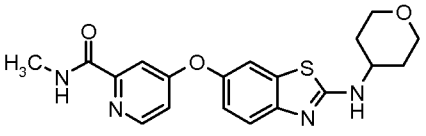
13	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(1-methylpiperidin-4-yl)picolinamide	482.2, 1.85
14	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(1-methylpiperidin-3-yl)picolinamide	482.2, 1.87
15	171		N-(2-acetamidoethyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	470.2, 1.86
16	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(2-(pyrrolidin-1-yl)ethyl)picolinamide	482.2, 1.84
17	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((tetrahydrofuran-2-yl)methyl)picolinamide	469.2, 2.16
18	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((tetrahydro-2H-pyran-4-yl)methyl)picolinamide	483.2, 2.12
19	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-((1-methylpiperidin-4-yl)methyl)picolinamide	496.2, 1.84
20	171		N-(((S)-1-ethylpyrrolidin-2-yl)methyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	496.2, 1.88
21	200		N-methyl-4-(2-(phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	377.1, 2.70

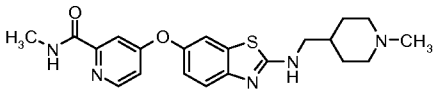
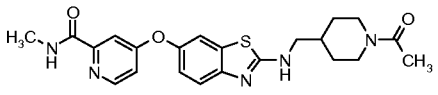
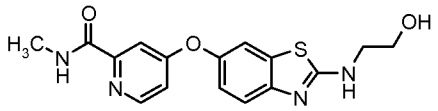
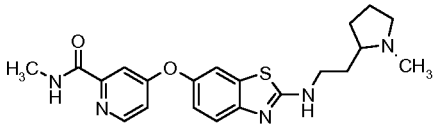
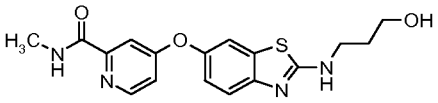
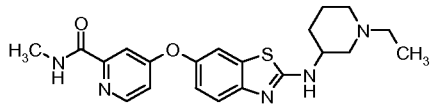
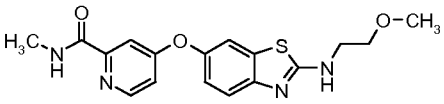
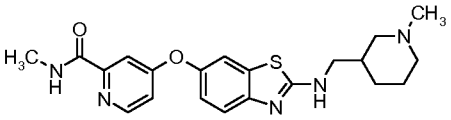
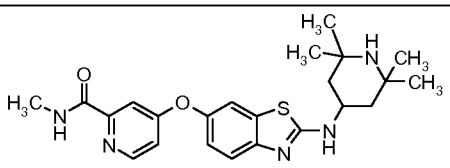
22	200		N-methyl-4-(2-(2-(trifluoromethyl)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	445.1, 2.84
23	200		4-(2-(2-bromophenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	455.0/457.0, 2.88
24	200		4-(2-(2-isopropylphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	419.2, 2.82
25	200		4-(2-(2-tert-butylphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	433.2, 2.87
26	200		N-methyl-4-(2-(2-morpholinophenylamino)benzo[d]thiazol-6-yloxy)picolinamide	462.1, 2.70
27	200		4-(2-(2-ethoxyphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.92
28	200		N-methyl-4-(2-(2-(trifluoromethoxy)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	461.1, 3.15
29	200		N-methyl-4-(2-(2-phenoxyphenylamino)benzo[d]thiazol-6-yloxy)picolinamide	469.1, 3.29
30	200		4-(2-(2-(benzyloxy)phenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	483.2, 3.19

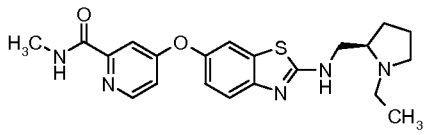
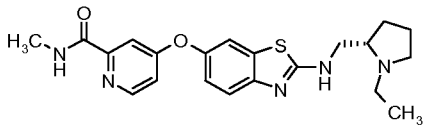
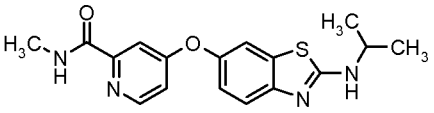
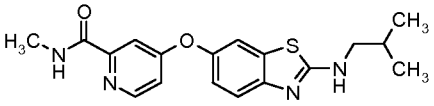
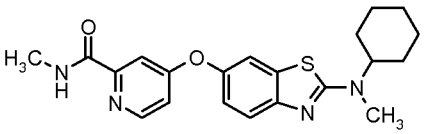
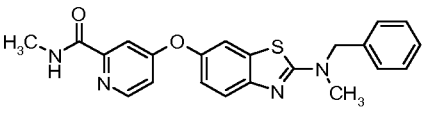
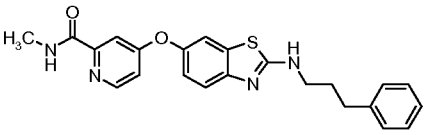
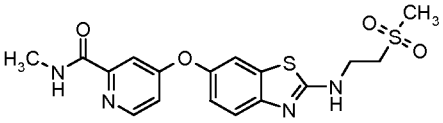
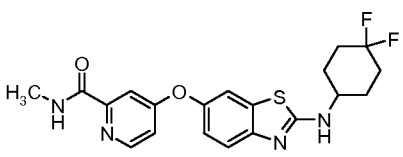
31	200		4-(2-(3-chlorophenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	411.1, 3.09
32	200		4-(2-(3-methoxyphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	407.1, 2.74
33	200		N-methyl-4-(2-(3-(1,1,2,2-tetrafluoroethoxy)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	493.1, 3.07
34	200		4-(2-(2-(1H-pyrazol-1-yl)phenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	443.1, 2.85
35	200		N-methyl-4-(2-(3-(pyrrolidin-1-yl)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	446.2, 2.63
36	200		N-methyl-4-(2-(3-morpholinophenylamino)benzo[d]thiazol-6-yloxy)picolinamide	462.1, 2.42
37	200		4-(2-(3-carbamoylphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	**421.1, 2.38**
38	200		4-(2-(3-chloro-4-morpholinophenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	496.1, 2.88
39	200		4-(2-(3-methoxy-5-(trifluoromethyl)phenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	475.1, 3.25

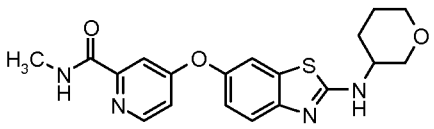
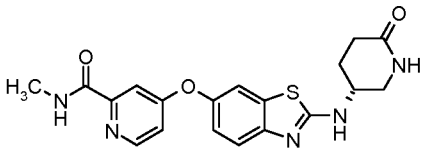
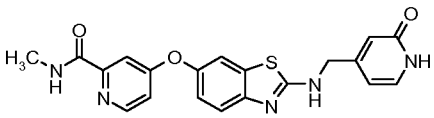
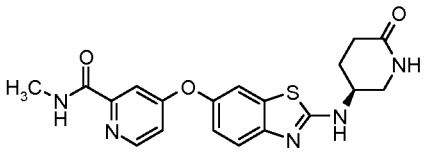
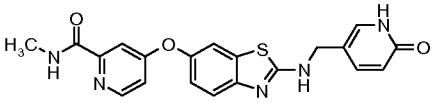
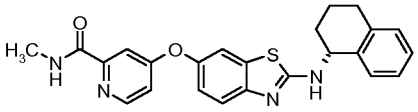
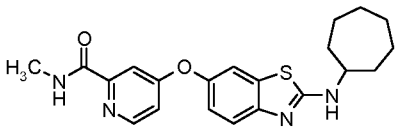
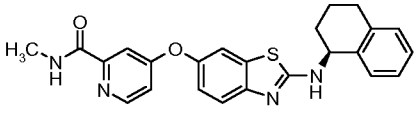
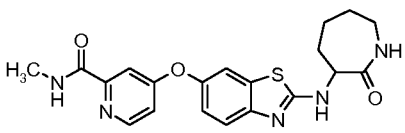
40	200		4-(2-(3,5-dimethoxyphenylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	437.1, 2.79
41	200		N-methyl-4-(2-(4-morpholinophenylamino)benzo[d]thiazol-6-yloxy)picolinamide	462.2, 2.20
42	162		(R)-4-(2-(2-hydroxy-2-phenylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.13
43	162		(R)-4-(2-(1-cyclohexyl-2-hydroxyethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	427.2, 2.30
44	162		(S)-4-(2-(1-cyclohexyl-2-hydroxyethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	427.2, 2.29
45	200		N-methyl-4-(2-(2-(pyrrolidin-1-yl)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	446.1, 2.24
46	200		N-methyl-4-(2-(2-(2-oxopyrrolidin-1-yl)phenylamino)benzo[d]thiazol-6-yloxy)picolinamide	460.1, 2.35
47	171		N-ethyl-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	413.2, 2.09
48	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-(2,2,2-trifluoroethyl)picolinamide	467.1, 2.37

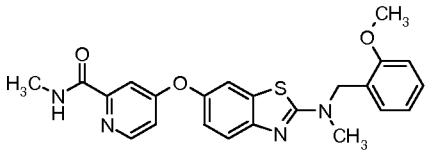
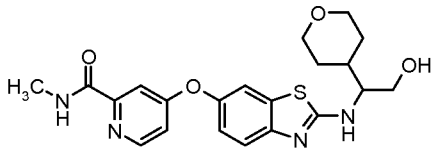
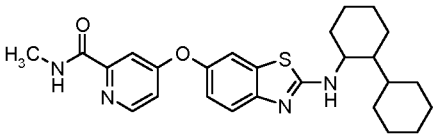
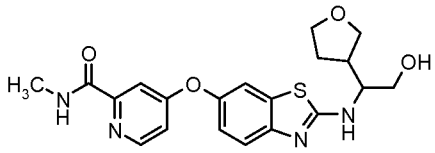
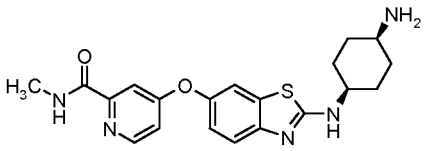
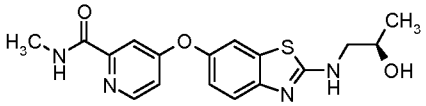
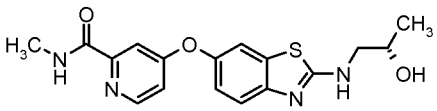
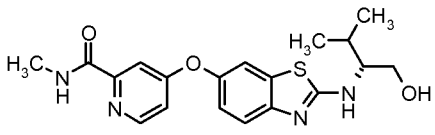
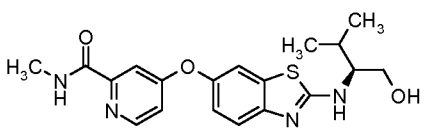
49	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-propylpicolinamide	427.1, 2.25
50	171		N-(cyclopropylmethyl)-4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	439.2, 2.32
51	171		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isopropylpicolinamide	427.2, 2.24
52	205		N-(cyclohexylmethyl)-6-(2-(4-phenyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	482.2, 2.57
53	205		N-(cyclohexylmethyl)-6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	434.2, 2.33
54	206		N-(cyclohexylmethyl)-6-(2-(4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	474.2, 2.87
55	178		N-(cyclohexylmethyl)-6-(3-fluoropyridin-4-yloxy)benzo[d]thiazol-2-amine	358.1, 2.35
56	162		4-(2-(2-hydroxy-3-morpholinopropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	444.2, 1.72
57	162		N-methyl-4-(2-(2-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	419.1, 2.51

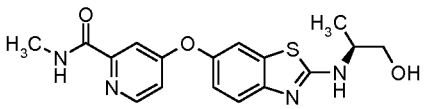
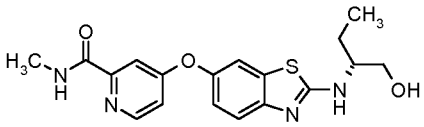
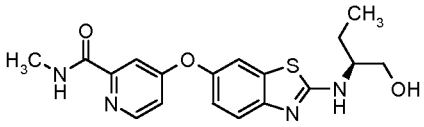
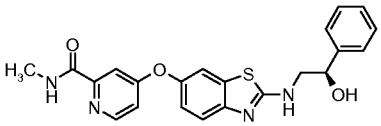
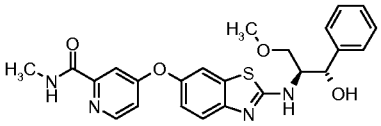
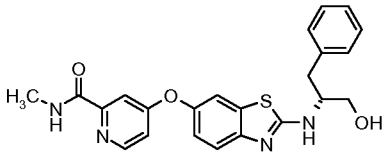
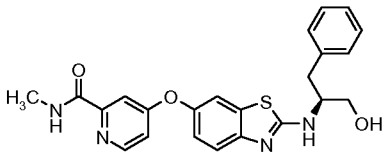
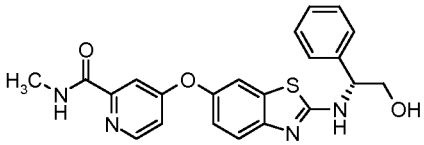
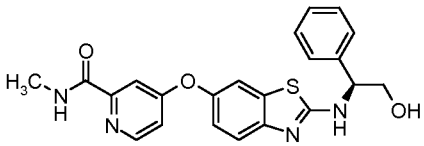
58	205		N-(cyclohexylmethyl)-6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	420.1, 2.26
59	162		4-(2-(cyclopropylmethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	355.1, 2.03
60	162		4-(2-(2-acetamidoethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	386.1, 1.70
61	162		N-methyl-4-(2-(2-(2-oxopyrrolidin-1-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	412.1, 1.82
62	162		N-methyl-4-(2-(2-morpholinoethylamino)benzo[d]thiazol-6-yloxy)picolinamide	414.1, 1.79
63	162		(R)-N-methyl-4-(2-((tetrahydrofuran-2-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	385.2, 1.93
64	162		(S)-N-methyl-4-(2-((tetrahydrofuran-2-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	385.2, 1.95
65	162		N-methyl-4-(2-(2-(pyrrolidin-1-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	398.2, 1.83
66	162		N-methyl-4-(2-(tetrahydro-2H-pyran-4-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	385.2, 1.88

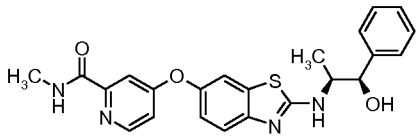
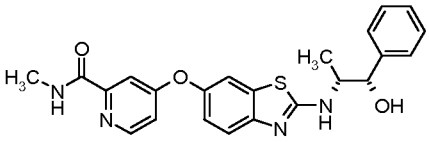
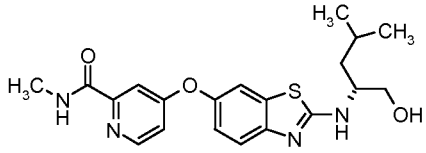
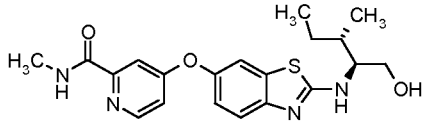
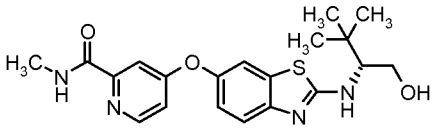
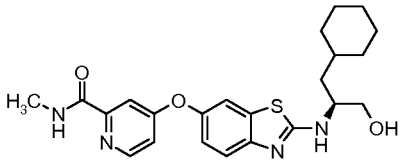
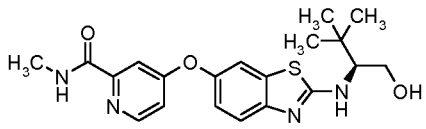
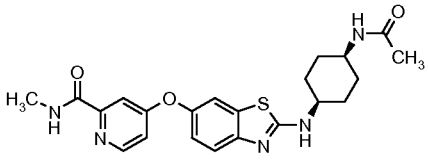
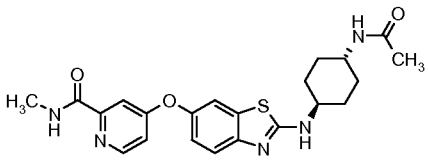
67	162		N-methyl-4-(2-((1-methylpiperidin-4-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	412.2, 1.70
68	162		4-(2-((1-acetylpiperidin-4-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.86
69	162		4-(2-(2-hydroxyethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	345.1, 1.65
70	162		N-methyl-4-(2-(2-(1-methylpyrrolidin-2-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	412.2, 1.75
71	162		4-(2-(3-hydroxypropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	359.1, 1.70
72	162		4-(2-(1-ethylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	412.2, 1.84
73	162		4-(2-(2-methoxyethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	359.1, 1.83
74	162		N-methyl-4-(2-((1-methylpiperidin-3-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	412.2, 1.75
75	162		N-methyl-4-(2-(2,2,6,6-tetramethylpiperidin-4-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	440.2, 1.89

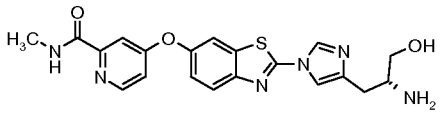
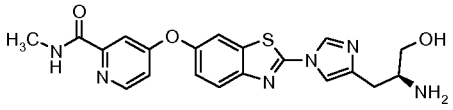
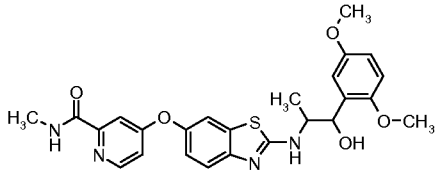
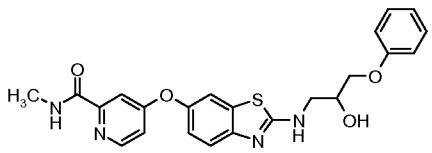
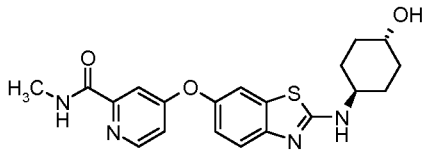
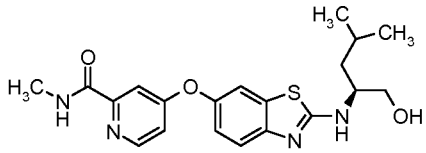
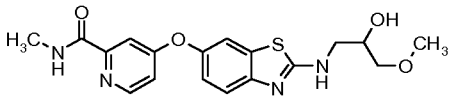
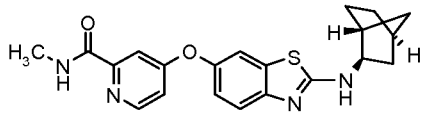
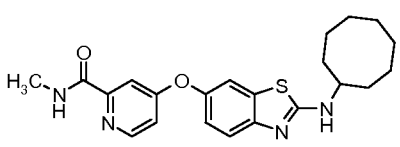
76	162		(R)-4-(2-((1-ethylpyrrolidin-2-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	412.2, 1.92
77	162		(S)-4-(2-((1-ethylpyrrolidin-2-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	412.2, 1.92
78	162		4-(2-(isopropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	343.1, 1.92
79	162		4-(2-(isobutylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	357.1, 2.10
80	162		4-(2-(cyclohexyl(methyl)amino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	397.2, 2.49
81	162		4-(2-(benzyl(methyl)amino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	405.1, 2.63
82	162		N-methyl-4-(2-(3-phenylpropylamino)benzo[d]thiazol-6-yloxy)picolinamide	419.2, 2.45
83	162		N-methyl-4-(2-(2-(methylsulfonyl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	407.1, 1.85
84	162		4-(2-(4,4-difluorocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	419.2, 2.31

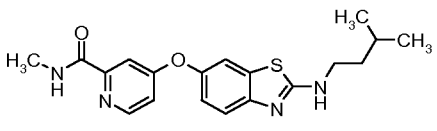
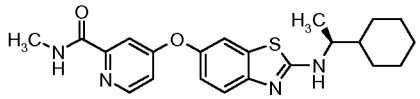
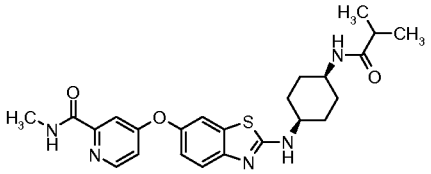
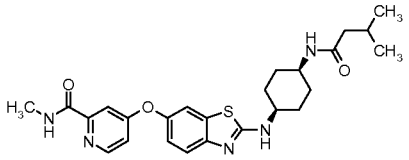
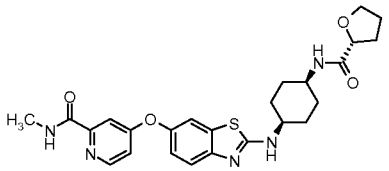
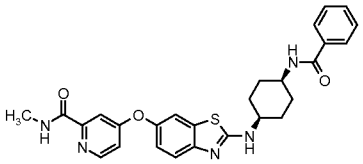
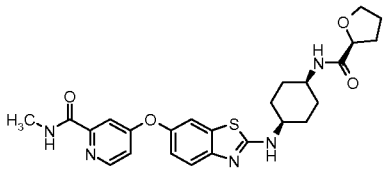
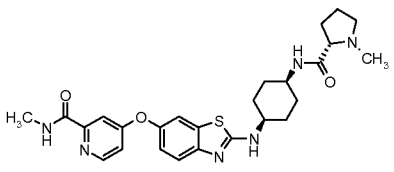
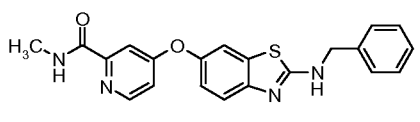
85	162		N-methyl-4-(2-(tetrahydro-2H-pyran-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	385.1, 1.95
86	162		(R)-N-methyl-4-(2-(6-oxopiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	398.1, 1.76
87	162		N-methyl-4-(2-((2-oxo-1,2-dihydropyridin-4-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	408.1, 1.79
88	162		(S)-N-methyl-4-(2-(6-oxopiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	398.1, 1.76
89	162		N-methyl-4-(2-((6-oxo-1,6-dihydropyridin-3-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	408.1, 1.77
90	162		(R)-N-methyl-4-(2-(1,2,3,4-tetrahydronaphthalen-1-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	431.2, 2.58
91	162		4-(2-(cycloheptylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	397.2, 2.41
92	162		(S)-N-methyl-4-(2-(1,2,3,4-tetrahydronaphthalen-1-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	431.2, 2.57
93	162		N-methyl-4-(2-(2-oxoazepan-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	412.1, 1.95

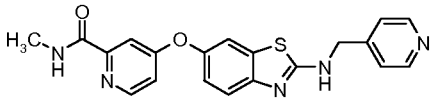
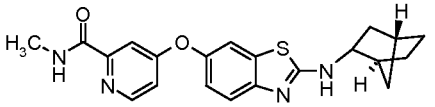
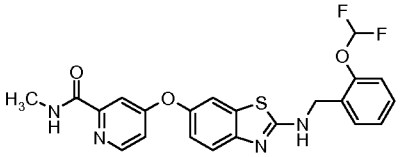
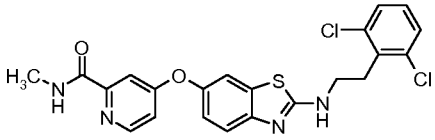
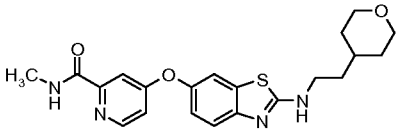
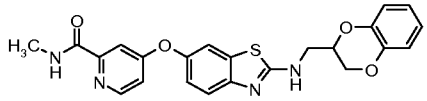
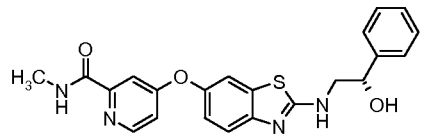
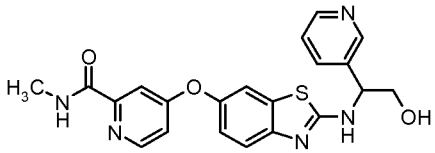
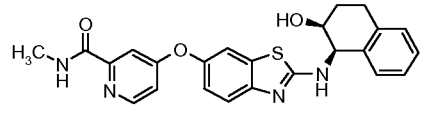
94	162		4-(2-((2-methoxybenzyl)(methyl)amino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.2, 2.56
95	162		4-(2-(2-hydroxy-1-(tetrahydro-2H-pyran-4-yl)ethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	429.2, 1.83
96	162		4-(2-(bi(cyclohexan)-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	465.2, 3.05
97	162		4-(2-(2-hydroxy-1-(tetrahydrofuran-3-yl)ethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	415.1, 1.79
98	189		4-(2-((1s,4s)-4-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	398.1, 1.73
99	162		(R)-4-(2-(2-hydroxypropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	359.1, 1.75
100	162		(S)-4-(2-(2-hydroxypropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	359.1, 1.74
101	162		(R)-4-(2-(1-hydroxy-3-methylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	387.2, 1.98
102	162		(S)-4-(2-(1-hydroxy-3-methylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	387.2, 1.96

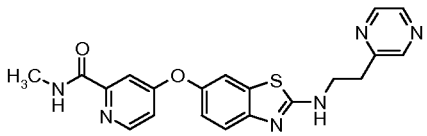
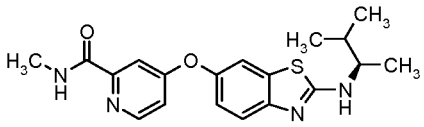
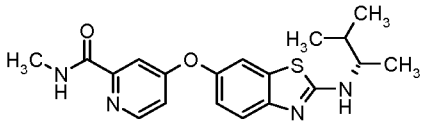
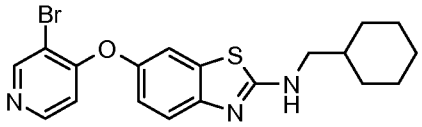
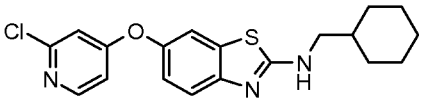
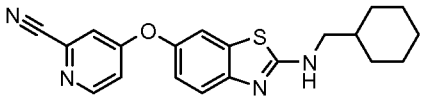
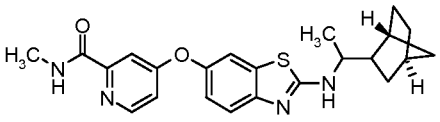
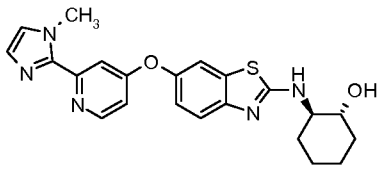
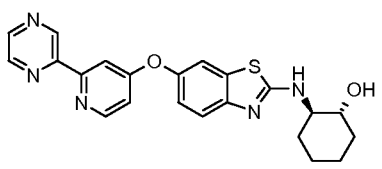
103	162		(S)-4-(2-(1-hydroxypropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	359.1, 1.75
104	162		(R)-4-(2-(1-hydroxybutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	373.1, 1.84
105	162		(S)-4-(2-(1-hydroxybutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	373.1, 1.87
106	162		(R)-4-(2-(2-hydroxy-2-phenylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.13
107	162		4-(2-((1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	465.2, 2.21
108	162		(R)-4-(2-(1-hydroxy-3-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.2, 2.17
109	162		(S)-4-(2-(1-hydroxy-3-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.2, 2.18
110	162		(R)-4-(2-(2-hydroxy-1-phenylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.15
111	162		(S)-4-(2-(2-hydroxy-1-phenylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.16

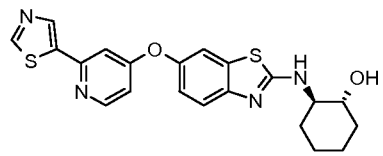
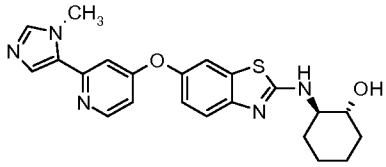
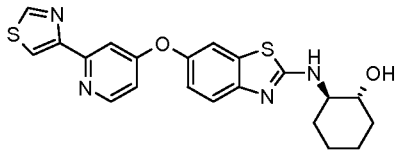
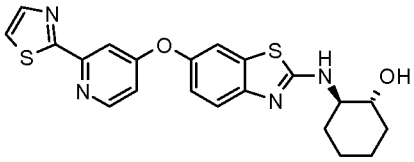
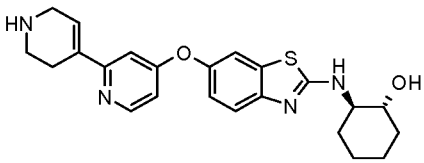
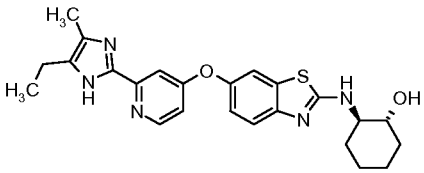
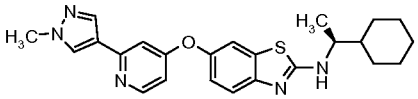
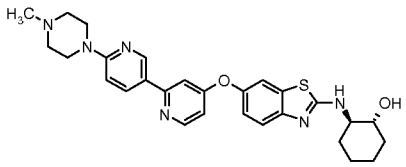
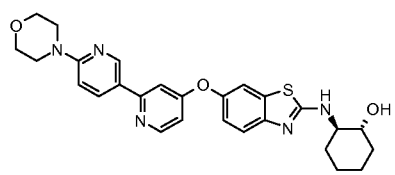
112	162		4-(2-((1R,2S)-1-hydroxy-1-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.2, 2.20
113	162		4-(2-((1S,2R)-1-hydroxy-1-phenylpropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.2, 2.19
114	162		(R)-4-(2-(1-hydroxy-4-methylpentan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	401.2, 2.13
115	162		4-(2-((2S,3S)-1-hydroxy-3-methylpentan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	401.2, 2.10
116	162		(R)-4-(2-(1-hydroxy-3,3-dimethylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	401.2, 2.08
117	162		(S)-4-(2-(1-cyclohexyl-3-hydroxypropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	441.2, 2.45
118	162		(S)-4-(2-(1-hydroxy-3,3-dimethylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	401.2, 2.08
119	190		4-(2-((1s,4s)-4-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.85
120	190		4-(2-((1r,4r)-4-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.85

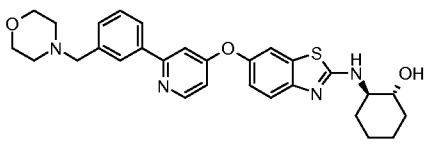
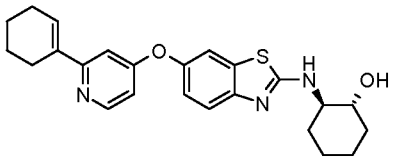
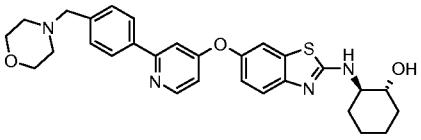
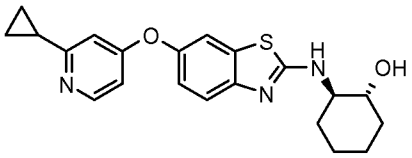
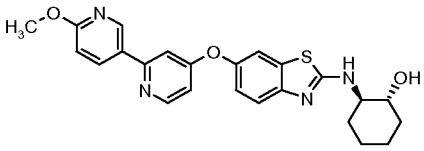
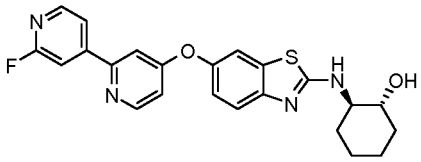
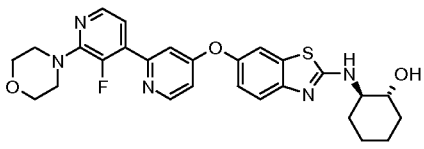
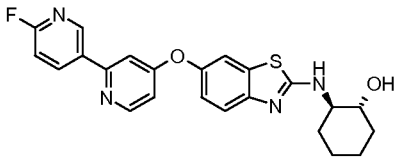
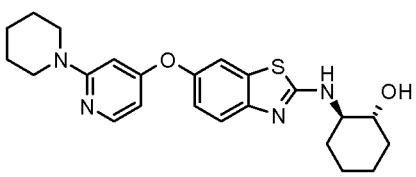
121	162		(R)-4-(2-(4-(2-amino-3-hydroxypropyl)-1H-imidazol-1-yl)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	425.2, 1.67
122	162		(S)-4-(2-(4-(2-amino-3-hydroxypropyl)-1H-imidazol-1-yl)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	425.2, 1.68
123	162		4-(2-(1-(2,5-dimethoxyphenyl)-1-hydroxypropan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	495.2, 2.29
124	162		4-(2-(2-hydroxy-3-phenoxypropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	451.1, 2.26
125	162		4-(2-((1r,4r)-4-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	399.1, 1.83
126	162		(S)-4-(2-(1-hydroxy-4-methylpentan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	401.1, 2.14
127	162		4-(2-(2-hydroxy-3-methoxypropylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	389.1, 1.77
128	162		4-(2-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	395.2, 2.36
129	162		4-(2-(cyclooctylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	411.2, 2.60

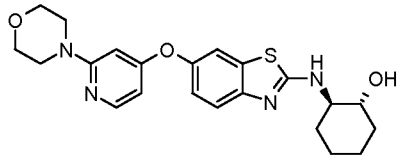
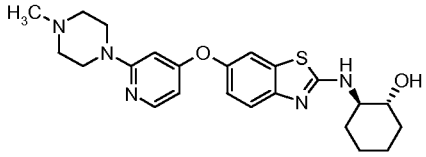
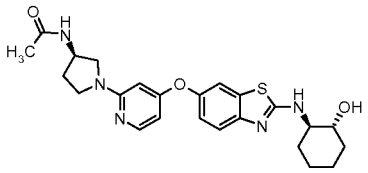
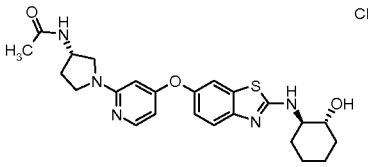
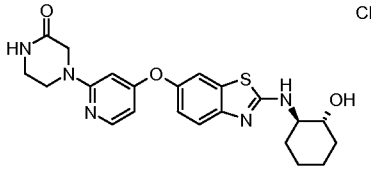
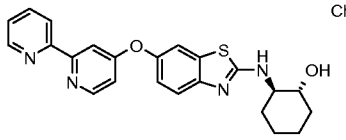
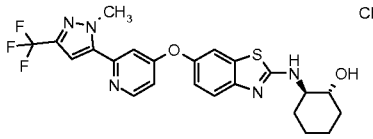
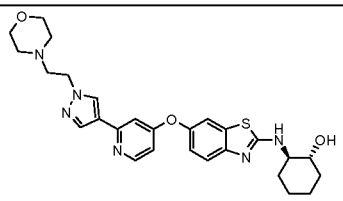
130	162		4-(2-(isopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	371.2, 2.31
131	162		(S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	411.2, 2.59
132	191		4-(2-((1s,4s)-4-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	468.3, 2.03
133	191		N-methyl-4-(2-((1s,4s)-4-(3-methylbutanamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	482.2, 2.14
134	191		N-methyl-4-(2-((1S,4s)-4-((R)-tetrahydrofuran-2-carboxamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	496.2, 2.01
135	191		4-(2-((1s,4s)-4-benzamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	502.2, 2.21
136	191		N-methyl-4-(2-((1R,4s)-4-((S)-tetrahydrofuran-2-carboxamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	496.2, 2.01
137	191		N-methyl-4-(2-((1R,4s)-4-((S)-1-methylpyrrolidine-2-carboxamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	509.3, 1.83
138	162		4-(2-(benzylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	391.1, 2.35

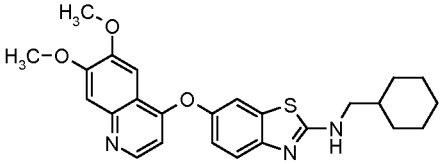
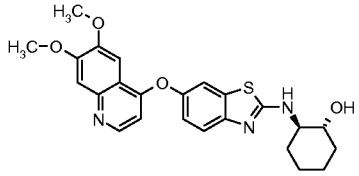
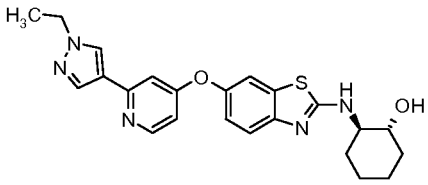
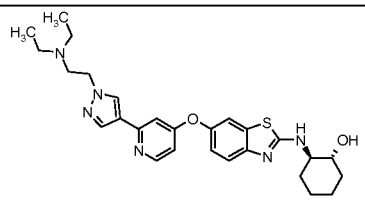
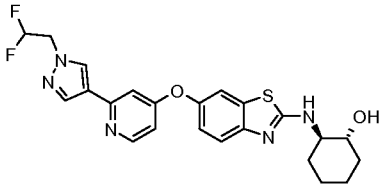
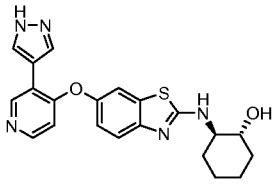
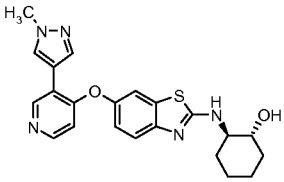
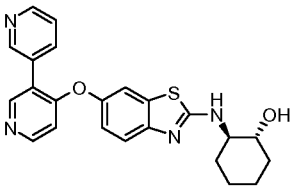
139	162		N-methyl-4-(2-(pyridin-4-ylmethylamino)benzo[d]thiazol-6-yloxy)picolinamide	392.1, 1.78
140	162		4-(2-((1S,4R)-bicyclo[2.2.1]heptan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	395.2, 2.35
141	162		4-(2-(2-(difluoromethoxy)benzylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	457.1, 2.53
142	162		4-(2-(2,6-dichlorophenethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	473.0, 2.68
143	162		N-methyl-4-(2-(2-(tetrahydro-2H-pyran-4-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	413.2, 2.02
144	162		4-(2-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	449.1, 2.52
145	162		(S)-4-(2-(2-hydroxy-2-phenylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	421.1, 2.13
146	162		4-(2-(2-hydroxy-1-(pyridin-3-yl)ethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	422.1, 1.75
147	162		4-(2-((1R,2S)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	447.2, 2.25

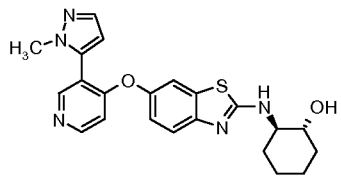
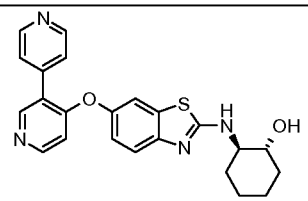
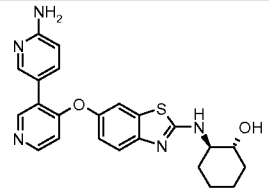
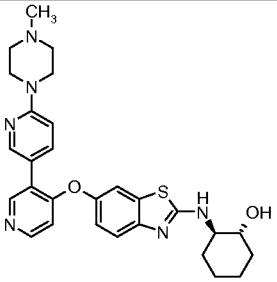
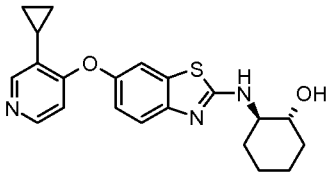
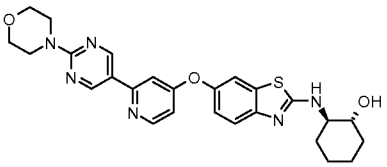
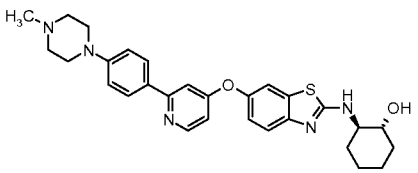
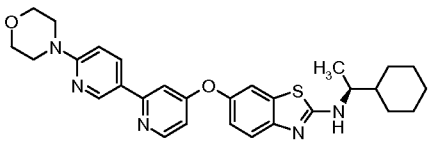
148	162		N-methyl-4-(2-(2-(pyrazin-2-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	407.1, 1.85
149	162		(R)-N-methyl-4-(2-(3-methylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	371.2, 2.20
150	162		(S)-N-methyl-4-(2-(3-methylbutan-2-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	371.2, 2.20
151	178		6-(3-bromopyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine	418.1/420.1, 2.48
152	180		6-(2-chloropyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine	374.1, 2.86
153	180		4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile	365.1, 2.74
154	162		4-(2-(1-((1R,4S)-bicyclo[2.2.1]heptan-2-yl)ethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	423.2, 2.31
155	175		(1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.83
156	175		(1R,2R)-2-(6-(2-(pyrazin-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1, 1.91

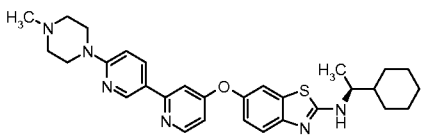
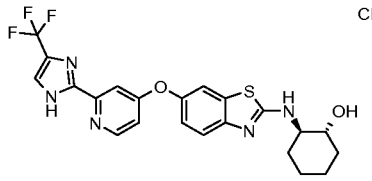
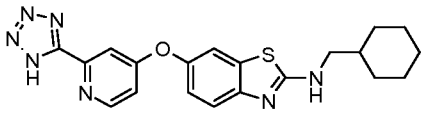
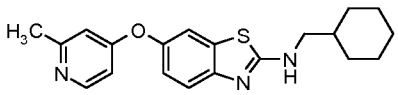
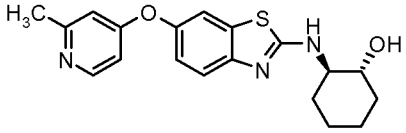
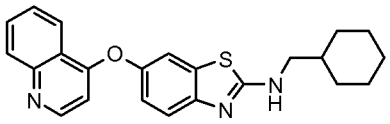
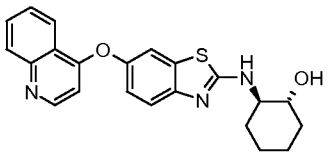
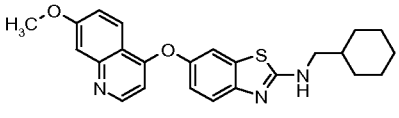
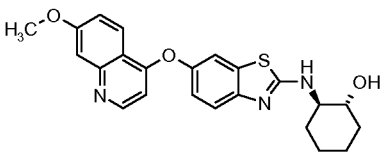
157	175		(1R,2R)-2-(6-(2-(thiazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 2.05
158	175		(1R,2R)-2-(6-(2-(1-methyl-1H-imidazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.84
159	175		(1R,2R)-2-(6-(2-(thiazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 1.85
160	175		(1R,2R)-2-(6-(2-(thiazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.0, 2.28
161	188		(1R,2R)-2-(6-(2-(1,2,3,6-tetrahydropyridin-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	423.1, 1.38
162	177		(1R,2R)-2-(6-(2-(5-ethyl-4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.1, 1.82
163	185		(S)-N-(1-cyclohexylethyl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	434.1, 2.31
164	174		(1R,2R)-2-(6-(6'-(4-methylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.75
165	174		(1R,2R)-2-(6-(6'-morpholino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	504.1, 1.93

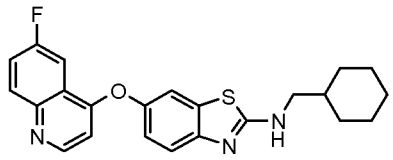
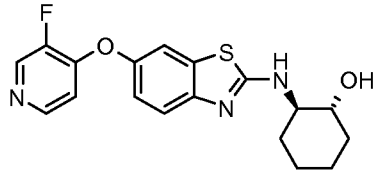
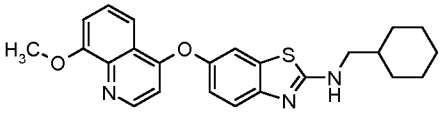
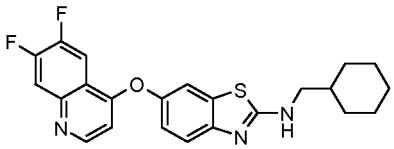
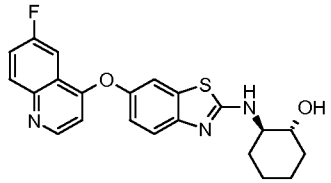
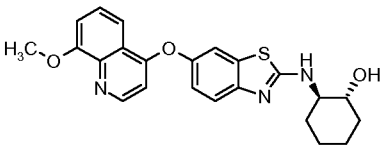
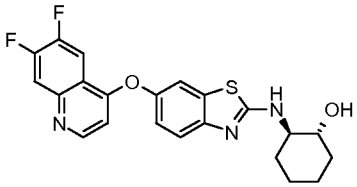
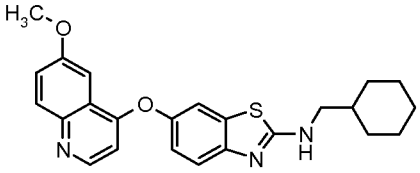
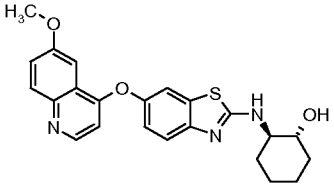
166	174		(1R,2R)-2-(6-(2-(3-(morpholinomethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.1, 1.78
167	174		(1R,2R)-2-(6-(2-cyclohexenylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 2.07
168	174		(1R,2R)-2-(6-(2-(4-(morpholinomethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.76
169	174		(1R,2R)-2-(6-(2-cyclopropylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	382.1, 1.84
170	174		(1R,2R)-2-(6-(6'-methoxy-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	449.1, 1.98
171	174		(1R,2R)-2-(6-(2'-fluoro-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	437.1, 2.22
172	174		(1R,2R)-2-(6-(3'-fluoro-2'-morpholino-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	522.2, 2.17
173	174		(1R,2R)-2-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	437.1, 2.04
174	183		(1R,2R)-2-(6-(2-(piperidin-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	425.1, 1.98

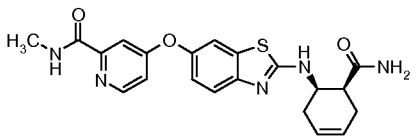
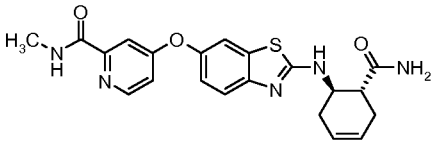
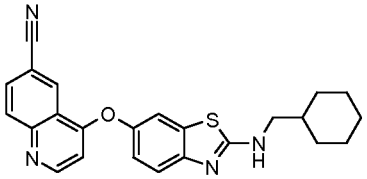
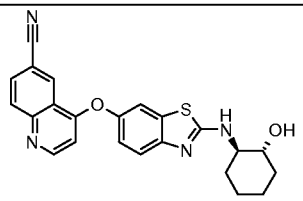
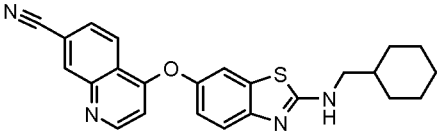
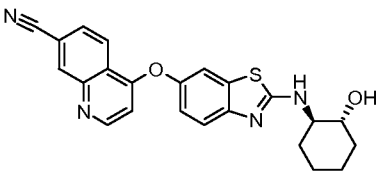
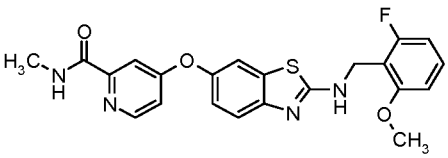
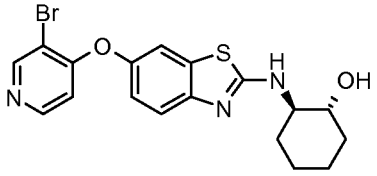
175	183		(1R,2R)-2-(6-(2-morpholinopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	427.1, 1.80
176	183		(1R,2R)-2-(6-(2-(4-methylpiperazin-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	440.1, 1.66
177	183		N-((R)-1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyrrolidin-3-yl)acetamide	468.1, 1.78
178	183	Chiral 	N-((S)-1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyrrolidin-3-yl)acetamide	468.1, 1.77
179	183	Chiral 	4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)piperazin-2-one	440.1, 1.70
180	175	Chiral 	(1R,2R)-2-(6-(2,2'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.0, 1.87
181	175	Chiral 	(1R,2R)-2-(6-(2-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	490.1, 2.60
182	174		(1R,2R)-2-(6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	521.1, 1.71

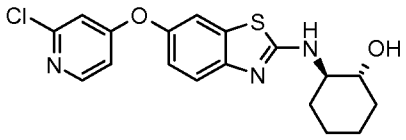
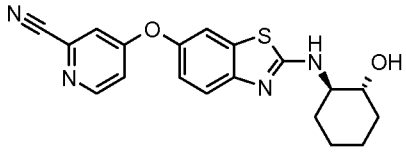
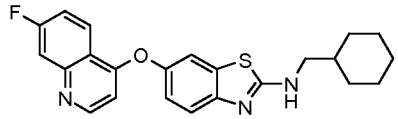
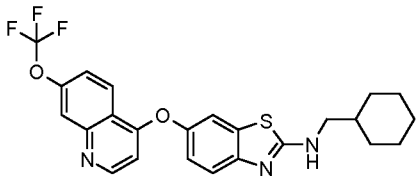
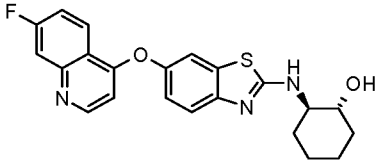
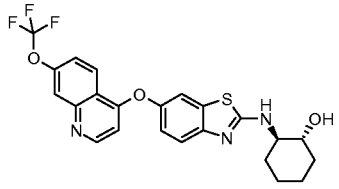
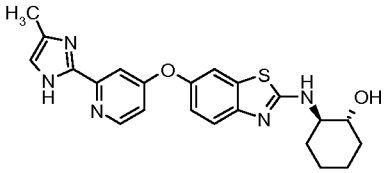
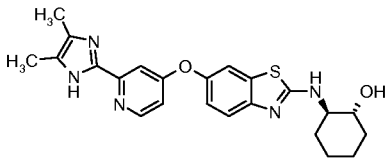
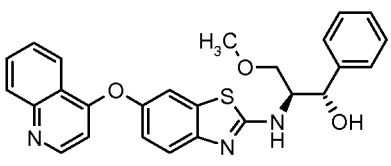
183	192		N-(cyclohexylmethyl)-6-(6,7-dimethoxyquinolin-4-yloxy)benzo[d]thiazol-2-amine	450.1, 2.43
184	192		(1R,2R)-2-(6-(6,7-dimethoxyquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	452.1, 2.00
185	176		(1R,2R)-2-(6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.0, 1.89
186	176		(1R,2R)-2-(6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	507.1, 1.75
187	176		(1R,2R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	472.0, 1.90
188	179		(1R,2R)-2-(6-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.70
189	179		(1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.79
190	179		(1R,2R)-2-(6-(3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.66

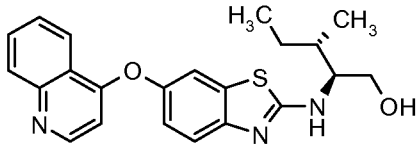
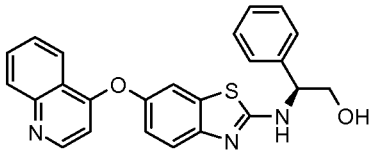
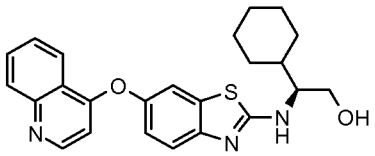
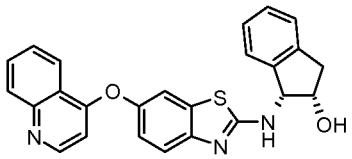
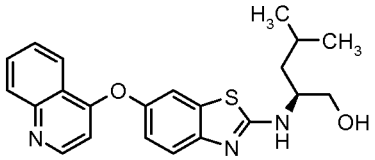
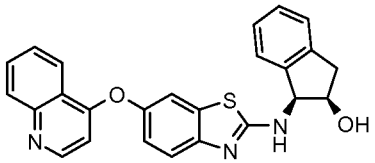
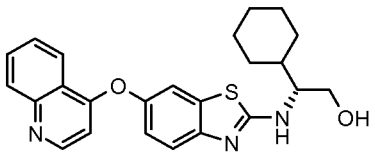
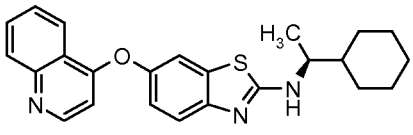
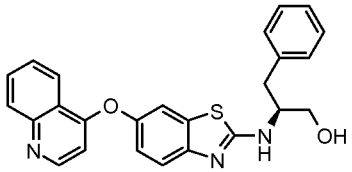
191	179		(1R,2R)-2-(6-(3-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.83
192	179		(1R,2R)-2-(6-(3,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.61
193	179		(1R,2R)-2-(6-(6'-amino-3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	434.1, 1.60
194	179		(1R,2R)-2-(6-(6'-(4-methylpiperazin-1-yl)-3,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.64
195	179		(1R,2R)-2-(6-(3-cyclopropylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	382.1, 1.97
196	174		(1R,2R)-2-(6-(2-(2-morpholinopyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	505.1, 2.03
197	174		(1R,2R)-2-(6-(2-(4-(4-methylpiperazin-1-yl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	516.2, 1.85
198	185		(S)-N-(1-cyclohexylethyl)-6-(6'-morpholino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-amine	516.1, 2.50

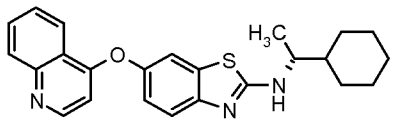
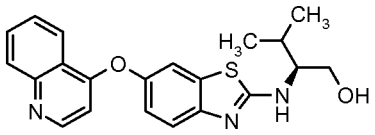
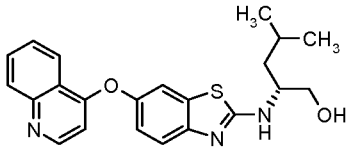
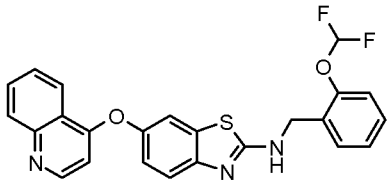
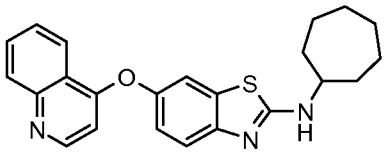
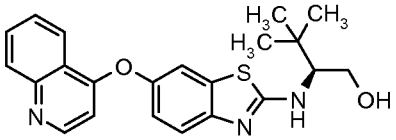
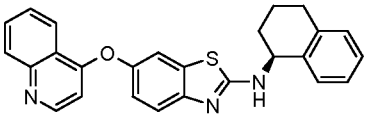
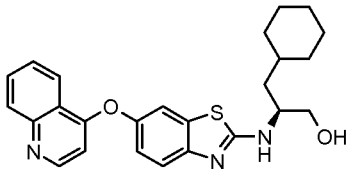
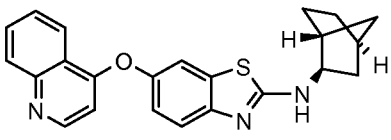
199	185		(S)-N-(1-cyclohexylethyl)-6-(6'-(4-methylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-amine	529.2, 2.25
200	177	 Chiral	(1R,2R)-2-(6-(2-(4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	476.1, 2.35
201	181		6-(2-(1H-tetrazol-5-yl)pyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine	408.2, 2.35
202	192		N-(cyclohexylmethyl)-6-(2-methylpyridin-4-yloxy)benzo[d]thiazol-2-amine	354.2, 2.19
203	192		(1R,2R)-2-(6-(2-methylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	356.1, 1.73
204	192		N-(cyclohexylmethyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	390.1, 2.38
205	192		(1R,2R)-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	392.2, 1.93
206	192		N-(cyclohexylmethyl)-6-(7-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-amine	420.2, 2.49
207	192		(1R,2R)-2-(6-(7-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 2.03

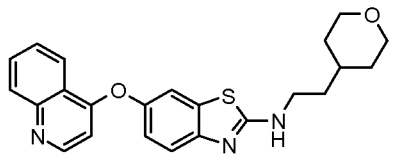
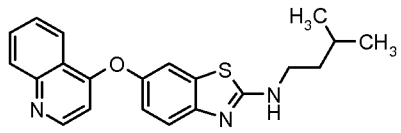
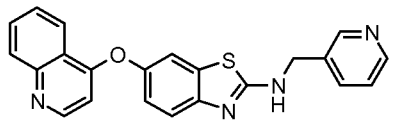
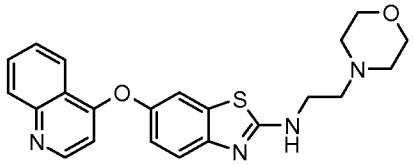
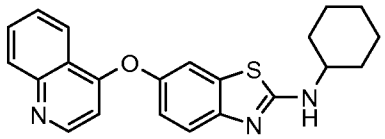
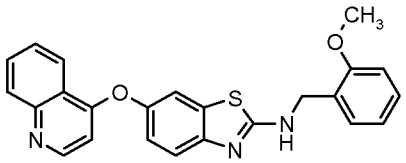
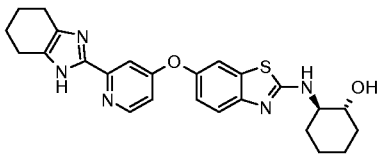
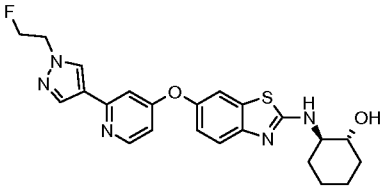
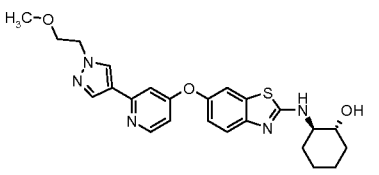
208	192		N-(cyclohexylmethyl)-6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-amine	408.2, 2.45
209	192		(1R,2R)-2-(6-(3-fluoropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	360.1, 1.83
210	192		N-(cyclohexylmethyl)-6-(8-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-amine	420.2, 2.46
211	192		N-(cyclohexylmethyl)-6-(6,7-difluoroquinolin-4-yloxy)benzo[d]thiazol-2-amine	426.2, 2.61
212	192		(1R,2R)-2-(6-(6-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	410.1, 1.98
213	192		(1R,2R)-2-(6-(8-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.96
214	192		(1R,2R)-2-(6-(6,7-difluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	428.1, 2.08
215	192		N-(cyclohexylmethyl)-6-(6-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-amine	420.2, 2.47
216	192		(1R,2R)-2-(6-(6-methoxyquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.98

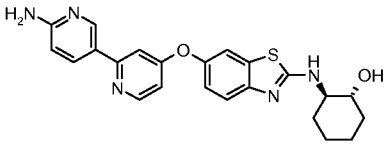
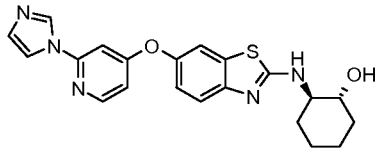
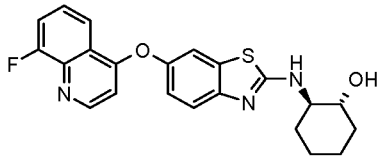
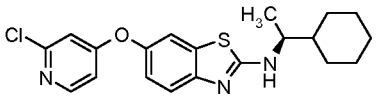
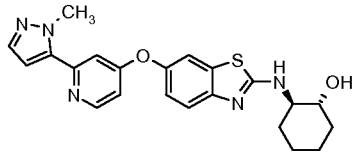
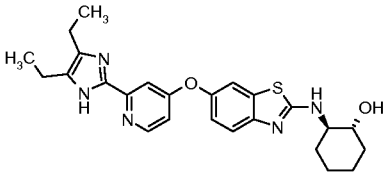
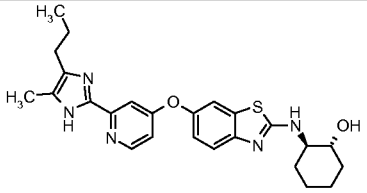
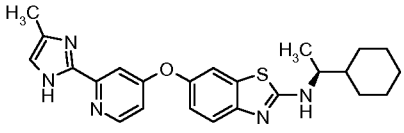
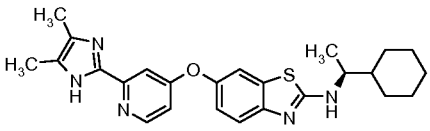
217	162		4-(2-((1R,6S)-6-carbamoylcyclohex-3-enylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	424.1, 1.86
218	162		4-(2-((1R,6R)-6-carbamoylcyclohex-3-enylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	424.1, 1.90
219	192		4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)quinoline-6-carbonitrile	415.1, 2.50
220	192		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)quinoline-6-carbonitrile	417.1, 1.99
221	192		4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)quinoline-7-carbonitrile	415.1, 2.52
222	192		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)quinoline-7-carbonitrile	417.1, 1.98
223	162		4-(2-(2-fluoro-6-methoxybenzylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	439.1, 2.40
224	178		(1R,2R)-2-(6-(3-bromopyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1/422.0, 1.81

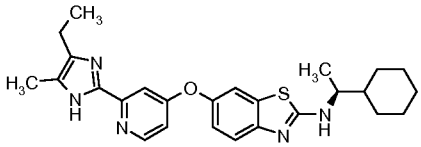
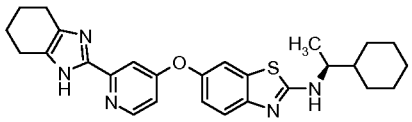
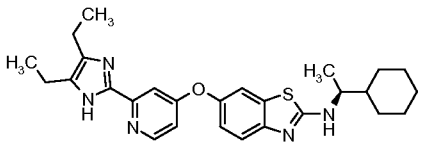
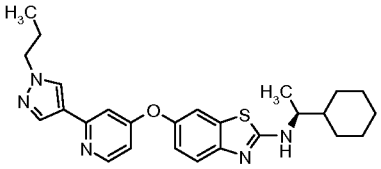
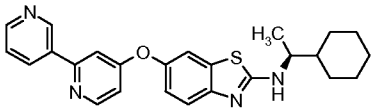
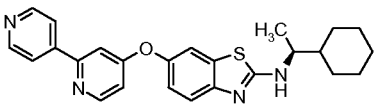
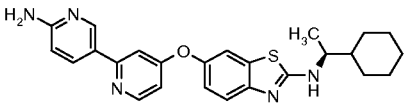
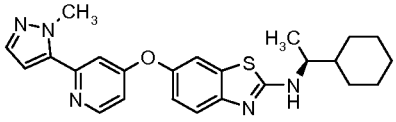
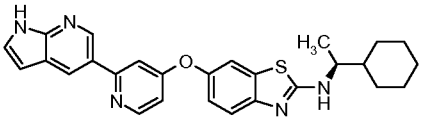
225	173		(1R,2R)-2-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	376.1, 2.13
226	173		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)picolinonitrile	367.1, 2.03
227	192		N-(cyclohexylmethyl)-6-(7-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-amine	408.1, 2.44
228	192		N-(cyclohexylmethyl)-6-(7-(trifluoromethoxy)quinolin-4-yloxy)benzo[d]thiazol-2-amine	474.1, 2.76
229	192		(1R,2R)-2-(6-(7-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	410.1, 1.95
230	192		(1R,2R)-2-(6-(7-(trifluoromethoxy)quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	476.1, 2.25
231	177		(1R,2R)-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.88
232	177		(1R,2R)-2-(6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.1, 1.93
233	182		(1S,2S)-3-methoxy-1-phenyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)propan-1-ol	458.1, 2.18

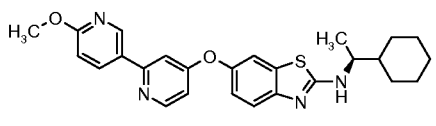
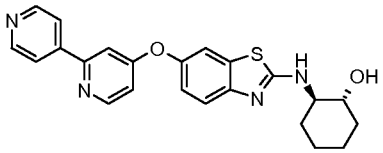
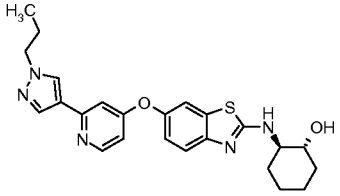
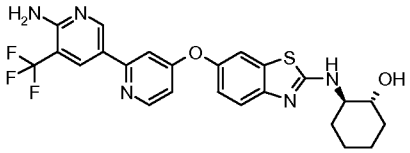
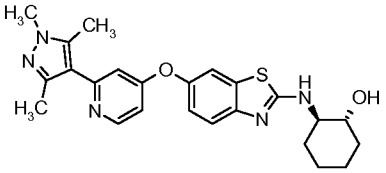
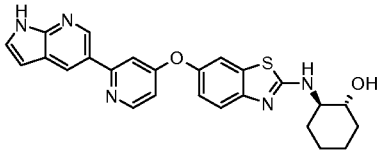
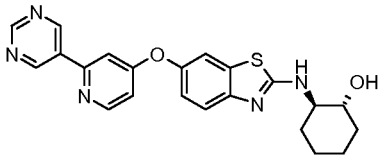
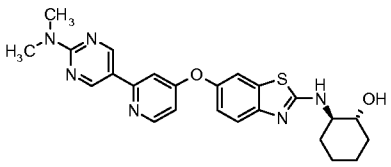
234	182		(2S,3S)-3-methyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	394.2, 2.08
235	182		(S)-2-phenyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)ethanol	414.1, 2.11
236	182		(S)-2-cyclohexyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)ethanol	420.2, 2.21
237	182		(1R,2S)-1-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	426.1, 2.20
238	182		(S)-4-methyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	394.2, 2.09
239	182		(1S,2R)-1-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	426.1, 2.20
240	182		(R)-2-cyclohexyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)ethanol	420.2, 2.21
241	182		(S)-N-(1-cyclohexylethyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	404.1, 2.48
242	182		(S)-3-phenyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)propan-1-ol	428.0, 2.13

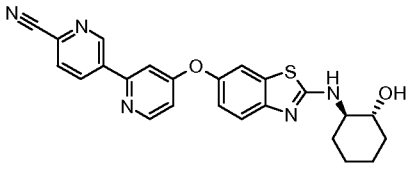
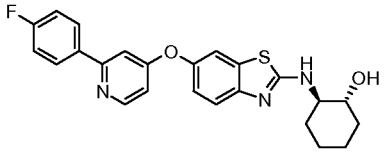
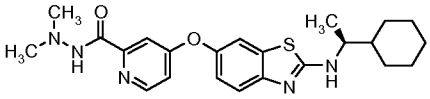
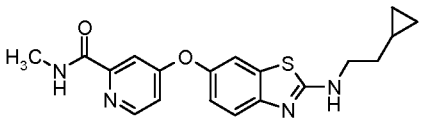
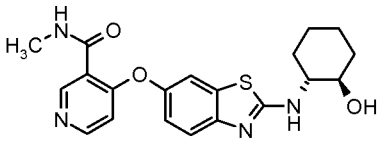
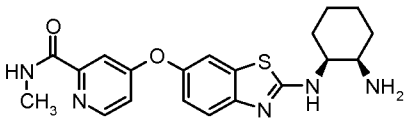
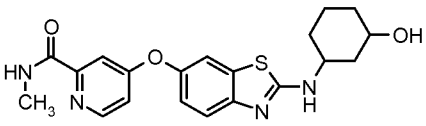
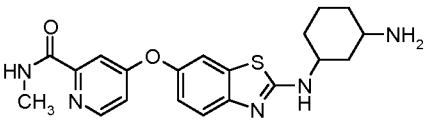
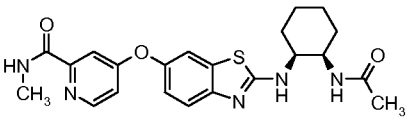
243	182		(R)-N-(1-cyclohexylethyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	404.1, 2.48
244	182		(S)-3-methyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)butan-1-ol	380.1, 1.95
245	182		(R)-4-methyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	394.2, 2.09
246	182		N-(2-(difluoromethoxy)benzyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	450.1, 2.47
247	182		N-cycloheptyl-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	390.1, 2.36
248	182		(S)-3,3-dimethyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)butan-1-ol	394.1, 2.05
249	182		(S)-6-(quinolin-4-yloxy)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzo[d]thiazol-2-amine	424.1, 2.54
250	182		(S)-3-cyclohexyl-2-(6-(quinolin-4-yloxy)benzo[d]thiazol-2-ylamino)propan-1-ol	434.2, 2.37
251	182		N-((1R,2R,4S)-bicyclo[2.2.1]heptan-2-yl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	388.1, 2.29

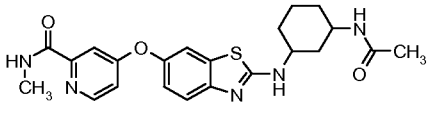
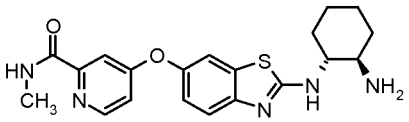
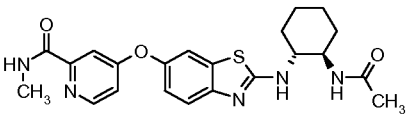
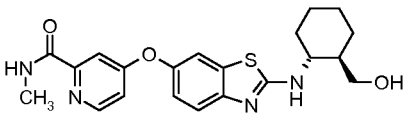
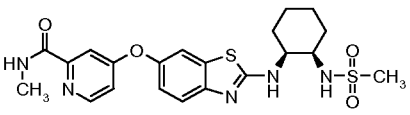
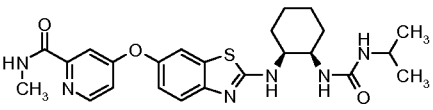
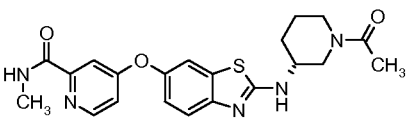
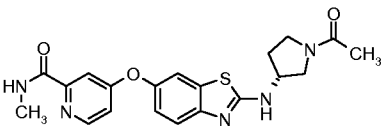
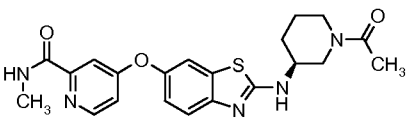
252	182		6-(quinolin-4-yloxy)-N-(2-(tetrahydro-2H-pyran-4-yl)ethyl)benzo[d]thiazol-2-amine	406.1, 2.00
253	182		N-isopentyl-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	364.1, 2.24
254	182		N-(pyridin-3-ylmethyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	385.1, 1.78
255	182		N-(2-morpholinoethyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	407.1, 1.77
256	182		N-cyclohexyl-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	376.1, 2.21
257	182		N-(2-methoxybenzyl)-6-(quinolin-4-yloxy)benzo[d]thiazol-2-amine	414.1, 2.29
258	177		(1R,2R)-2-(6-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	462.2, 2.03
259	176		(1R,2R)-2-(6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	454.2, 1.89
260	176		(1R,2R)-2-(6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	466.2, 1.89

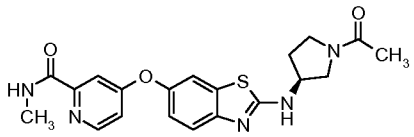
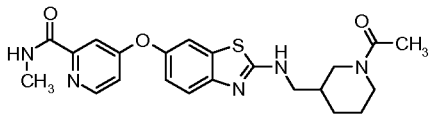
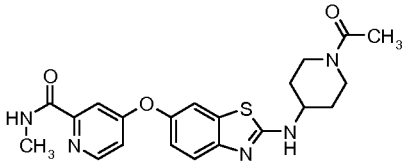
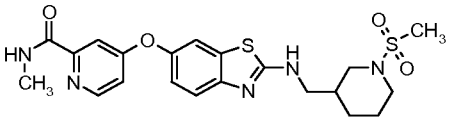
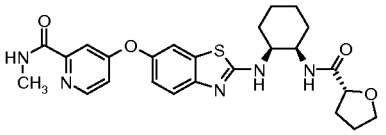
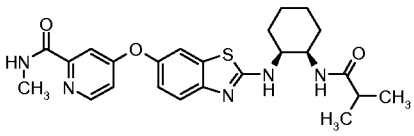
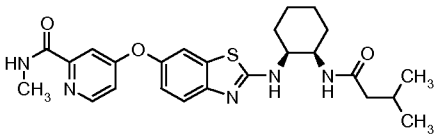
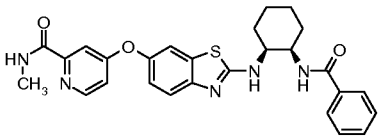
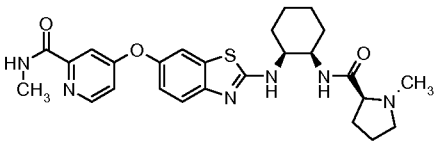
261	174		(1R,2R)-2-(6-(6'-amino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	434.2, 1.78
262	187		(1R,2R)-2-(6-(2-(1H-imidazol-1-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.2, 1.85
263	192		(1R,2R)-2-(6-(8-fluoroquinolin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	410.1, 1.95
264	184		(S)-6-(2-chloropyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine	388.1, 2.95
265	174		(1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.1, 1.93
266	177		(1R,2R)-2-(6-(2-(4,5-diethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.2, 2.10
267	177		(1R,2R)-2-(6-(2-(5-methyl-4-propyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.2, 2.10
268	186		(S)-N-(1-cyclohexylethyl)-6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	434.2, 2.35
269	186		(S)-N-(1-cyclohexylethyl)-6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	448.2, 2.43

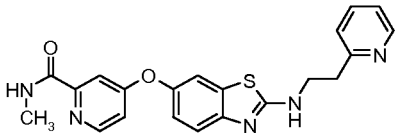
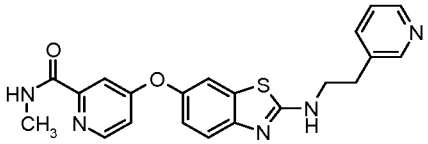
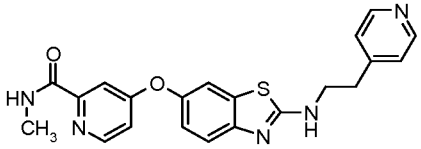
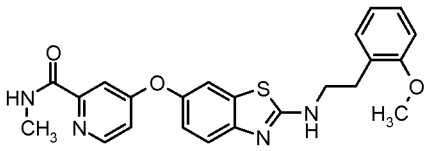
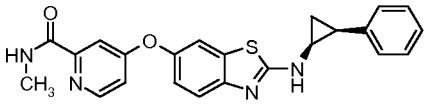
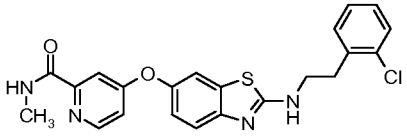
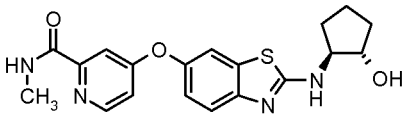
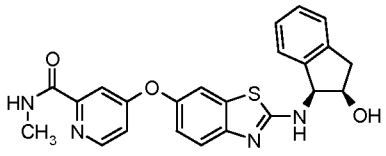
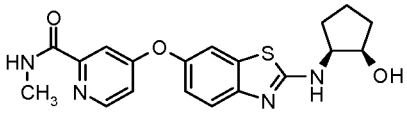
270	186		(S)-N-(1-cyclohexylethyl)-6-(2-(4-ethyl-5-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	462.2, 2.49
271	186		(S)-N-(1-cyclohexylethyl)-6-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	474.2, 2.54
272	186		(S)-N-(1-cyclohexylethyl)-6-(2-(4,5-diethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	476.2, 2.62
273	185		(S)-N-(1-cyclohexylethyl)-6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	462.2, 2.53
274	185		(S)-6-(2,3'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine	431.2, 2.35
275	185		(S)-6-(2,4'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine	431.2, 2.35
276	185		(S)-6-(6'-amino-2,3'-bipyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine	446.1, 2.25
277	185		(S)-N-(1-cyclohexylethyl)-6-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	434.2, 2.58
278	185		(S)-6-(2-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yloxy)-N-(1-cyclohexylethyl)benzo[d]thiazol-2-amine	470.2, 2.46

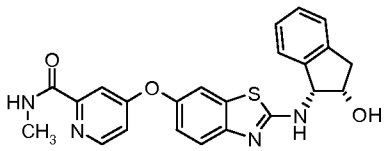
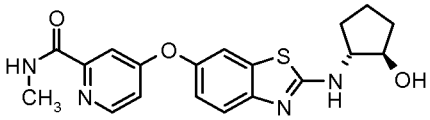
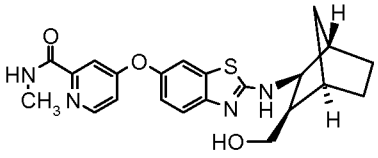
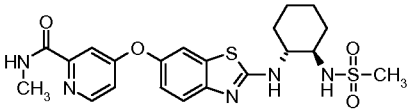
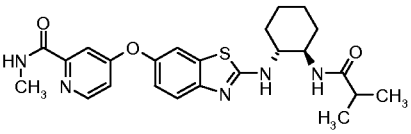
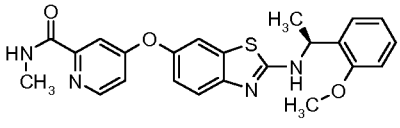
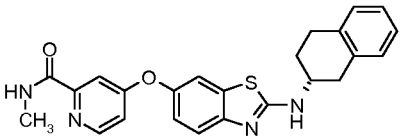
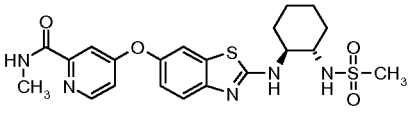
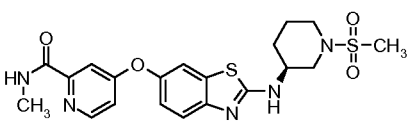
279	185		(S)-N-(1-cyclohexylethyl)-6-(6'-methoxy-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-amine	461.2, 2.58
280	174		(1R,2R)-2-(6-(2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.0, 1.68
281	174		(1R,2R)-2-(6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.0, 2.02
282	174		(1R,2R)-2-(6-(6'-amino-5'-(trifluoromethyl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	502.0, 2.02
283	174		(1R,2R)-2-(6-(2-(1,3,5-trimethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	450.0, 1.86
284	174		(1R,2R)-2-(6-(2-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	458.0, 1.91
285	174		(1R,2R)-2-(6-(2-(pyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	420.1, 1.90
286	174		(1R,2R)-2-(6-(2-(2-(dimethylamino)pyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	463.1, 1.96

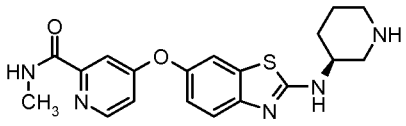
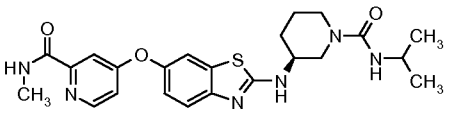
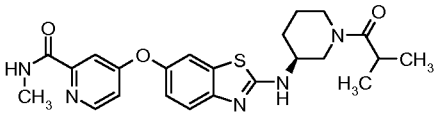
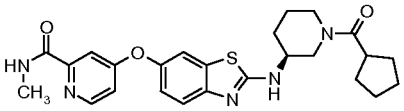
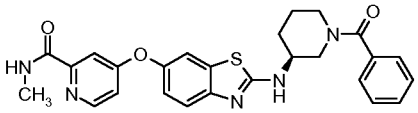
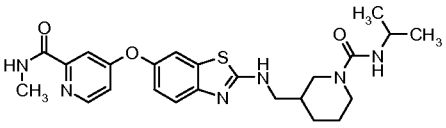
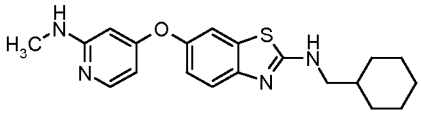
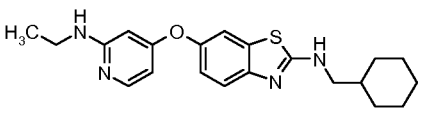
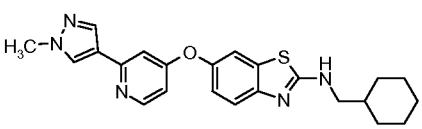
287	174		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,3'-bipyridine-6'-carbonitrile	444.0, 2.18
288	174		(1R,2R)-2-(6-(2-(4-fluorophenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	436.0, 2.06
289	195		(S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)-N',N'-dimethylpicolinohydrazide	440.1, 2.33
290	162		4-(2-(2-cyclopropylethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	369.0, 2.03
291	195		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylnicotinamide	399.1, 1.72
292	162		4-(2-((1S,2R)-2-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	398.1, 1.79
293	162		4-(2-(3-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	399.1, 1.76
294	162		4-(2-(3-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	398.1, 1.65
295	163		4-(2-((1S,2R)-2-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.96

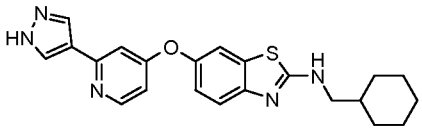
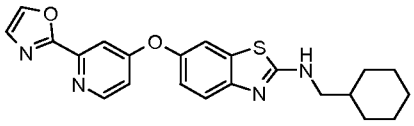
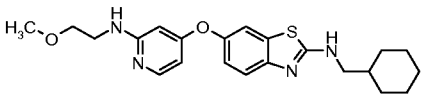
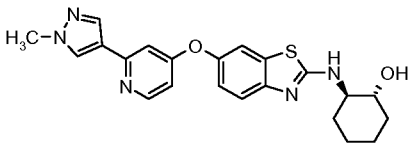
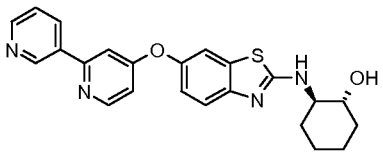
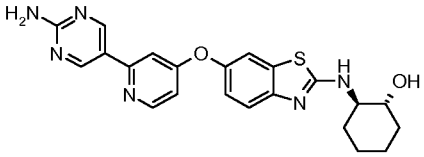
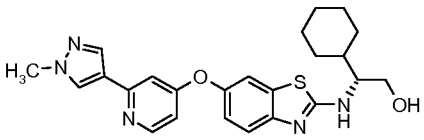
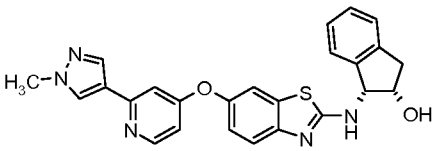
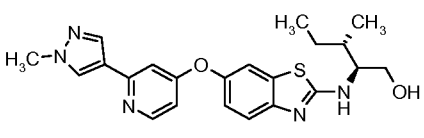
296	163		4-(2-(3-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.87
297	163		4-(2-((1R,2R)-2-aminocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	398.2 1.79
298	163		4-(2-((1R,2R)-2-acetamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.2, 1.84
299	162		4-(2-((1R,2R)-2-(hydroxymethyl)cyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	413.1, 1.92
300	164		N-methyl-4-(2-((1S,2R)-2-(methylsulfonamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	476.1, 2.05
301	167		4-(2-((1S,2R)-2-(3-isopropylureido)cyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	483.2, 2.0
302	165		(R)-4-(2-(1-acetylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	426.2, 1.91
303	165		(R)-4-(2-(1-acetylpyrrolidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	412.2, 1.84
304	165		(S)-4-(2-(1-acetylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	426.2, 1.91

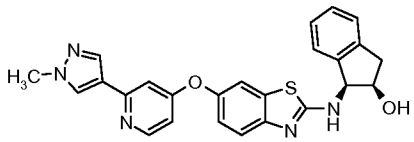
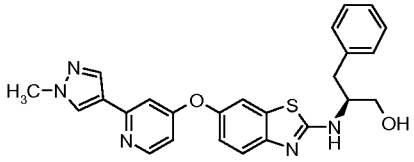
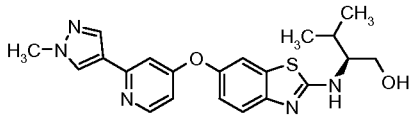
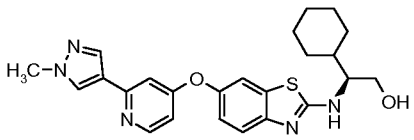
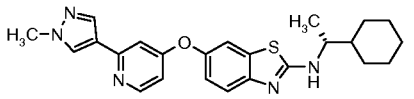
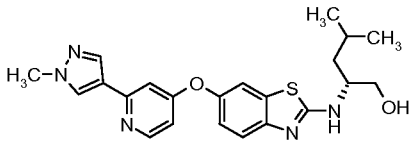
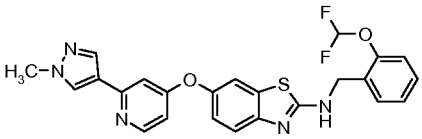
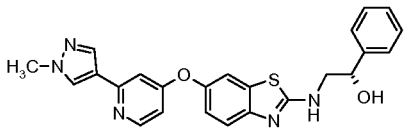
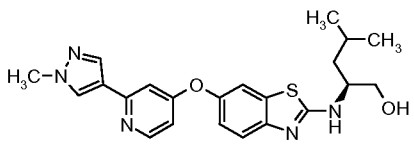
305	165		(S)-4-(2-(1-acetylpyrrolidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	412.21, 1.84
306	165		4-(2-((1-acetylpiperidin-3-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	440.1, 2.04
307	165		4-(2-(1-acetylpiperidin-4-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	426.2, 1.85
308	165		N-methyl-4-(2-((1-(methylsulfonyl)piperidin-3-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	476.1, 1.96
309	166		N-methyl-4-(2-((1S,2R)-2-((R)-tetrahydrofuran-2-carboxamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	496.2, 2.13
310	166		4-(2-((1S,2R)-2-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	468.2, 2.14
311	166		N-methyl-4-(2-((1S,2R)-2-(3-methylbutanamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	482.2, 2.28
312	166		4-(2-((1S,2R)-2-benzamidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	502.2, 2.22
313	166		N-methyl-4-(2-((1S,2R)-2-((S)-1-methylpyrrolidine-2-carboxamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	509.2, 1.82

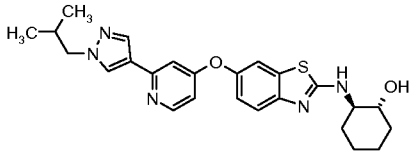
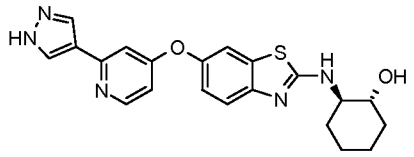
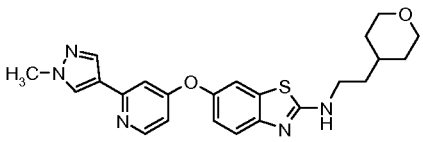
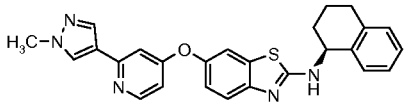
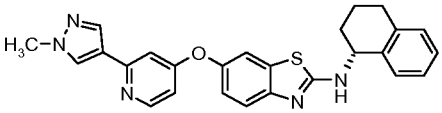
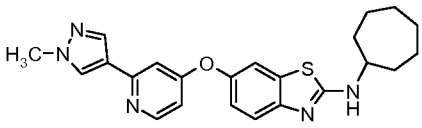
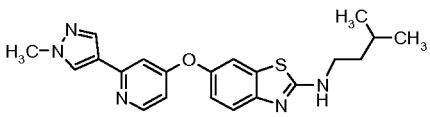
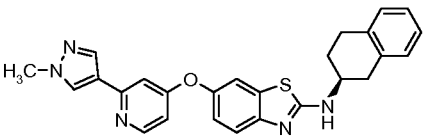
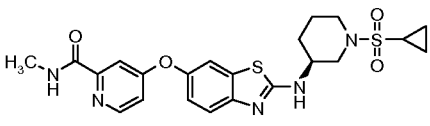
314	162		N-methyl-4-(2-(2-(pyridin-2-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	406.1, 1.67
315	162		N-methyl-4-(2-(2-(pyridin-3-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	406.1, 1.63
316	162		N-methyl-4-(2-(2-(pyridin-4-yl)ethylamino)benzo[d]thiazol-6-yloxy)picolinamide	406.1, 1.63
317	162		4-(2-(2-methoxyphenethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.1, 2.29
318	162		N-methyl-4-(2-((1S,2S)-2-phenylcyclopropylamino)benzo[d]thiazol-6-yloxy)picolinamide	417.1, 2.51
319	162		4-(2-(2-chlorophenethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	439.1, 2.4
320	162		4-(2-((1S,2S)-2-hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.74
321	162		4-(2-((1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	433.1, 2.08
322	162		4-(2-((1S,2R)-2-hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.75

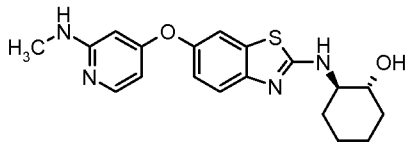
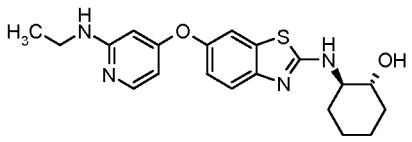
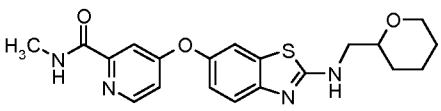
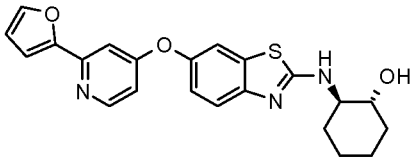
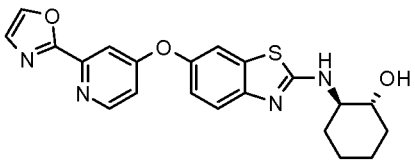
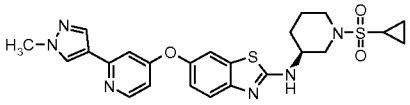
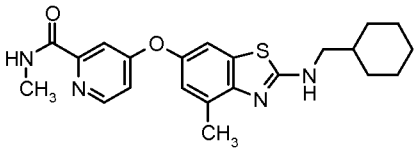
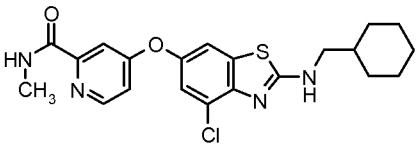
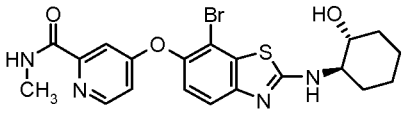
323	162		4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	433.1, 2.08
324	162		4-(2-((1R,2R)-2-hydroxycyclopentylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	385.1, 1.75
325	162		4-(2-((1S,3R,4R)-3-(hydroxymethyl)bicyclo[2.2.1]heptan-2-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	425.1, 1.92
326	164		N-methyl-4-(2-((1R,2R)-2-(methylsulfonamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	476.1, 1.87
327	166		4-(2-((1R,2R)-2-isobutyramidocyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	468.1, 2.02
328	162		(S)-4-(2-(1-(2-methoxyphenyl)ethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	435.1, 2.32
329	162		(R)-N-methyl-4-(2-(1,2,3,4-tetrahydronaphthalen-2-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	431.1, 2.55
330	164		N-methyl-4-(2-((1S,2S)-2-(methylsulfonamido)cyclohexylamino)benzo[d]thiazol-6-yloxy)picolinamide	476.1, 1.87
331	164		(S)-N-methyl-4-(2-(1-(methylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	462.1, 1.90

332	162		(S)-N-methyl-4-(2-(piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)picolinamide	384.1, 1.65
333	167		(S)-4-(2-(1-(isopropylcarbamoyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	469.2, 1.94
334	166		(S)-4-(2-(1-isobutyrylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	454.2, 1.99
335	166		(S)-4-(2-(1-(cyclopentanecarbonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	480.2, 2.2
336	166		(S)-4-(2-(1-benzoylpiperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	488.2, 2.09
337	166		4-(2-((1-(isopropylcarbamoyl)piperidin-3-yl)methylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	483.2, 2.09
338	170		N-(cyclohexylmethyl)-6-(2-(methylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine	369.1, 2.09
339	170		N-(cyclohexylmethyl)-6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine	383.1, 2.33
340	174		N-(cyclohexylmethyl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	420.2, 2.13

341	174		6-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(cyclohexylmethyl)benzo[d]thiazol-2-amine	406.1, 2.12
342	175		N-(cyclohexylmethyl)-6-(2-(oxazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	407.1, 2.36
343	170		N-(cyclohexylmethyl)-6-(2-(2-methoxyethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-amine	413.2, 2.16
344	174		(1R,2R)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	422.2, 1.68
345	174		(1R,2R)-2-(6-(2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	419.1, 1.69
346	174		(1R,2R)-2-(6-(2-(2-aminopyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	435.2, 1.61
347	168		(R)-2-cyclohexyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)ethanol	450.2, 1.96
348	168		(1R,2S)-1-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	456.1, 1.94
349	168		(2S,3S)-3-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	424.2, 1.83

350	168		(1S,2R)-1-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	456.1, 1.95
351	168		(S)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-3-phenylpropan-1-ol	458.1, 1.89
352	168		(S)-3-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)butan-1-ol	410.1, 1.70
353	168		(S)-2-cyclohexyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)ethanol	450.1, 1.97
354	168		(R)-N-(1-cyclohexylethyl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	434.1, 2.21
355	168		(R)-4-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	423.1, 1.85
356	168		N-(2-(difluoromethoxy)benzyl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	480.1, 2.20
357	168		(S)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-1-phenylethanol	444.1. 1.85
358	168		(S)-4-methyl-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	424.1, 1.85

359	174		(1R,2R)-2-(6-(2-(1-isobutyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	464.4, 1.95
360	174		(1R,2R)-2-(6-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.63
361	168		6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(2-(tetrahydro-2H-pyran-4-yl)ethyl)benzo[d]thiazol-2-amine	436.2, 1.74
362	168		(S)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzo[d]thiazol-2-amine	454.2, 2.25
363	168		(R)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1,2,3,4-tetrahydronaphthalen-1-yl)benzo[d]thiazol-2-amine	454.2, 2.24
364	168		N-cycloheptyl-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	420.2, 2.08
365	168		N-isopentyl-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	394.2, 1.98
366	168		(S)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1,2,3,4-tetrahydronaphthalen-2-yl)benzo[d]thiazol-2-amine	454.2, 2.22
367	169		(S)-4-(2-(1-(cyclopropylsulfonyl)piperidin-3-ylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	488.0, 2.17

368	170		(1R,2R)-2-(6-(2-(methylamino)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	371.1, 1.79
369	170		(1R,2R)-2-(6-(2-(ethylamino)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	385.1, 1.74
370	162		N-methyl-4-(2-((tetrahydro-2H-pyran-2-yl)methylamino)benzo[d]thiazol-6-yloxy)picolinamide	399.1, 2.16
371	175		(1R,2R)-2-(6-(2-(furan-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.1, 1.94
372	175		(1R,2R)-2-(6-(2-(oxazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	409.1, 1.98
373	169		(S)-N-(1-(cyclopropylsulfonyl)piperidin-3-yl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	511.2, 2.0
374	193		4-(2-(cyclohexylmethylamino)-4-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide	411;2.81
375	194		4-(4-chloro-2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	431;3.31
376	195		4-(7-bromo-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	479, 2.37

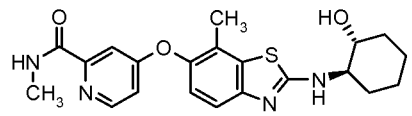
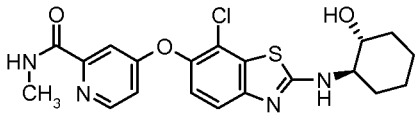
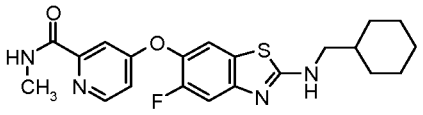
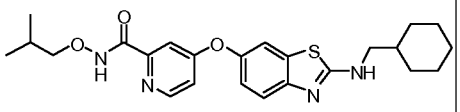
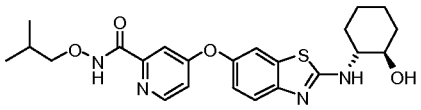
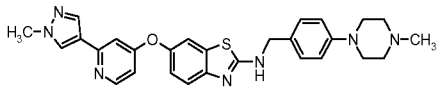
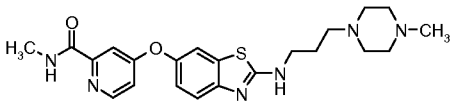
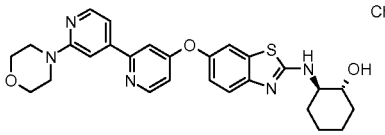
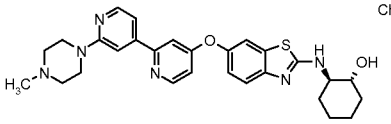
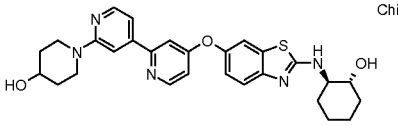
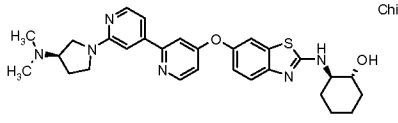
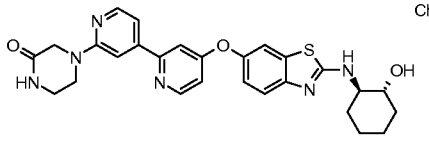
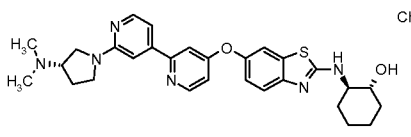
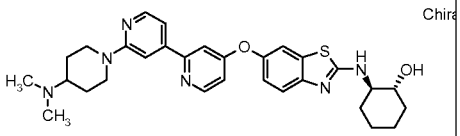
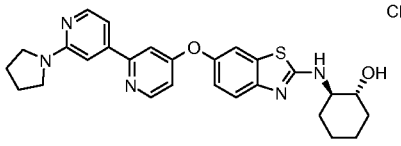
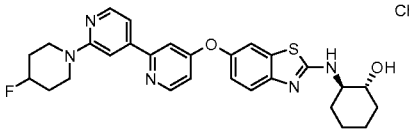
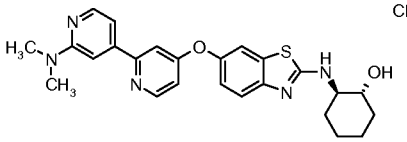
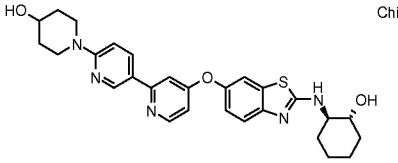
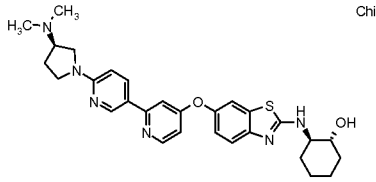
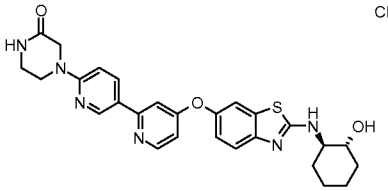
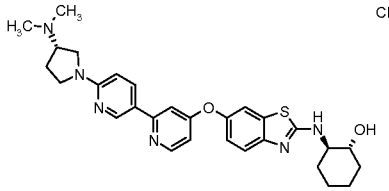
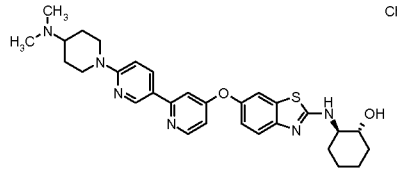
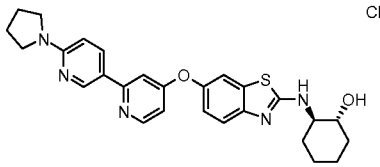
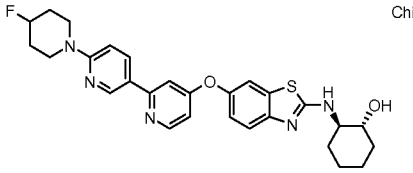
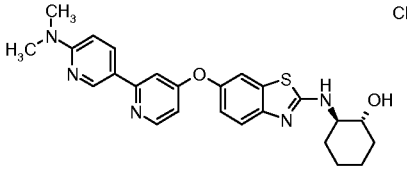
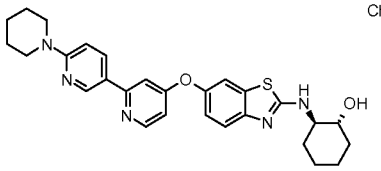
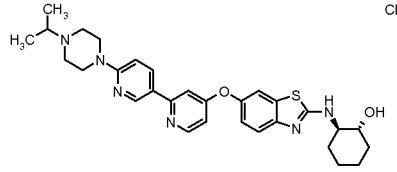
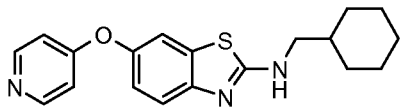
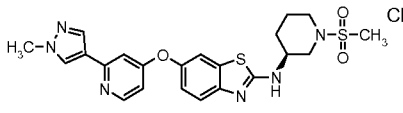
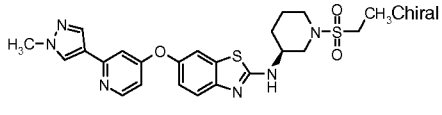
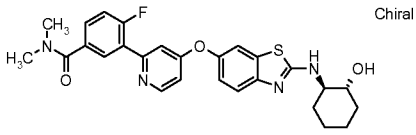
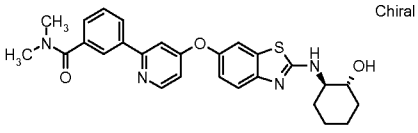
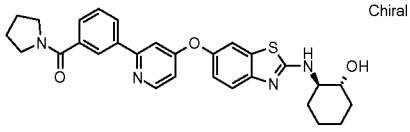
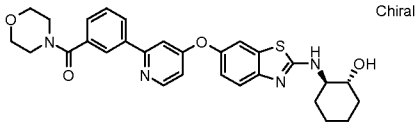
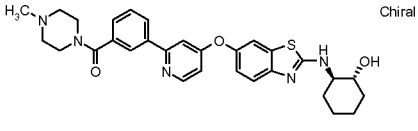
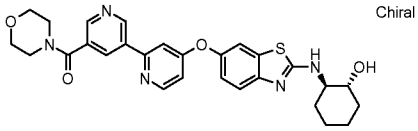
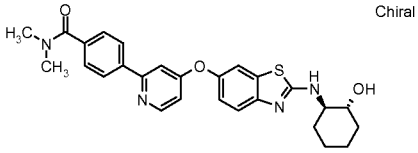
377	196		4-(2-((1R,2R)-2-hydroxycyclohexylamino)-7-methylbenzo[d]thiazol-6-yloxy)-N-methylpicolinamide	413, 2.09
378	197		4-(7-chloro-2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	433, 2.33
379	198		4-(2-(cyclohexylmethylamino)-5-fluorobenzo[d]thiazol-6-yloxy)-N-methylpicolinamide	415, 2.81
380	203		4-(2-(cyclohexylmethylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide	455.1, 2.90
381	204		4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-isobutoxypicolinamide	457.0, 2.35

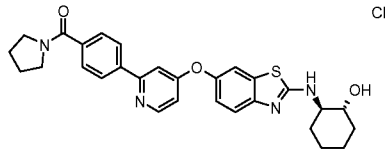
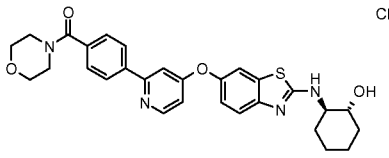
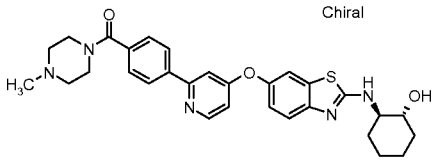
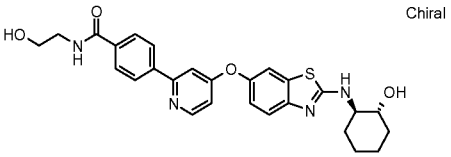
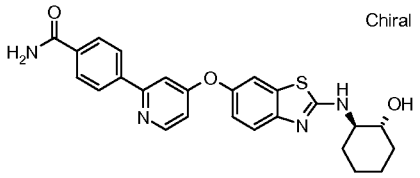
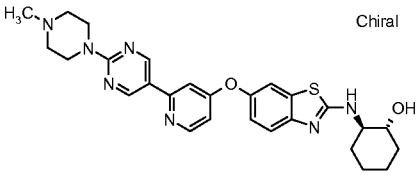
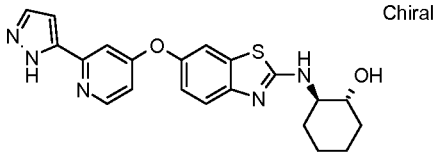
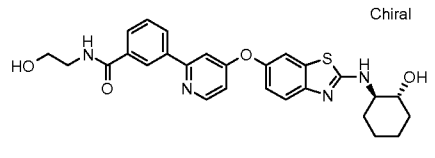
Table 4

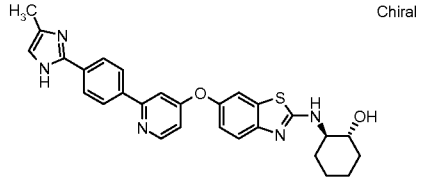
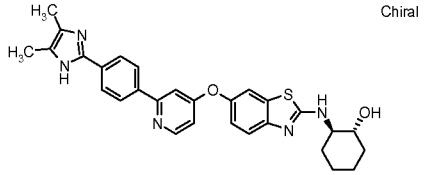
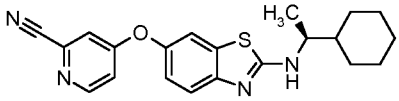
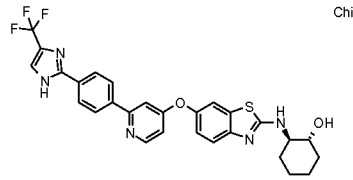
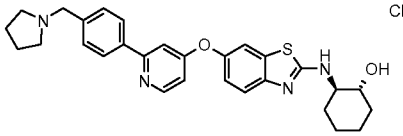
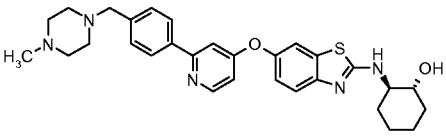
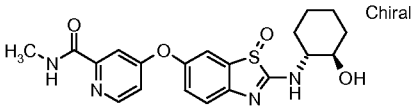
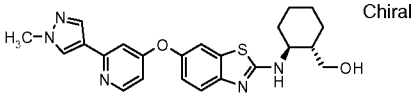
Cmpd	Ex Prep	Structure	Name	(M+H)+, Rt(min.)
1	168		6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(4-(4-methylpiperazin-1-yl)benzyl)benzo[d]thiazol-2-amine	512.2, 1.79
2	199		N-methyl-4-(2-(3-(4-methylpiperazin-1-yl)propylamino)benzo[d]thiazol-6-yloxy)picolinamide	441.0;1.66
3	207		(1R,2R)-2-(6-(2'-morpholino-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	504.1, 1.99
4	207		(1R,2R)-2-(6-(2'-(4-methylpiperazin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	517.2, 1.86
5	207		1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,4'-bipyridin-2'-yl)piperidin-4-ol	518.2, 1.93
6	207		(1R,2R)-2-(6-(2'-((R)-3-(dimethylamino)pyrrolidin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	531.2, 1.85
7	207		4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,4'-bipyridin-2'-yl)piperazin-2-one	517.2, 1.89
8	207		(1R,2R)-2-(6-(2'-((S)-3-(dimethylamino)pyrrolidin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	531.2, 1.85

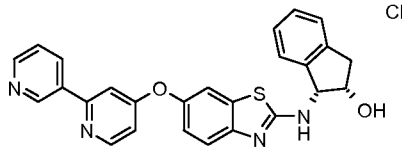
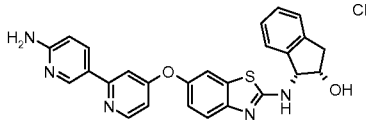
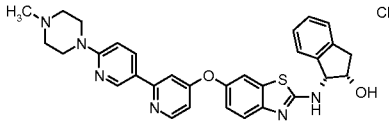
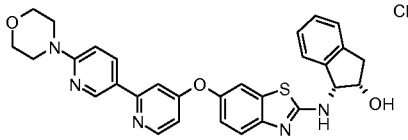
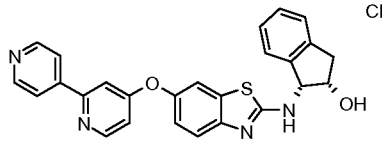
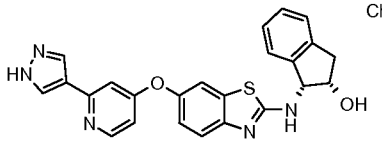
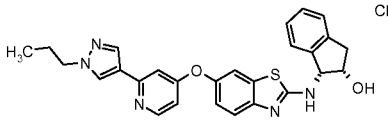
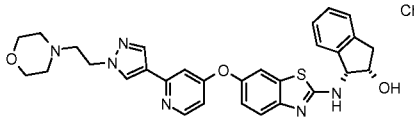
9	207	 Chira	(1R,2R)-2-(6-(2'-(4-(dimethylamino)piperidin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	545.2, 1.87
10	207	 Chiral	(1R,2R)-2-(6-(2'-(pyrrolidin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	488.2, 2.05
11	207	 Chiral	(1R,2R)-2-(6-(2'-(4-fluoropiperidin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	520.2, 2.10
12	207	 Chiral	(1R,2R)-2-(6-(2'-(dimethylamino)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	462.1, 1.95
13	207	 Chiral	1-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,3'-bipyridin-6'-yl)piperidin-4-ol	518.2, 1.88
14	207	 Chiral	(1R,2R)-2-(6-(6'-((R)-3-(dimethylamino)pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	531.2, 1.80
15	207	 Chiral	4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,3'-bipyridin-6'-yl)piperazin-2-one	517.2, 1.86
16	207	 Chiral	(1R,2R)-2-(6-(6'-((S)-3-(dimethylamino)pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	531.2, 1.80

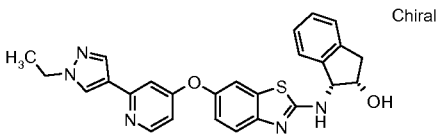
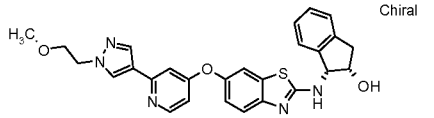
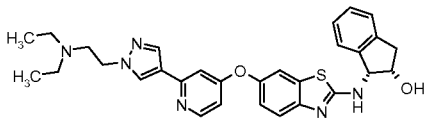
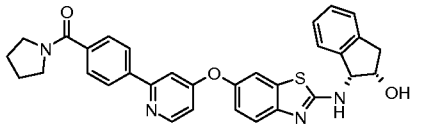
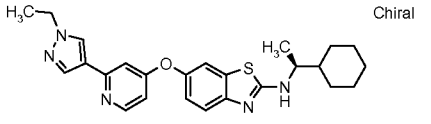
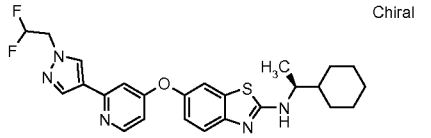
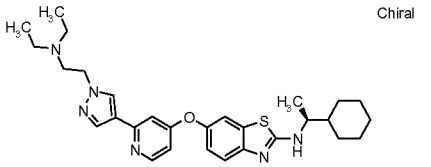
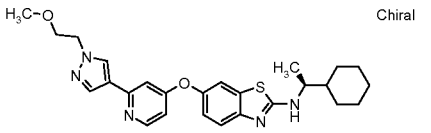
17	207	 Chiral	(1R,2R)-2-(6-(6'-(4-(dimethylamino)piperidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	545.2, 1.83
18	207	 Chiral	(1R,2R)-2-(6-(6'-(pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	488.1, 1.95
19	207	 Chiral	(1R,2R)-2-(6-(6'-(4-fluoropiperidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	520.2, 2.10
20	207	 Chiral	(1R,2R)-2-(6-(6'-(dimethylamino)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	462.1, 1.88
21	207	 Chiral	(1R,2R)-2-(6-(6'-(piperidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	502.2, 2.08
22	207	 Chiral	(1R,2R)-2-(6-(6'-(4-isopropylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	545.2, 1.87
23	210		N-(cyclohexylmethyl)-6-(pyridin-4-yloxy)benzo[d]thiazol-2-amine	340.1, 2.11
24	169	 Chiral	(S)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1-(methylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	485.0, 1.91

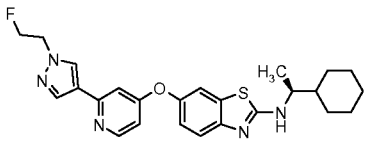
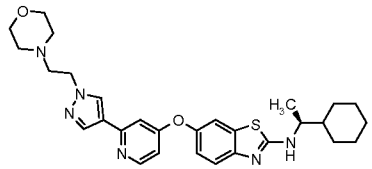
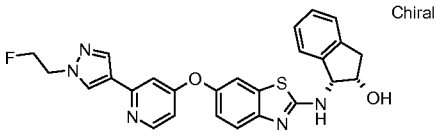
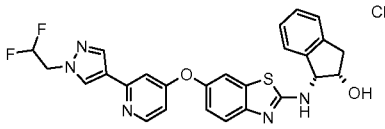
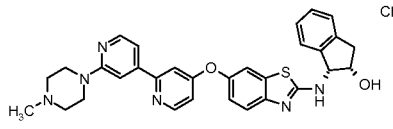
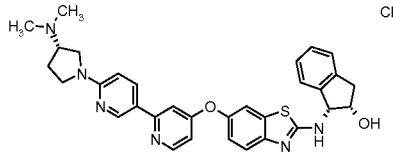
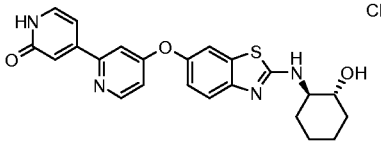
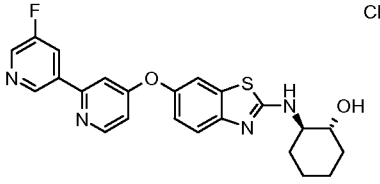
25	169		(S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	499.0, 1.98
26	179		4-fluoro-3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-N,N-dimethylbenzamide	507.1, 1.95
27	179		3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-N,N-dimethylbenzamide	489.1, 1.95
28	179		(3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(pyrrolidin-1-yl)methanone	515.2, 2.05
29	179		(3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(morpholino)methanone	531.2, 1.95
30	179		(3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(4-methylpiperazin-1-yl)methanone	544.1, 1.72
31	179		(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-2,3'-bipyridin-5'-yl)(morpholino)methanone	532.1, 1.86
32	179		4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-N,N-dimethylbenzamide	489.2, 1.95

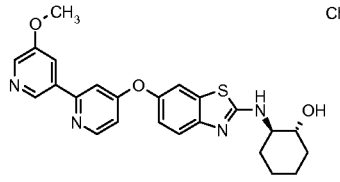
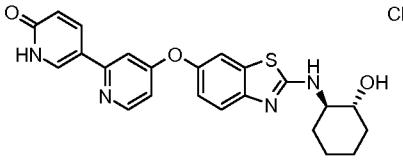
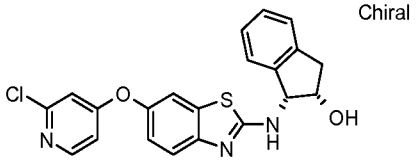
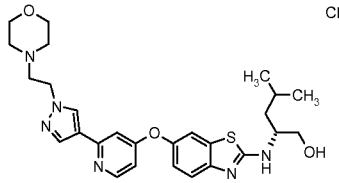
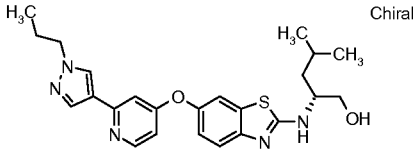
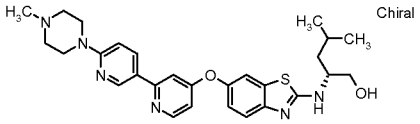
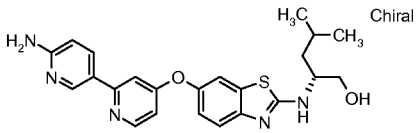
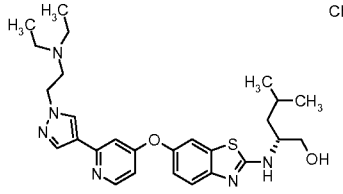
33	179	 Chiral	(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(pyrrolidin-1-yl)methanone	515.2, 2.05
34	179	 Chiral	(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(morpholino)methanone	531.2, 1.95
35	179	 Chiral	(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(4-methylpiperazin-1-yl)methanone	544.2, 1.80
36	179	 Chiral	4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-N-(2-hydroxyethyl)benzamide	505.2, 1.84
37	179	 Chiral	4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)benzamide	461.1, 1.85
38	179	 Chiral	(1R,2R)-2-(6-(2-(2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	518.2, 1.81
39	185	 Chiral	(1R,2R)-2-(6-(2-(1H-pyrazol-5-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	408.0, 1.78
40	185	 Chiral	3-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-N-(2-hydroxyethyl)benzamide	505.1, 1.86

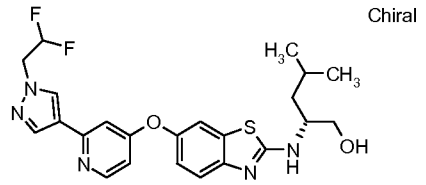
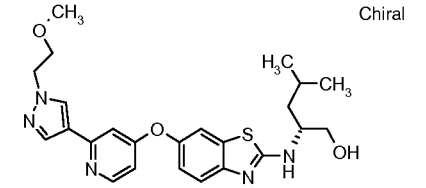
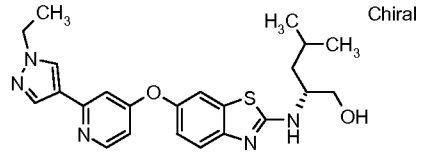
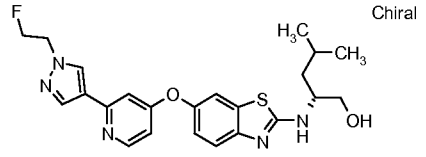
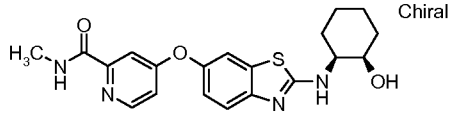
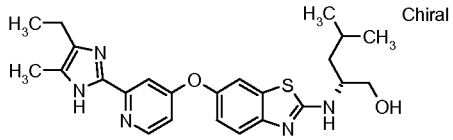
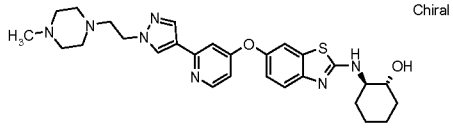
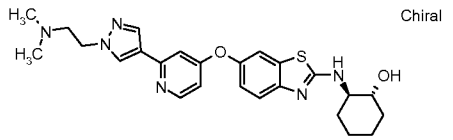
41	177	 Chiral	(1R,2R)-2-(6-(2-(4-(4-methyl-1H-imidazol-2-yl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	498.1, 1.89
42	177	 Chiral	(1R,2R)-2-(6-(2-(4-(4,5-dimethyl-1H-imidazol-2-yl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	512.2, 1.93
43	180	 Chiral	(S)-4-(2-(1-cyclohexylethylamino)benzo[d]thiazol-6-yloxy)picolinonitrile	379.1, 2.94
44	177	 Chiral	(1R,2R)-2-(6-(2-(4-(4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	552.1, 2.26
45	208	 Chiral	(1R,2R)-2-(6-(2-(4-(pyrrolidin-1-ylmethyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	501.2, 1.85
46	208	 Chiral	(1R,2R)-2-(6-(2-(4-((4-methylpiperazin-1-yl)methyl)phenyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	530.2, 1.82
47	211	 Chiral	4-(2-((1R,2R)-2-hydroxycyclohexylamino)-1-oxo-benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	415.1, 1.81
48	168	 Chiral	((1S,2S)-2-(6-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexyl)methanol	436.0, 1.90

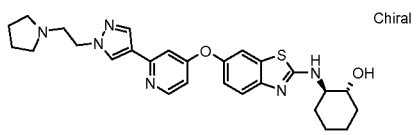
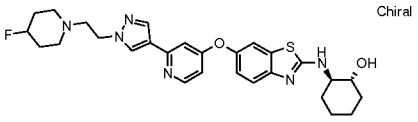
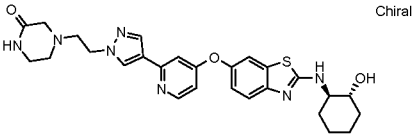
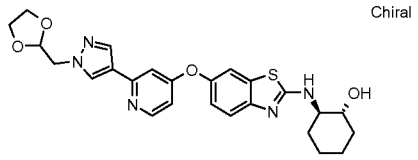
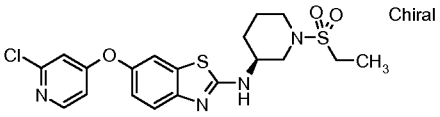
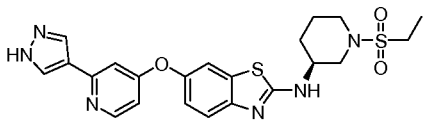
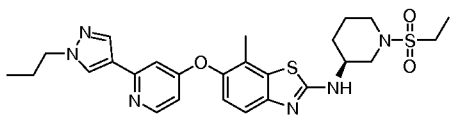
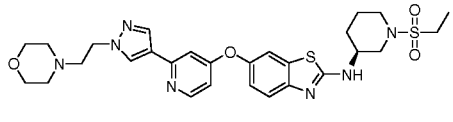
49	179	 Chiral	(1R,2S)-1-(6-(2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	453.0, 2.09
50	179	 Chiral	(1R,2S)-1-(6-(6'-amino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	468.0, 2.02
51	179	 Chiral	(1R,2S)-1-(6-(6'-(4-methylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	551.1, 1.96
52	179	 Chiral	(1R,2S)-1-(6-(6'-morpholino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	538.1, 2.18
53	179	 Chiral	(1R,2S)-1-(6-(2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	453.1, 2.15
54	179	 Chiral	(1R,2S)-1-(6-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	442.0, 2.01
55	179	 Chiral	(1R,2S)-1-(6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	484.1, 2.25
56	179	 Chiral	(1R,2S)-1-(6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	555.1, 1.92

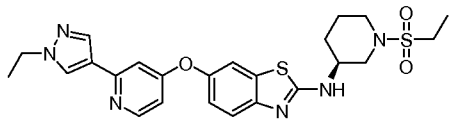
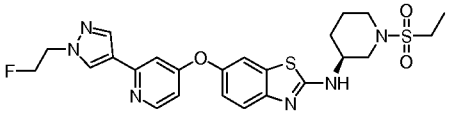
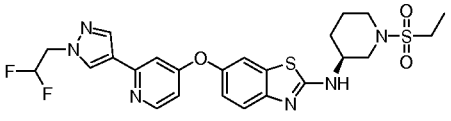
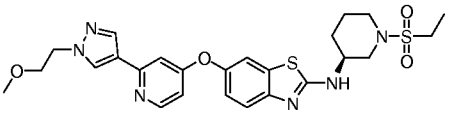
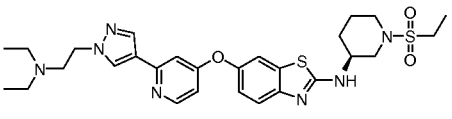
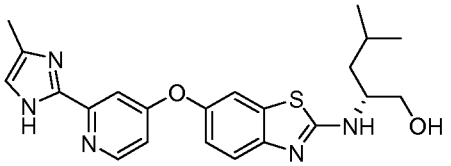
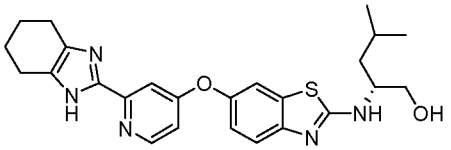
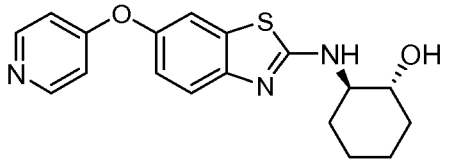
57	176		(1R,2S)-1-(6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	470.0, 2.16
58	176		(1R,2S)-1-(6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	500.0, 2.12
59	176		(1R,2S)-1-(6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	541.1, 1.97
60	179		(4-(4-(2-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-ylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)phenyl)(pyrrolidin-1-yl)methanone	549.2, 2.25
61	212		(S)-N-(1-cyclohexylethyl)-6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	448.1, 2.79
62	212		(S)-N-(1-cyclohexylethyl)-6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	484.1, 2.44
63	212		(S)-N-(1-cyclohexylethyl)-6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	519.2, 2.18
64	212		(S)-N-(1-cyclohexylethyl)-6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	478.1, 2.37

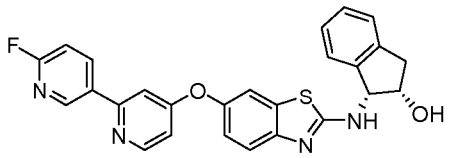
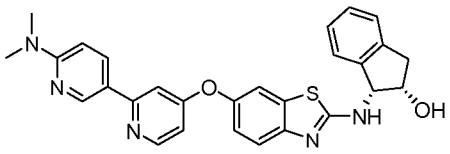
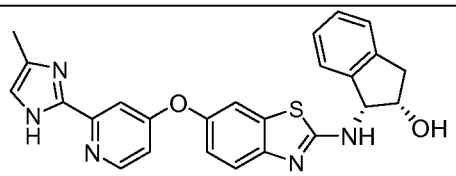
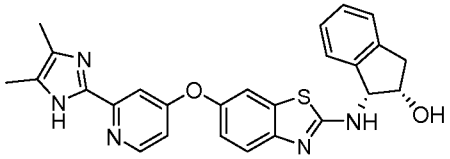
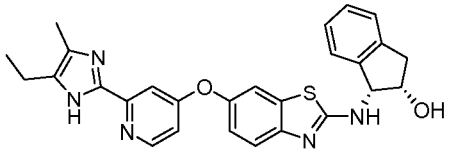
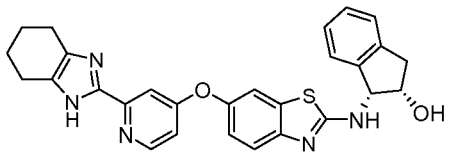
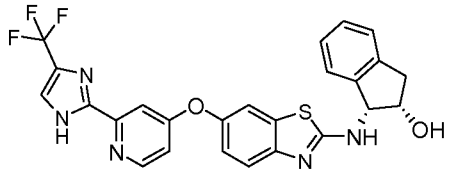
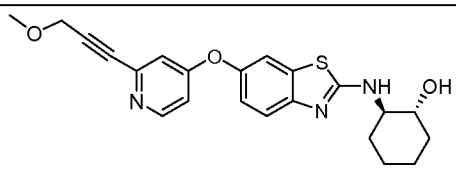
65	212	 Chiral	(S)-N-(1-cyclohexylethyl)-6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	466.1, 2.38
66	213	 Chiral	(S)-N-(1-cyclohexylethyl)-6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	533.1, 2.14min
67	176	 Chiral	(1R,2S)-1-(6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	488.1, 2.17
68	176	 Chiral	(1R,2S)-1-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	506.1, 2.25
69	179	 Chiral	(1R,2S)-1-(6-(2'-(4-methylpiperazin-1-yl)-2,4'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	551.2, 2.09
70	207	 Chiral	(1R,2S)-1-(6-(6'-((S)-3-(dimethylamino)pyrrolidin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	565.2, 2.02
71	179	 Chiral	4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyridin-2(1H)-one	435.1, 1.82
72	179	 Chiral	(1R,2R)-2-(6-(5'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	437.1, 2.07

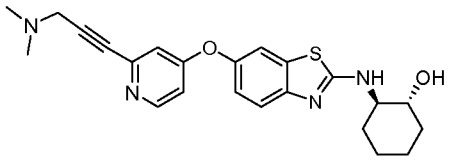
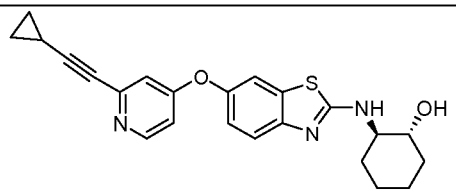
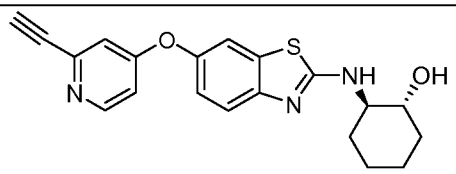
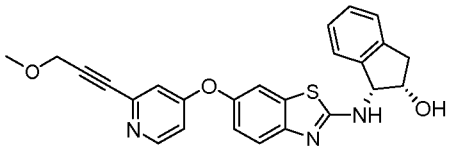
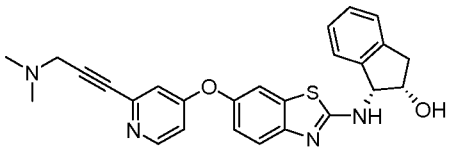
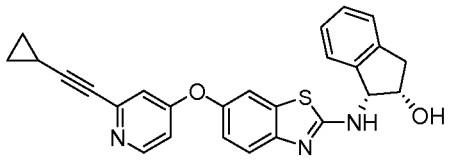
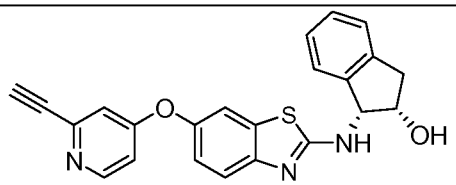
73	179	 Chiral	(1R,2R)-2-(6-(5'-methoxy-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	449.1, 2.00
74	179	 Chiral	5-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)pyridin-2(1H)-one	435.1, 1.77
75	173	 Chiral	(1R,2S)-1-(6-(2-chloropyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	410.0, 2.63
76	176	 Chiral	(R)-4-methyl-2-(6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	523.1, 1.84
77	176	 Chiral	(R)-4-methyl-2-(6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	452.1, 2.31
78	176	 Chiral	(R)-4-methyl-2-(6-(6'-(4-methylpiperazin-1-yl)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	519.1, 1.85
79	176	 Chiral	(R)-2-(6-(6'-amino-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	436.0, 1.94
80	176	 Chiral	(R)-2-(6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	509.1;1.89

81	176	 Chiral	(R)-2-(6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	474.0, 2.07
82	176	 Chiral	(R)-2-(6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	468.1, 2.00
83	176	 Chiral	(R)-2-(6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	438.1, 2.13
84	176	 Chiral	(R)-2-(6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	456.3, 2.11
85	16	 Chiral	4-(2-((1S,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide; 4-(2-((1R,2S)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)-N-methylpicolinamide	399.1, 2.07
86	177	 Chiral	(R)-2-(6-(2-(4-ethyl-5-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-4-methylpentan-1-ol	452.1, 2.18
87	209	 Chiral	(1R,2R)-2-(6-(2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	534.3, 1.78
88	209	 Chiral	(1R,2R)-2-(6-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	479.2, 1.77

89	209		(1R,2R)-2-(6-(2-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	505.2, 1.80
90	209		(1R,2R)-2-(6-(2-(1-(2-(4-fluoropiperidin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	537.2, 1.83
91	209		4-(2-(4-(4-(2-((1R,2R)-2-hydroxycyclohexylamino)benzo[d]thiazol-6-yloxy)pyridin-2-yl)-1H-pyrazol-1-yl)ethyl)piperazin-2-one	534.2, 1.73
92	179		(1R,2R)-2-(6-(2-(1-((1,3-dioxolan-2-yl)methyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	494.2, 1.92
93	214		(S)-6-(2-chloropyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	453.0, 2.59
94	217		(S)-6-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	485.1; 1.73
95	217		(S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	527.1; 2.24
96	217		(S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	598.3; 1.67

97	218		(S)-6-(2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	513.2; 1.89
98	218		(S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-(2-fluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	531.2, 1.87
99	218		(S)-6-(2-(1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	549.2; 1.93
100	218		(S)-N-(1-(ethylsulfonyl)piperidin-3-yl)-6-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)benzo[d]thiazol-2-amine	543.2; 2.10
101	218		(S)-6-(2-(1-(2-(diethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-N-(1-(ethylsulfonyl)piperidin-3-yl)benzo[d]thiazol-2-amine	589.2, 1.94
102	177		(R)-4-methyl-2-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	424.2; 2.03
103			(R)-4-methyl-2-(6-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)pentan-1-ol	
104	219		(1R,2R)-2-(6-(pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	342.1; 1.74

105	207		(1R,2S)-1-(6-(6'-fluoro-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	471.1; 2.32
106	207		(1R,2S)-1-(6-(6'-(dimethylamino)-2,3'-bipyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	496.1; 2.11
107			(1R,2S)-1-(6-(2-(4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	
108			(1R,2S)-1-(6-(2-(4,5-dimethyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	
109			(1R,2S)-1-(6-(2-(5-ethyl-4-methyl-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	
110			(1R,2S)-1-(6-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	
111			(1R,2S)-1-(6-(2-(4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	
112	216		(1R,2R)-2-(6-(2-(3-methoxyprop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	410.1; 1.96

113	216		(1R,2R)-2-(6-(2-(3-(dimethylamino)prop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	423.2; 1.80
114	216		(1R,2R)-2-(6-(2-(cyclopropylethynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	406.2; 2.04
115	215		(1R,2R)-2-(6-(2-ethynylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)cyclohexanol	366.1; 1.91
116	216		(1R,2S)-1-(6-(2-(3-methoxyprop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	444.1; 2.26
117	216		(1R,2S)-1-(6-(2-(3-(dimethylamino)prop-1-ynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	457.1; 2.05
118	216		(1R,2S)-1-(6-(2-(cyclopropylethynyl)pyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	440.0; 2.35
119	215		(1R,2S)-1-(6-(2-ethynylpyridin-4-yloxy)benzo[d]thiazol-2-ylamino)-2,3-dihydro-1H-inden-2-ol	400.1; 2.20

Each of the compounds listed in Table 2 were shown to have activity with respect to inhibition of CSF-1R with an IC_{50} of less than about 10 μM. Many of the compounds exhibited activity with an IC_{50} of less than about 1 μM, or less than about 0.1 μM, or less than about 0.01 μM with respect to CSF-1R inhibition. The compounds of Tables 3 and 4

were found to have an activity of less than 1 μM. As such, each of the compounds of Tables 2, 3, and 4 is preferred individually and as a member of a group.

In addition to CSF-1R inhibitory activity, many of the compounds of Tables 2, 3, and 4 were also screened for Raf inhibition (according to biochemical screens described in US 10/405,945, which is entirely incorporated by reference), as well as other kinases, and shown to inhibit CSF-1R significantly greater (between about 2 and about 1,000 fold greater) than Raf and other kinases screened. More particularly, many of the compounds screened had activity greater about 1 μM with respect to Raf inhibition, whereas many of the same compounds exhibited activities with respect to CSF-1R at less than about 0.1 μM. As such, many of the compounds of Tables 2, 3, and 4 are potent and selective inhibitors of CSF-1R.

BIOLOGICAL EXAMPLES

Biological Example 1

In Vitro Kinase Assays for Colony Stimulating Factor-1 Receptor (CSF-1R)

The kinase activity of various protein tyrosine kinases can be measured by providing ATP and a suitable peptide or protein tyrosine-containing substrate, and assaying the transfer of phosphate moiety to the tyrosine residue. Recombinant protein corresponding to the cytoplasmic domain of the human CSF-1R was purchased from Invitrogen Corporation, Carlsbad, CA U.S.A. (#PV3249). For each assay, test compounds were serially diluted, starting at 25 μM with 3 fold dilutions, in DMSO in 384 well plates then mixed with an appropriate kinase reaction buffer consisting of 50 mM Hepes, 5 mM $MgCl_2$, 10 mM $MnCl_2$, 0.1% BSA, pH 7.5, 1.0 mM dithiothreitol, 0.01% Tween 80 plus 1μM ATP. Kinase protein and an appropriate biotinylated peptide substrate at 50 nM were added to give a final volume of 20 μL, reactions were incubated for 2 hours at room temperature and stopped by the addition of 10 μL of 45mM EDTA, 50mM Hepes pH 7.5. Added to the stopped reaction mix was 30 μL of PT66 Alphascreen beads (Perkin Elmer, Boston, MA, U.S.A.). The reaction was incubated overnight and read on the Envision (Perkin Elmer). Phosphorylated peptide product was measured with the AlphaScreen system (Perkin Elmer) using acceptor beads coated with anti-phosphotyrosine antibody PT66 and donor beads coated with streptavidin that emit a fluorescent signal at the 520-620 nM emission wave

length if in close proximity. The concentration of each compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

CSF-1R kinase was assayed in 50 mM Hepes pH 7.0, 5 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 1 mg/ml BSA, 1.0 μM ATP, and 0.05 μM biotin-GGGGRPRAATF-NH_2 (SEQ ID NO:2) peptide substrate. CSF-1R kinase was added at final concentration of 4 nM.

Biological Example 2

In Vitro Inhibition of CSF-1R Receptor Tyrosine Phosphorylation

To test the inhibition of CSF-1R receptor tyrosine phosphorylation, HEK293H purchased from Invitrogen Cat. # 11631017 cells transfected with the full-length human CSF-1R receptor cloned in house into mammalian episomal transfection vector were incubated for 1 h with serial dilutions of compounds starting at 10μM with 3 fold dilutions and then stimulated for 8 min with 50 ng/ml MCSF. After the supernatant was removed, the cells were lysed on ice with lysis buffer (150 mM NaCl, 20 mM Tris, pH 7.5, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100 and NaF, protease and phosphatase inhibitors) and then shaken for 15-20 min at 4°C. The lysate was then transferred to total CSF-1R antibody coated 96- well plates that had already been blocked with 3% Blocker A from Mesoscale discovery (MSD) for 2 hours and washed afterwards. Lysates were incubated overnight at 4°C and the plates were then washed 4x with MSD Tris Wash Buffer. The SULFO-TAG anti-pTyr antibody from MSD was diluted to 20nM final in 1% Blocker A (MSD) solution and added to the washed plates and incubated for 1.5-2 h before addition of read buffer (MSD). The plates were read on the Sector 6000 instrument (MSD). Raw data was imported in Abase and EC_{50}s calculated with XL-fit data analysis software.

Biological Example 3

CSF-1R Inhibitors in MNFS-60 Pk/Pd Model

Five million MNFS-60 cells were implanted in HBSS/matrigel solution s.q. in the right flank. Approximately 3 weeks following tumor cell injection tumors were measured and selected mice were randomized (n=3 except for the vehicle group, where n=6) into groups based on their tumor size.

Compounds that inhibited M-CSF mediated proliferation in MNFS-60 cells and phosphorylation of CSF-1R with EC_{50}s <100 nM were tested in the MNFS-60 syngeneic tumor model (5 X 10^6 where implanted subcutaneously in matrigel and grown 3-4 weeks until they reached approximately 150 mm^2). A single 100 mg/kg dose of representative compounds disclosed herein was administered to MNFS-60 tumored animals; plasma and tumor samples were harvested at various time points after dosing starting at 1h up to 24h.

Several of the compounds disclosed herein were shown to inhibit Tyr723 phosphorylation of CSF-1R in tumor lysates at $\geq$ 50% compared to vehicle control 4 hrs after dosing as determined by Western Blot.

Additionally, several of the compounds disclosed herein were tested in a rapid onset severe arthritis mouse model (Terato, K. et al., *Journal of Immunology* 148:2103-2108; 1992) and treatment started on day three after injection of the anti-collagen antibody cocktail followed by LPS stimulation. Throughout the 12 days of treatment with CSF-1R inhibitors, the extent of swelling in the paws and bone resorption severity was scored. Significant attenuation of the swelling was not observed in the treated compared to control group; however, there was a trend toward improvement of bone resorption severity. There are no reports to date that CSF-1R inhibitors are effective in this arthritis model. The only successful reduction of disease progression was reported for inhibition by CSF-1R signaling with an Anti-MCSF antibody in a less severe, slower onset arthritis mouse model (Campbell et al *J. Leukoc. Biol.* 68: 144–150; 2000).

Biological Example 4

Inhibition of Raf Kinase Signaling in an *In Vitro* Biochemical Assay

The inhibitory effect of compounds on Raf was determined using the following biotinylated assay. The Raf kinase activity was measured by providing ATP, a recombinant kinase inactive MEK substrate and assaying the transfer of phosphate moiety to the MEK residue. Recombinant full length MEK with an inactivating K97R ATP binding site mutation (rendering kinase inactive) was expressed in *E. coli* and labelled with biotin post purification. The MEK cDNA was subcloned with an N-terminal $(His)_6$ tag and expressed in E. coli and the recombinant MEK substrate was purified from *E. coli* lysate by nickel affinity chromatography followed by anion exchange. The final MEK substrate preparation was biotinylated (Pierce EZ-Link Sulfo-NHS-LC-Biotin) and concentrated to 11.25μM.

Recombinant Raf (including c-Raf and mutant B-Raf isoforms) was obtained by purification from sf9 insect cells infected with the corresponding human Raf recombinant expression vectors. The recombinant Raf isoforms were purified via a Glu antibody interaction or by Metal Ion Chromatography.

For each assay, the compound was serially diluted, starting at 25 μM with 3-fold dilutions, in DMSO and then mixed with various Raf isoforms (0.50 nM each). The kinase inactive biotin-MEK substrate (50 nM) was added in reaction buffer plus ATP (1 μM). The reaction buffer contained 30 mM Tris-HCL_2 pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 4mM EDTA, 25 mM beta-glycerophosphate, 5 mM $MnCl_2$, and 0.01% BSA/PBS. Reactions were subsequently incubated for 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture was transferred to a neutradavin-coated plate (Pierce) and incubated for 1 hour. Phosphorylated product was measured with the DELFIA time-resolved fluorescence system (Wallac), using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence can be read on a Wallac 1232 DELFIA fluorometer. The concentration of the compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

Biological Example 5

Inhibition of cKIT and PDGFRb Kinase Signaling in an *In Vitro* Biochemical Assay

The IC50 values for the inhibition of RTKs were determined in the alphascreen format measuring the inhibition by compound of phosphate transfer to a substrate by the respective enzyme. Briefly, the respective RTK domain purchased as human recombinant protein (cKIT Upstate #14-559, PDGFRb Invitrogen #P3082) were incubated with serial dilutions of compound in the presence of substrate and ATP concentrations within 3 times the Km of the enzyme.

The kinase domain of cKIT was assayed in 50mM Hepes, pH=7.5, 5 mM MgCl2, 10 mM MnCl2, 1mM DTT, 0.1% BSA with 0.06 uM biotinylated peptide substrate (GGLFDDPSYVNVQNL-NH2) and 15 uM ATP (ATP KM apparent = 15 uM). The kinase domain of PDGFRβ was assayed in 50mM Hepes, pH=7.5, 20mM MgCl2, 1mM DTT, 0.1% BSA with 0.1 uM biotinylated peptide substrate (GGLFDDPSYVNVQNL-NH2) and

10 uM ATP (ATP KM apparent = 25 uM). Reactions were incubated at room temperature for 3 to 4 hr and stopped with buffer (20 mM EDTA, 0.01% Tween-20 for both PDGFRb and cKIT). Alphascreen PY20 beads were added to the stopped cKIT reactions and PY20 Ab / Protein A Alphascreen beads were added to the PDGFRβ stopped reactions. Both reactions were incubated overnight and read on the Alphascreen reader. The concentration of compound for 50% inhibition (IC_{50}) was calculated employing non-linear regression using XL-Fit data analysis software. As a control compou239d, staurosporine is run in every assay and a Z'>0.5 is required to validate results.

Biological Example 6

Cell viability assay in MCSF dependent MNFS60 cells

Cell viability was assessed by Cell Titer Glo, Promega. MNFS60 (murine AML cells) were seeded in TC treated 96-well plates at a density of 5,000 cells per well in RPMI-1640, 10%FBS, and 1% Penicillin Streptomycin prior to addition of compound. Test compounds were serially diluted (3 fold) in DMSO to 500x the final concentration. For each concentration of test compound, 2 µl (500x) aliquots of compound or 100% DMSO (control) were diluted in 500µl of culture medium that contained 2x final concentration of growth factor MCSF for 2 x concentration and then diluted 1x on the cells. Final concentration of MCSF is 10 ng/ml. Cells were incubated for 72hrs at 37°C, 5% CO_2. After the incubation 100 µl Cell Titer Glo is added to each well to determine viable cells. The assay was performed according to the manufacturer's instruction (Promega Corporation, Madison,WI. USA). Each experimental condition was performed in triplicate. Raw data was imported in Abase and EC_{50}s calculated with XL-fit data analysis software. Relative light units of wells that contained cells without MCSF in the media and as a consequence didn't grow were defined as 100% inhibited.

Biological Example 7

Tumor Induced Osteolysis Model

Tumor-induced osteolysis (TIO) models have been shown to recapitulate gross bone destruction seen in cancer patients with osteolytic tumor metastasis and have been reported extensively in both the bisphosphonate literature and in conjunction with the testing of novel anti-osteolytic agents. Results from these studies correlate well with human clinical activity (Kim S-J et al., 2005, Canc. Res., 65(9): 3707; Corey, E et al., 2003, Clin. Canc.

Res., 9:295; Alvarez, E. et al., 2003, Clin. Canc. Res., 9: 5705). The procedure includes injection of tumor cells directly into the proximal tibia. Once the cells are established, they proliferate and secrete factors that potentiate osteoclast activity, resulting in trabecular and cortical bone resorption. Animals are treated with anti-resorptive agents following tumor cell implantation and bone destruction is measured in a number of ways at the end of the study.

The tumor cell lines utilized in this protocol are of human origin and represent tumor lines that have been previously modified such that they now express the enzyme Luciferase in order to track tumor cells in the animal using the Xenogen system. The strength of the light signal also gives an indication of approximately how many tumor cells are located at a particular site.

Mice are injected subcutaneously with either 2.5 mg/kg flunixin meglumine 30 minutes prior to cell inoculation to provide post-procedural analgesia. The mice are then be anesthetized by isoflurane inhalation (ketamine/xylazine injection may be used if isoflurane is not available). Anesthetized animals are placed in the supine position and following tumor cell aspiration into a 50 or 100 µl micro-syringe fitted with a 26- or 27-gauge needle, the needle will be inserted through the cortex of the anterior tuberosity of the right tibia with a rotating "drill-like" movement to minimize the chance for cortical fracture. Successful passage of the needle through the cortex and into the marrow is indicated by loss of resistance against the forward movement of the needle. Once the bone cortex is traversed, 10-20 µl of cell suspension (6X10^5 MDA-MB-231Luc breast carcinoma or 3X10^5 PC-3MLuc prostate carcinoma cells) will be injected into the tibia bone marrow. Animals will be observed to ensure uneventful recovery (warming pad or lamp) until they have recovered from anesthesia.

Progression of tumor growth in the bone can be divided into five stages (Stages 0-4). The stages are defined as follows and can be monitored by comparison to the uninjected (left) leg of the mouse:

Stage 0: normal, no sign of any change in the bone.

Stage 1: Equivocal or minimal lesion; cortex/architecture normal.

Stage 2: Definite lesion; minimal cortex/architecture disruption.

Stage 3: Large lesion; cortex/architecture disruption.

Stage 4: Gross destruction; no preservation of architecture, "late stage". Animals reaching this stage will be taken off the study and euthanized.

Photon imaging of the legs are used to assess the tumor growth at the injection and remote sites during study using the Xenogen system to quantitate tumor cells in the tibia and confirm lack of leakage into other areas. Radiograms of the legs are taken up to once a week through the end of the study using Faxitron X-ray Unit to assess cortical bone destruction at the injection site. While using more invasive cell lines such as the PC-3M-Luc, we monitor bone damage one to two weeks after injection and weekly thereafter. For cell lines that form lesions at a slower rate, such as the MDA-MB-231Luc, which does not manifest bone damage until 4-5 weeks post-implantation, first radiographic images are taken approximately 4 weeks after animals have been intratibially implanted with cells to establish baseline controls and then once a week to measure bone damage starting at a time point when lesions begin to develop based on model development pilot studies. For example, in mice injected with MDA-MB-231Luc, an image would be taken approximately 4 weeks post-implantation, with weekly images thereafter.

Animals may be dosed with small molecules, monoclonal antibodies, or proteins once or twice daily, by any standard routes.

The endpoint of this study is the time point at which the majority of untreated (negative control) animals have reached late stage disease (Stage 4) and have been euthanized. At that point, the remaining animals in the study are euthanized, regardless of the stage of their tumors. Studies last approximately 5-10 weeks depending on the cell line. After the final x-ray is taken, blood is drawn from the animals by cardiac puncture (for assaying serum bone markers; see below). Endpoint x-ray images are then distributed to 5 volunteers who score each image according to the scoring system detailed above. Scores for each mouse are averaged and expressed as mean osteolytic score or percent of animals with severe osteolysis (animals with scores greater than 2).

Biological Example 8

Mouse Trap5b Assay (IDS Inc., Fountain Hills, AZ)

This assay is a solid phase immunofixed enzyme activity assay for the determination of osteoclast-derived tartrate-resistant acid phosphatase 5b in mouse serum samples. Trap5b is expressed by bone resorbing osteoclasts and secreted into the circulation. Thus,

serum Trap5b is considered to be a useful marker of osteoclast activity, number and bone resorption.

The mouse Trap5b assay uses a polyclonal antibody prepared using recombinant mouse Trap5b as antigen. In the test, the antibody is incubated in anti-rabbit IgG-coated microtiter wells. After washing, standard, controls and diluted serum samples are incubated in the wells, and bound Trap5b activity is determined with a chromogenic substrate to develop color. The reaction is stopped and the absorbance of the reaction mixture read in a microtiter plate reader at 405 nm. Color intensity is directly proportional to the amount and activity of Trap5b present in the sample. By plotting the mean absorbance for each standard on the ordinate against concentration on the abscissa, values for unknown samples can be read from the standard curve and expressed in U/L Trap5b. Analytical sensitivity of the assay is 0.1 U/L and inter- and intra-assay variation are below 10%. Trap5b levels were found to correlate well with mean osteolytic score (assessed by x-ray).

While a number of preferred embodiments of the invention and variations thereof have been described in detail, other modifications and methods of use will be readily apparent to those of skill in the art. Accordingly, it should be understood that various applications, modifications and substitutions may be made of equivalents without departing from the spirit of the invention or the scope of the claims.

The percent inhibition activities of the compounds of Tables 2, 3, and 4 when tested at about 1μM in the indicated assay as described in the Biological Examples are shown respectively in Tables 5, 6, and 7. It is contemplated that compounds having 0 % inhibition at 1μM will exhibit inhibitory activities at a higher concentration. An "N/D" means that the compound was not tested in the particular assay.

Table 5. Activities of the compounds of Table 2

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
1	N/D	99	N/D	21	N/D
2	N/D	100	N/D	63	80
3	N/D	96	N/D	0	N/D
4	N/D	100	N/D	100	91
5	N/D	99	N/D	100	93
6	N/D	85	N/D	N/D	N/D
7	N/D	94	N/D	17	21

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
8	N/D	99	N/D	60	92
9	N/D	99	N/D	58	75
10	35	99	N/D	62	79
11	96	99	N/D	26	N/D
12	12	99	N/D	30	N/D
13	65	99	N/D	76	75
14	85	99	N/D	56	71
15	88	100	N/D	97	92
16	20	99	N/D	25	81
17	10	100	85	81	94
18	35	100	N/D	91	74
19	2	100	N/D	36	N/D
20	0	15	N/D	N/D	N/D
21	0	99	N/D	55	65
22	0	21	N/D	N/D	N/D
23	0	50	N/D	N/D	N/D
24	20	99	N/D	12	N/D
25	7	98	N/D	42	35
26	100	98	N/D	24	N/D
27	28	99	N/D	97	96
28	98	99	N/D	98	88
29	51	99	N/D	0	N/D
30	14	25	N/D	N/D	N/D
31	N/D	100	18	57	79
32	22	100	N/D	70	93
33	35	98	N/D	35	83
34	89	99	N/D	68	65
35	9	19	N/D	N/D	N/D
36	6	78	0	N/D	N/D
37	16	79	N/D	N/D	N/D
38	14	34	N/D	N/D	N/D
39	10	67	N/D	N/D	N/D
40	6	99	N/D	0	N/D
41	30	100	N/D	100	94
42	12	99	N/D	100	97
43	15	26	N/D	N/D	N/D
44	15	37	N/D	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
45	14	11	N/D	N/D	N/D
46	15	94	N/D	1	N/D
47	12	13	N/D	N/D	N/D
48	0	84	N/D	0	N/D
49	25	55	63	N/D	N/D
50	8	56	59	N/D	N/D
51	2	95	40	N/D	N/D
52	50	100	12	56	71
53	0	95	21	N/D	N/D
54	7	100	17	64	60
55	11	97	21	N/D	N/D
56	0	66	55	N/D	N/D
57	3	97	35	35	N/D
58	85	98	48	30	N/D
59	0	97	21	N/D	N/D
60	2	92	6	N/D	N/D
61	0	94	74	35	N/D
62	5	19	7	N/D	N/D
63	3	45	6	N/D	N/D
64	21	77	0	N/D	N/D
65	38	99	98	100	97
66	37	100	55	18	37
67	1	97	8	10	0
68	3	99	6	18	N/D
69	0	100	0	0	N/D
70	0	99	0	0	N/D
71	0	100	27	11	N/D
72	0	100	65	48	N/D
73	2	100	21	0	N/D
74	31	100	34	14	N/D
75	0	99	7	0	N/D
76	0	98	9	0	N/D
77	15	100	92	79	94
78	0	87	9	N/D	N/D
79	0	100	31	57	94
80	0	87	7	N/D	N/D
81	0	54	16	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
82	0	46	9	N/D	N/D
83	0	99	12	26	N/D
84	0	99	12	32	44
85	N/D	99	79	100	98
87	N/D	99	42	21	N/D
88	N/D	100	98	100	96
90	N/D	99	22	18	N/D
91	N/D	99	93	87	97
92	N/D	99	98	17	N/D
94	N/D	99	14	28	N/D
95	8	98	40	N/D	N/D
96	3	99	33	75	89
97	5	99	99	67	84
98	0	26	7	N/D	N/D
99	9	63	12	N/D	N/D
100	9	99	10	N/D	N/D
101	91	99	85	85	91
102	0	83	14	N/D	N/D
103	14	60	8	N/D	N/D
104	10	99	18	47	63
105	8	99	22	49	70
106	0	99	2	N/D	N/D
107	0	67	8	N/D	N/D
108	40	99	100	100	98
109	75	100	53	81	90
110	8	85	16	N/D	N/D
111	2	25	15	N/D	N/D
112	5	28	0	N/D	N/D
113	17	97	7	19	N/D
114	15	100	92	36	N/D
115	18	99	88	21	N/D
116	18	100	100	10	N/D
117	0	100	96	61	88
118	49	100	95	83	69
119	32	99	18	13	N/D
120	0	75	5	N/D	N/D
121	30	100	9	17	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
122	0	100	53	19	N/D
123	2	99	15	0	N/D
124	0	99	32	51	94
125	0	100	35	44	45
126	99	68	83	N/D	N/D
127	20	100	81	95	95
128	83	100	90	95	95
129	34	99	92	94	92
130	25	99	87	72	85
131	55	99	96	100	98
132	58	99	98	100	98
133	3	99	53	45	92
134	0	98	98	93	93
135	20	100	68	96	91
136	84	100	88	100	97
137	98	100	45	100	98
138	93	99	93	100	88
139	0	100	21	48	94
140	0	100	92	52	90
141	0	100	1	22	N/D
142	97	99	98	100	88
143	4	99	33	97	91
144	100	99	100	100	N/D
145	25	99	34	100	98
146	3	99	5	56	86
147	0	98	90	90	97
148	100	99	99	100	98
149	0	99	4	67	92
150	1	99	34	49	87
151	0	99	5	26	N/D
152	82	99	100	100	98
153	91	97	0	63	N/D
154	18	99	17	48	93
155	8	87	0	N/D	N/D
156	41	100	27	63	16
157	20	100	20	100	99
158	2	99	11	1	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
159	1	99	12	17	N/D
160	18	99	13	30	N/D
161	94	100	0	38	N/D

Table 6. Activities of the compounds of Table 3

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
1	7	100	36	34	N/D
2	18	100	64	N/D	N/D
3	0	100	14	89	72
4	14	99	0	15	N/D
5	29	100	0	76	79
6	29	100	61	65	74
7	9	100	12	35	N/D
8	31	95	99	0	N/D
9	84	100	14	2	N/D
10	9	67	0	N/D	N/D
11	60	100	0	69	92
12	1	95	0	N/D	N/D
13	0	93	9	N/D	N/D
14	0	96	3	N/D	N/D
15	7	99	15	4	N/D
16	9	99	12	30	N/D
17	12	99	19	23	N/D
18	23	99	80	22	N/D
19	0	96	8	23	N/D
20	0	76	0	N/D	N/D
21	7	100	64	11	N/D
22	21	100	6	36	N/D
23	20	57	48	34	N/D
24	8	100	40	65	80
25	33	99	65	13	N/D
26	8	100	18	37	N/D
27	13	100	38	71	95
28	6	100	20	53	83
29	12	100	64	48	72
30	12	100	25	28	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
31	20	100	50	57	84
32	11	100	45	65	93
33	2	100	18	54	66
34	0	100	21	43	62
35	24	100	59	56	57
36	24	100	73	85	80
37	0	55	19	N/D	N/D
38	21	99	99	N/D	N/D
39	5	100	60	76	61
40	18	100	92	90	92
41	0	94	52	N/D	N/D
42	6	100	4	44	87
43	18	100	8	100	98
44	98	100	87	100	99
45	11	99	35	58	66
46	30	55	46	N/D	N/D
47	4	100	0	55	83
48	16	99	14	26	
49	12	100	21	33	77
50	14	99	13	18	N/D
51	0	95	10	N/D	N/D
52	47	100	61	47	N/D
53	96	100	100	100	N/D
54	65	100	40	39	N/D
55	46	100	40	42	53
56	8	96	20	13	N/D
57	19	95	38	N/D	N/D
58	93	100	96	100	N/D
59	0	98	12	5	28
60	4	69	0	N/D	N/D
61	12	95	3	N/D	N/D
62	0	99	14	3	56
63	7	100	1	28	44
64	0	100	1	16	49
65	0	87	1	N/D	N/D
66	0	89	13	N/D	N/D
67	0	55	7	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
68	0	96	17	19	54
69	0	90	6	N/D	N/D
70	5	94	16	N/D	N/D
71	1	75	13	N/D	N/D
72	0	95	8	N/D	N/D
73	5	96	13	N/D	N/D
74	4	79	3	N/D	N/D
75	2	76	11	N/D	N/D
76	0	64	5	N/D	N/D
77	2	88	7	N/D	N/D
78	8	88	11	N/D	N/D
79	0	99	6	22	34
80	14	99	0	8	19
81	6	100	71	9	18
82	0	100	31	50	92
83	3	100	8	28	62
84	14	100	45	80	90
85	0	99	8	24	46
86	32	63	15	N/D	N/D
87	5	99	30	20	6
88	1	67	12	N/D	N/D
89	2	100	15	15	65
90	42	100	64	97	96
91	83	100	86	100	96
92	25	100	97	100	97
93	0	100	12	23	47
94	9	100	90	17	38
95	2	100	0	60	65
96	0	70	29	N/D	N/D
97	0	100	7	50	59
98	0	60	6	N/D	N/D
99	0	86	0	N/D	N/D
100	6	81	0	N/D	N/D
101	0	99	5	20	N/D
102	9	100	0	75	88
103	7	95	0	N/D	N/D
104	0	86	0	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
105	6	100	7	31	N/D
107	99	100	19	100	96
108	4	100	10	70	94
109	16	100	13	67	N/D
110	0	98	0	34	N/D
111	71	100	76	100	98
112	5	100	8	46	90
113	0	97	6	14	N/D
114	0	100	4	86	97
115	55	100	18	97	82
116	0	100	21	41	N/D
117	48	100	70	63	92
118	25	100	18	71	67
119	0	94	1	N/D	N/D
120	0	65	0	N/D	N/D
121	0	61	4	N/D	N/D
122	0	67	0	N/D	N/D
123	0	62	1	N/D	N/D
124	10	99	0	18	N/D
125	9	99	2	17	N/D
126	83	100	36	100	97
127	0	95	0	N/D	N/D
128	20	100	29	82	88
129	99	100	99	N/D	N/D
130	70	100	90	79	N/D
131	23	100	35	98	96
132	30	80	18	N/D	N/D
133	14	67	19	N/D	N/D
134	13	53	11	N/D	N/D
135	11	75	21	N/D	N/D
136	0	86	3	N/D	N/D
137	2	71	8	N/D	N/D
138	37	100	100	105	N/D
139	19	100	24	46	88
140	100	100	27	25	N/D
141	80	100	100	100	99
142	84	100	100	97	96

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
143	22	100	63	80	90
144	12	100	38	41	N/D
145	33	100	39	58	86
146	8	100	24	32	N/D
147	100	100	93	100	97
148	2	96	23	1	N/D
149	21	100	29	48	N/D
150	2	100	24	22	N/D
151	38	100	46	43	N/D
152	21	97	25	13	N/D
153	23	97	17	15	N/D
154	95	100	96	86	83
155	18	99	34	0	N/D
156	3	100	36	33	N/D
157	17	100	43	42	N/D
158	1	99	27	0	N/D
159	23	100	29	98	96
160	19	100	95	30	N/D
161	26	54	20	N/D	N/D
162	30	100	20	100	99
163	39	100	32	100	99
164	87	100	79	100	100
165	83	100	83	100	98
166	0	100	13	49	78
167	0	100	16	24	N/D
168	43	100	40	100	99
169	0	75	12	N/D	N/D
170	23	100	28	100	96
171	18	100	25	96	95
172	18	100	22	100	97
173	8	100	18	52	81
174	3	86	18	N/D	N/D
175	1	100	11	17	N/D
176	0	63	12	N/D	N/D
177	0	67	15	N/D	N/D
178	-3	82	17	N/D	N/D
179	16	98	10	27	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
180	12	100	23	96	93
181	17	72	27	N/D	N/D
182	4	100	16	100	98
183	99	100	100	100	98
184	84	100	45	100	95
185	29	100	32	100	94
186	14	100	13	100	99
187	25	100	32	100	98
188	35	100	55	38	N/D
189	23	100	31	26	N/D
190	19	98	22	5	N/D
191	15	45	19	N/D	N/D
192	22	99	56	14	N/D
193	15	95	27	0	N/D
194	16	77	20	N/D	N/D
195	25	81	90	N/D	N/D
196	23	100	29	100	98
197	89	100	93	100	98
198	39	100	48	100	94
199	81	100	61	100	97
200	19	100	29	69	83
201	22	52	17	N/D	N/D
202	19	100	32	17	N/D
203	15	98	22	20	N/D
204	74	100	92	85	N/D
205	39	100	24	96	93
206	98	100	100	100	N/D
207	72	100	36	100	98
208	80	100	99	83	N/D
209	1	100	17	36	N/D
210	26	100	19	26	N/D
211	50	100	85	23	N/D
212	28	100	37	97	94
213	0	100	30	34	N/D
214	13	100	30	60	76
215	80	100	100	86	N/D
216	45	100	59	98	93

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
217	23	99	16	0	N/D
218	23	100	28	16	N/D
219	85	100	97	53	N/D
220	65	100	48	84	91
221	88	100	97	52	N/D
222	69	100	52	91	68
223	28	100	54	100	97
224	0	100	26	33	N/D
225	0	90	21	N/D	N/D
226	0	80	20	N/D	N/D
227	47	100	100	65	N/D
228	26	100	70	32	N/D
229	30	100	21	80	92
230	14	100	6	58	65
231	49	100	9	100	99
232	64	100	34	100	99
233	84	100	85	59	N/D
234	56	100	64	78	N/D
235	81	100	100	100	N/D
236	97	100	100	100	N/D
237	13	100	24	100	94
238	90	100	100	100	N/D
239	25	100	100	90	N/D
240	16	100	21	66	71
241	23	100	25	51	65
242	35	100	97	51	N/D
243	69	100	100	76	N/D
244	35	100	25	67	85
245	21	100	16	53	81
246	82	100	100	100	N/D
247	80	100	100	100	N/D
248	41	100	33	51	39
249	0	100	69	100	N/D
250	0	97	98	20	N/D
251	28	100	56	80	74
252	6	100	100	81	N/D
253	6	100	100	86	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
254	0	100	98	100	N/D
255	8	100	92	69	N/D
256	3	100	71	87	87
257	11	100	100	100	N/D
258	62	100	44	100	99
259	6	100	24	100	98
260	0	100	25	100	98
261	30	100	25	100	98
262	3	100	20	46	48
263	0	99	12	22	24
264	4	97	25	3	N/D
265	12	100	9	32	N/D
266	21	100	18	100	94
267	26	100	16	100	96
268	29	100	25	84	87
269	13	100	18	75	85
270	11	98	21	50	74
271	24	98	46	54	55
272	7	98	24	38	N/D
273	14	100	41	95	88
274	12	100	28	76	82
275	16	100	45	89	94
276	26	100	39	100	97
277	5	100	26	24	N/D
278	12	100	38	82	75
279	7	100	30	60	59
280	22	100	11	100	65
281	36	100	22	100	96
282	7	99	23	22	N/D
283	20	99	38	0	N/D
284	53	100	61	100	N/D
285	8	99	33	0	N/D
286	0	100	23	71	94
287	20	100	57	35	N/D
288	24	100	78	70	N/D
289	2	99	28	0	N/D
290	15	100	10	2	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
291	0	48	4	N/D	N/D
292	0	95	3	N/D	N/D
293	0	100	22	67	82
294	0	87	1	N/D	N/D
295	0	85	5	N/D	N/D
296	9	97	1	N/D	N/D
297	9	98	0	42	90
298	0	98	13	41	N/D
299	57	100	32	94	95
300	0	99	2	14	N/D
301	7	55	0	N/D	N/D
302	0	68	20	N/D	N/D
303	12	74	24	N/D	N/D
304	18	100	9	23	N/D
305	7	87	15	N/D	N/D
306	0	99	6	48	N/D
307	6	90	15	N/D	N/D
308	27	100	51	54	81
309	13	74	6	N/D	N/D
310	13	15	13	N/D	N/D
311	88	93	22	N/D	N/D
312	14	76	0	N/D	N/D
313	2	52	23	N/D	N/D
314	12	99	13	20	N/D
315	0	98	17	27	N/D
316	12	99	8	41	98
317	12	100	70	50	95
318	13	100	47	24	78
319	24	100	93	61	91
320	20	100	16	25	N/D
321	41	100	52	82	97
322	11	99	18	21	N/D
323	24	100	25	100	98
324	19	99	21	15	N/D
325	43	100	27	66	N/D
326	7	65	44	33	81
327	0	47	6	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
328	0	100	14	63	80
329	17	100	59	84	92
330	8	99	41	58	50
331	10	100	41	68	79
332	10	48	38	N/D	N/D
333	6	86	21	N/D	N/D
334	15	100	20	67	71
335	0	100	21	57	50
336	14	94	23	17	N/D
337	0	95	14	19	N/D
338	52	100	51	44	N/D
339	69	100	66	66	84
340	98	100	100	100	96
341	88	100	99	99	96
342	61	100	84	75	87
343	28	100	59	57	N/D
344	65	100	45	100	95
345	13	100	19	97	93
346	0	100	13	67	84
347	58	100	37	100	99
348	55	100	47	100	90
349	73	100	77	100	N/D
350	91	100	100	100	N/D
351	79	100	98	100	N/D
352	74	100	45	100	97
353	100	100	100	100	N/D
354	98	100	100	100	N/D
355	27	100	27	100	99
356	99	100	100	100	N/D
357	44	100	91	100	N/D
358	99	100	100	100	N/D
359	19	100	31	95	93
360	16	100	29	100	98
361	75	100	100	N/D	N/D
362	92	100	99	100	100
363	99	100	100	N/D	N/D
364	100	100	100	N/D	N/D

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
365	79	100	100	100	97
366	26	100	94	100	98
367	7	100	13	81	89
368	8	100	24	12	N/D
369	12	100	26	44	N/D
370	34	100	64	60	81
371	9	100	29	69	79
372	8	100	21	75	88
373	0	101	51	100	91
374	41	99	98	3	N/D
375	38	100	97	19	N/D
376	28	100	72	87	77
377	49	100	75	93	N/D
378	43	100	62	90	87
379	36	77	16	N/D	N/D
380	49	100	53	79	94
381	20	100	30	100	99

Table 7. Activities of the compounds of Table 4

Cmpd	PDGFRβ	CSF-1R	cKit	M-NFS-60 CP	pCSF1R
1	13	100	73	50	47
2	8	80	14	N/D	N/D
3	1	100	15	67	85
4	0	100	29	92	94
5	8	100	18	91	92
6	26	100	26	100	99
7	5	100	23	54	N/D
8	35	100	25	100	98
9	45	100	15	100	98
10	9	100	6	76	83
11	4	100	8	38	N/D
12	6	100	14	100	95
13	45	100	73	N/D	N/D
14	85	100	71	N/D	N/D
15	60	100	59	100	99
16	59	100	41	100	100

17	72	100	61	100	100
18	28	100	45	100	100
19	19	100	33	100	100
20	12	100	30	100	99
21	22	100	32	N/D	N/D
22	90	100	89	N/D	N/D
23	0	100	29	7	N/D
24	0	100	26	100	100
25	1	100	33	100	86
26	0	100	29	33	N/D
27	0	100	67	N/D	N/D
28	0	100	98	N/D	N/D
29	0	100	65	73	90
30	0	100	18	73	93
31	0	96	26	N/D	N/D
32	0	100	71	N/D	N/D
33	0	100	65	100	98
34	1	100	90	N/D	N/D
35	90	100	46	100	98
36	26	100	45	5	N/D
37	24	100	88	N/D	N/D
38	16	100	27	100	99
39	9	100	98	N/D	N/D
40	0	100	27	83	96
41	19	100	66	100	97
42	28	100	28	100	99
43	0	95	14	N/D	N/D
44	24	100	45	94	53
45	44	100	53	100	99
46	42	100	24	100	99
47	31	100	55	58	79
48	98	100	79	100	100
49	1	100	11	100	99
50	14	100	10	100	99
51	78	100	36	100	100
52	42	100	27	100	100
53	14	100	12	100	99
54	1	100	11	100	99

55	2	100	11	100	95
56	11	100	13	100	99
57	11	100	15	100	99
58	0	100	11	100	95
59	27	100	25	100	99
60	0	100	9	100	99
61	23	100	3	100	98
62	27	100	5	97	97
63	21	100	10	100	99
64	16	100	7	91	96
65	21	100	6	100	98
66	28	100	12	100	99
67	42	100	97	100	98
68	100	100	57	100	99
69	28	100	12	100	99
70	86	100	26	100	100
71	25	100	5	73	95
72	20	100	6	65	95
73	20	100	3	56	96
74	22	100	0	60	97
75	10	99	0	0	N/D
76	15	100	8	95	96
77	25	100	6	100	99
78	71	100	7	100	100
79	28	100	2	99	99
80	25	100	0	46	N/D
81	18	100	4	87	97
82	24	100	2	92	99
83	36	100	7	100	99
84	30	100	11	100	97
85	53	100	13	100	53
86	25	99	22	85	60
87	N/D	100	19	N/D	N/D
88	N/D	100	14	N/D	N/D
89	N/D	100	18	N/D	N/D
90	N/D	100	18	N/D	N/D
91	N/D	100	17	N/D	N/D
92	N/D	100	15	N/D	N/D

93	N/D	99	5	N/D	N/D
94	N/D	100	12	N/D	N/D
95	N/D	100	42	N/D	N/D
96	N/D	100	7	N/D	N/D
97	N/D	100	14	N/D	N/D
98	N/D	100	8	N/D	N/D
99	N/D	100	0	N/D	N/D
100	N/D	100	5	N/D	N/D
101	N/D	100	10	N/D	N/D
102	N/D	100	18	N/D	N/D
103	N/D	N/D	N/D	N/D	N/D
104	N/D	100	4	N/D	N/D
105	N/D	100	10	N/D	N/D
106	N/D	100	17	N/D	N/D
107	N/D	N/D	N/D	N/D	N/D
108	N/D	N/D	N/D	N/D	N/D
109	N/D	N/D	N/D	N/D	N/D
110	N/D	N/D	N/D	N/D	N/D
111	N/D	N/D	N/D	N/D	N/D
112	N/D	100	11	N/D	N/D
113	N/D	92	10	N/D	N/D
114	N/D	100	6	N/D	N/D
115	N/D	95	12	N/D	N/D
116	N/D	100	13	N/D	N/D
117	N/D	100	11	N/D	N/D
118	N/D	100	11	N/D	N/D
119	N/D	95	16	N/D	N/D

The following references are cited in the specification.

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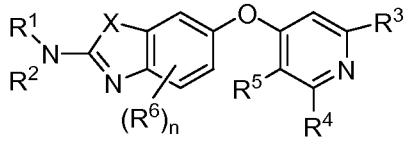
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WHAT IS CLAIMED IS:

1. A compound, stereoisomer, tautomer, solvate, oxide, ester, or prodrug of Formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein X is O, S, or S(O);

R^1 and R^2 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; or R^1 and R^2 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

R^3 is selected from the group consisting of hydrogen, halo, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbonitrile, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl;

each R^6 is independently alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, or halo;

n is 0, 1, or 2; and

when X is O, R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl, or R^4 and R^5 are taken together to form a group selected from heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

when X is S or S(O), R^4 is hydrogen, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and R^5 is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aminocarbonyl, halo, heteroaryl, substituted heteroaryl, cycloalkyl, or substituted cycloalkyl.

2. A compound of Claim 1, wherein X is O.

3. A compound of Claim 1, wherein X is S.

4. A compound of Claim 1, wherein R^2 is hydrogen or methyl.

5. A compound of Claim 1, wherein R^1 is alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxyl, and substituted sulfonyl.

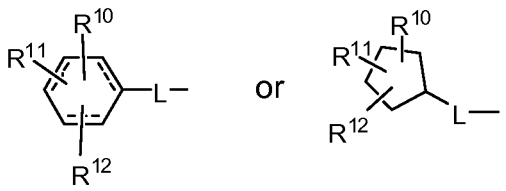
6. A compound of Claim 1, wherein R^1 is LR^{1a} wherein L is a covalent bond, alkylidene, or substituted alkylidene, and R^{1a} selected from cycloalkyl, cycloalkenyl, aryl, heterocyclyl, and heteroaryl, wherein each R^{1a} is substituted or unsubstituted.

7. A compound of Claim 6, wherein R^{1a} is selected from phenyl, furan-2-yl, furan-3-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclohexenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2,3-dihydrobenzofuran, 2,3-dihydrobenzo[b][1,4]dioxine, 3,4-dihydro-2H-benzo[b][1,4]dioxepine, pyrazinyl, pyrrolidinyl, piperidinyl, piperidinone, pyrrolidinone, pyridin-2(1H)-one, morpholino, napthyl, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, 1,2,3,4-tetrahydronaphthalene, 2,3-dihydro-1H-indene, and azepan-2-one, wherein each R^{1a} is substituted or unsubstituted.

8. A compound of Claim 7, wherein L is a covalent bond.

9. A compound of Claim 6, wherein L is alkylidene substituted with 0, 1, 2, or 3 substituents independently selected from alkyl, substituted alkyl, hydroxy, alkoxy, haloalkoxy, aminocarbonyl, carboxyl ester, and carboxyl.

10. A compound of Claim 1, wherein R^1 is



wherein the dashed lines are saturated bonds or unsaturated bonds;

wherein L is a covalent bond, alkylidene, or substituted alkylidene; and

R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or R^{11} is taken together with R^{12} to form a group selected from the group consisting of aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

11. A compound of Claim 10, wherein the dashed lines are saturated bonds, thereby forming cyclohexyl group.

12. A compound of Claim 10, wherein L is a covalent bond.

13. A compound of Claim 10, wherein L is methylene or substituted methylene.

14. A compound of Claim 13, wherein L is substituted with alkyl, substituted alkyl, carboxyl, aminocarbonyl, and carboxyl ester.

15. A compound of Claim 10, wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxyl, alkyl, substituted alkyl, and alkoxy.

16. A compound of Claim 10, wherein at least one of R^{10}, R^{11}, and R^{12} is hydroxy.

17. A compound of Claim 10, wherein R^{11} is taken together with R^{12} to form aryl or substituted aryl.

18. A compound of Claim 1, wherein R^1 is alkyl or substituted alkyl.

19. A compound of Claim 18, wherein R^1 is substituted alkyl, wherein the substituent of R^1 is selected from the group consisting of alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

20. A compound of Claim 19, wherein R^1 is substituted alkyl, wherein the substituent of R^1 is cycloalkyl or substituted cycloalkyl.

21. A compound of Claim 1, wherein R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl.

22. A compound of Claim 21, wherein R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

23. A compound of Claim 1, wherein R^3 is acylamino or aminocarbonyl.

24. A compound of Claim 23, wherein R^3 is $-C(O)NH-LR^{3a}$, wherein L is a covalent bond, alkylidene, or substituted alkylidene, and R^{3a} is selected from the group consisting of alkyl, haloalkyl, amino, acylamino, (carboxyl ester)amino, hydroxy, alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

25. A compound of Claim 24, wherein R^3 is $-C(O)NHCH_3$.

26. A compound of Claim 1, wherein R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

27. A compound of Claim 1, wherein R^3 is substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, or substituted cycloalkenyl.

28. A compound of Claim 1, wherein R^3 is selected from the group consisting of pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, pyrimidin-4-yl, pyrimidin-3-yl, pyrimidin-2-yl, thiazoyl, tetrazolyl, imidazol-1-yl, imidazol-2-yl, imidazol-3-yl, pyrazinyl, phenyl, tetrahydropyridine, 1H-pyrrolo[2,3-b]pyridine, furanyl, oxazole, oxadiazole, cyclopropyl, cyclohexyl, cyclohexenyl, piperidinyl, morpholino, tetrahydro-1H-benzo[d]imidazole, pyrrolidinyl, piperazinyl, and piperzin-2-one, wherein each R^3 is substituted or unsubstituted.

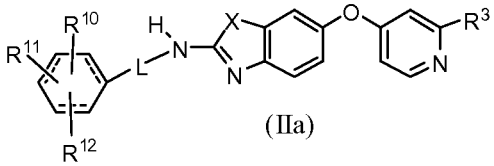
29. A compound of Claim 1, wherein R^4 is hydrogen.

30. A compound of Claim 1, wherein R^5 is hydrogen.

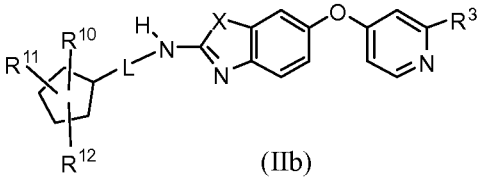
31. A compound of any one of Claims 1 to 30 wherein n is 0, R^4 and R^5 are hydrogen, and R^3 is selected from the group consisting of hydrogen, halo, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

32. A compound of Claim 1, wherein R^4 and R^5 are taken together to form an aryl or substituted aryl group.

33. A compound, stereoisomer, tautomer, or solvate of Claim 1 having Formula (IIa) or (IIb) or a pharmaceutically acceptable salt thereof:


(IIa)

or


(IIb)

wherein X is O or S;

the dashed lines are saturated bonds or unsaturated bonds;

L is a covalent bond or is alkylidene or substituted alkylidene;

R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, substituted amino, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or R^{11} is taken together with R^{12} to form a group selected from the group consisting of aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

34. A compound of Claim 33, wherein the dashed lines are saturated bonds, thereby forming cyclohexyl group.

35. A compound of Claim 33, wherein X is O.

36. A compound of Claim 33, wherein X is S.

37. A compound of Claim 33, wherein L is a covalent bond.

38. A compound of Claim 33, wherein L is methylene or substituted methylene.

39. A compound of Claim 33, wherein L is substituted with alkyl, substituted alkyl, carboxyl, aminocarbonyl, or carboxyl ester.

40. A compound of Claim 33, wherein R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, halo, hydroxyl, alkyl, substituted alkyl, and alkoxy.

41. A compound of Claim 38, wherein at least one of R^{10}, R^{11}, and R^{12} is hydroxy.

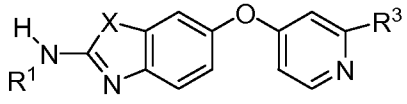
42. A compound of Claim 33, wherein R^{11} is taken together with R^{12} to form aryl or substituted aryl.

43. A compound of Claim 33, wherein R^3 is acylamino or aminocarbonyl.

44. A compound of Claim 43, wherein R^3 is $-C(O)NHCH_3$.

45. A compound of Claim 33, wherein R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

46. A compound, stereoisomer, tautomer, or solvate of Claim 1 having Formula (IIIa) or a pharmaceutically acceptable salt thereof:



(IIIa)

wherein X is O or S;

R^1 is alkyl or alkyl substituted with a substituent selected from the group consisting of aryl, cycloalkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

47. A compound of Claim 46, wherein X is O.

48. A compound of Claim 46, wherein X is S.

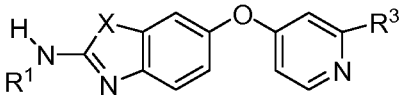
49. A compound of Claim 46, wherein R^1 is alkyl substituted with cycloalkyl.

50. A compound of Claim 46, wherein R^3 is acylamino or aminocarbonyl.

51. A compound of Claim 50, wherein R^3 is $-C(O)NHCH_3$.

52. A compound of Claim 46, wherein R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

53. A compound, stereoisomer, tautomer, or solvate of Claim 1 having Formula (IIIb) or a pharmaceutically acceptable salt thereof:



(IIIb)

wherein X is O or S;

R^1 is selected from the group consisting of acyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclyl, substituted heterocyclyl, heteroaryl, and substituted heteroaryl; and

R^3 is selected from the group consisting of hydrogen, halogen, substituted alkyl, carbonitrile, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, amino, substituted amino, acyl, acylamino, alkoxy, substituted alkoxy, carboxyl, carboxyl ester, substituted sulfonyl, aminosulfonyl, and aminocarbonyl.

54. A compound of Claim 53, wherein X is O.

55. A compound of Claim 53, wherein X is S.

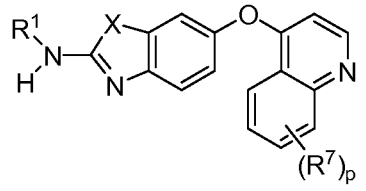
56. A compound of Claim 53, wherein R^1 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, heterocyclyl, and substituted heterocyclyl.

57. A compound of Claim 53, wherein R^3 is acylamino or aminocarbonyl.

58. A compound of Claim 57, wherein R^3 is $-C(O)NHCH_3$.

59. A compound of Claim 53, wherein R^3 is hydrogen, carboxyl, substituted alkyl, carbonitrile, heteroaryl, or substituted heteroaryl.

60. A compound, stereoisomer, tautomer, solvate, oxide, ester, or prodrug of Formula (IV) or a pharmaceutically acceptable salt thereof:



(IV)

wherein X is O or S;

R^7 is independently selected from the group consisting of alkoxy, haloalkoxy, halo, and carbonitrile;

p is 0, 1, or 2;

R^1 is $-LR^8$ or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

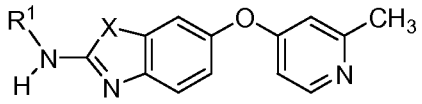
L is a covalent bond, alkylidene, or substituted alkylidene; and

R^8 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, pyridyl, and when p is 0, R^8 is optionally 2-methoxyphenyl.

61. A compound of Claim 53, wherein X is S.

62. A compound of Claim 53, wherein p is 0.

63. A compound, stereoisomer, tautomer, solvate, oxide, ester, or prodrug of Formula (V) or a pharmaceutically acceptable salt thereof:



(V)

wherein X is O or S;

R^1 is $-LR^9$ or alkyl substituted with 0, 1, 2, or 3 substituents independently selected from halo, hydroxy, haloalkyl, alkoxy, haloalkoxy, aryloxy, aminocarbonyl, carboxyl ester, carboxy, and substituted sulfonyl;

L is a covalent bond, alkylidene, or substituted alkylidene; and

R^9 is selected from the group consisting of cycloalkyl, substituted cycloalkyl, tetrahydropyranyl, morpholino, and pyridyl.

64. A compound of Claim 60, wherein X is S.

65. A compound of Claim 60, wherein L is a covalent bond or is alkylidene.

66. A compound of Claim 60, wherein R^8 is cyclohexyl or substituted cyclohexyl.

67. A compound of Claim 1, 60, or 63 selected from Tables 2, 3, or 4 or a stereoisomer, tautomer, solvate, oxide, ester, prodrug, or pharmaceutically acceptable salt thereof.

68. The compound of Claim 2 selected from the group consisting of 4-[2-(4-Bromo-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Morpholin-4-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, (2,3-Dihydro-benzo[1,4]dioxin-6-yl)-[6-(6,7-dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-amine, 4-[2-(2,3-Dihydro-benzo[1,4]dioxin-6-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(1-Thiazol-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((S)-1-Phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(3-Methyl-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Methoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Ethoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1S,2S,3S,5R)-2,6,6-Trimethyl-bicyclo[3.1.1]hept-3-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, [6-(6,7-Dimethoxy-quinolin-4-yloxy)-benzooxazol-2-yl]-((R)-1-phenyl-ethyl)-amine, 4-{2-[((1S,2R,4R)-7,7-Dimethyl-bicyclo[2.2.1]hept-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-

[2-((R)-1-Naphthalen-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-1-Phenyl-propylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((S)-1-Naphthalen-2-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-Cyclobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-(2-Cyclopentylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Morpholin-4-ylmethyl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-Phenylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(4-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4-Dimethoxy-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, N-[4-(2-Cyclohexylamino-benzooxazol-6-yloxy)-pyridin-2-yl]-acetamide, 4-[2-(Tetrahydro-pyran-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, N-{4-[2-(2-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide, 4-[2-(2,5-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, N-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-acetamide, (R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid, 4-{2-[((R)-Methylcarbamoyl-phenyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, (S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid, 4-{2-[((S)-Methylcarbamoyl-phenyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[(Pyridin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-(2-Benzylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(3-Chloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(2-Pyrrolidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(4-Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Oxazol-5-yl-phenylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(2-

Methyl-imidazol-1-yl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-(2-Amino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-(2-Hydroxy-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-((1S,2R)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1R,2S)-2-Hydroxy-indan-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-3-Hydroxy-1-phenyl-propylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, (R)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester, 4-[2-((R)-1-Cyclohexyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, (S)-[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-phenyl-acetic acid methyl ester, 4-[2-((S)-2-Hydroxy-1-phenyl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(Pyridin-4-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[3-(2-Piperidin-1-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[(Pyridin-3-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid, 4-(2-Phenethylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-{2-[((R)-Cyclohexyl-methylcarbamoyl-methyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Pyrrolidin-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Piperidin-1-yl-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-((S)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-1-Cyclohexyl-2-hydroxy-ethylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, N'-{4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonyl}-hydrazinecarboxylic acid tert-butyl ester, 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid amide, 4-[2-(Cyclohex-3-enylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Bromo-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-

(2-Fluoro-5-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[3-(2-Morpholin-4-yl-ethyl)-phenylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid ethyl ester, 4-[2-(2,6-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,3-Dichloro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Chloro-6-fluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,3-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, {4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridin-2-yl}-methanol, Cyclohexylmethyl-[6-(2-[1,3,4]oxadiazol-2-yl-pyridin-4-yl-oxy)-benzooxazol-2-yl]-amine, 4-[2-(Cyclohexylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carbonitrile, 4-[2-(2,5-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,6-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Dimethylamino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Amino-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,6-Difluoro-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Morpholin-4-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Methyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(3,4-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,3-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4-Dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 1-{[6-(2-Methylcarbamoyl-pyridin-4-yloxy)-benzooxazol-2-ylamino]-methyl}-cyclohexanecarboxylic acid, 4-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(Benzo[1,3]dioxol-5-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Ethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Trifluoromethyl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-Isopropylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-(2-Isobutylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-(2-tert-Butylamino-benzooxazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(Cycloheptylmethyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(Tetrahydro-

furan-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(1-Benzyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(1,2,3,4-Tetrahydro-naphthalen-1-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Pyrazol-1-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(Benzyl-methyl-amino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(1-Phenyl-piperidin-4-ylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, Cyclohexylmethyl-{6-[2-(5-methyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-benzooxazol-2-yl}-amine, 4-{2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, [6-(2-Aminomethyl-pyridin-4-yloxy)-benzooxazol-2-yl]-cyclohexylmethyl-amine, 4-{2-[(1-Methylcarbamoyl-cyclohexylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4,6-Trimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(5-Chloro-2-methoxy-benzylamino)-benzooxazol-6-yl-oxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(5-Fluoro-2-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Fluoro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Chloro-3,4-dimethoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Piperidin-1-yl-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[(4-Benzyl-morpholin-2-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Chloro-6-methoxy-benzylamino)-benzooxazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-{2-[(2,3-Dihydro-benzofuran-5-ylmethyl)-amino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, and 4-{2-[1-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-ethylamino]-benzooxazol-6-yloxy}-pyridine-2-carboxylic acid methylamide;

or a pharmaceutically acceptable salt, tautomer, solvate, or stereoisomer thereof.

69. The compound of Claim 3 selected from the group consisting of 4-[2-(4-Chloro-3-trifluoromethyl-phenylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Chloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(Cyclohexylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(R)-1-(2-Methoxy-phenyl)-ethylamino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2,4-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-1-Phenyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Methoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-Phenethylamino-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(2,3-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-Cyclohexylamino-benzothiazol-6-yloxy)-pyridine-2-carboxylic acid methylamide, 4-[2-(3-Methyl-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1S,2S)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((R)-1-Cyclohexyl-ethylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,5-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Fluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(Tetrahydro-pyran-4-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Morpholin-4-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Pyrazol-1-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Dimethylamino-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,6-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,5-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,3-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(Cycloheptylmethyl-amino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,6-Difluoro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(Pyridin-2-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(3,4-Dimethoxy-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-{2-[(2,3-Dihydro-benzo-[1,4]dioxin-5-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-(2-Piperidin-1-yl-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-

carboxylic acid methylamide, 4-{2-[(Pyridin-3-ylmethyl)-amino]-benzothiazol-6-yloxy}-pyridine-2-carboxylic acid methylamide, 4-[2-((1R,2R)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1S,2S)-2-Benzyloxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-((1R,2R)-2-Hydroxy-cyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-[2-(2,6-Dichloro-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, 4-(2-(cyclohexylmethylamino)benzothiazol-6-yloxy)-N-(2-methoxyethyl)pyridine-2-carboxamide, 4-(2-(cyclohexylmethylamino)benzothiazol-6-yloxy)-N-(2-(dimethylamino)ethyl)pyridine-2-carboxamide, and 4-[2-(4-Sulfonamido-benzylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide;

or a stereoisomer, tautomer, or solvate thereof or pharmaceutically acceptable salt thereof.

70. A pharmaceutical composition comprising an effective amount of a compound, stereoisomer, tautomer, solvate, oxide, ester, or prodrug or pharmaceutically acceptable salt thereof of any one of Claims 1 to 69 and a pharmaceutically acceptable carrier.

71. A composition of Claim 70, wherein said compound exhibits an IC_{50} value with respect to CSF-1R inhibition of less than 1 μM.

72. A composition of Claim 70, further comprising an additional agent.

73. A composition of Claim 72, wherein said additional agent is a bisphosphonate.

74. A compound of any one of Claims 1 to 30, 32 to 66, 68, and 69 wherein said compound preferentially inhibits CSF-1R over Raf kinase.

75. A compound of Claim 74, wherein said compound inhibits CSF-1R at greater than about 5-fold the activity with respect to IC_{50} values than in Raf kinase.

76. A compound of Claim 74, wherein said compound inhibits CSF-1R at greater than about 10-fold, about 20-fold, about 30-fold, or about 50-fold the activity with respect to IC_{50} values than in Raf kinase.

77. A compound of Claim 74, wherein said compound inhibits CSF-1R at greater than about 100-fold, about 250-fold, about 500-fold, about 750-fold, about 1000-fold, or about 2000-fold the activity with respect to IC_{50} values than in Raf kinase.

78. A compound of Claim 74, wherein said compound inhibits Raf kinase at greater than 1 μM.

79. A method of treating a CSF-1R mediated disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of any one of Claims 1 to 69 effective to inhibit CSF-1R activity in the human or animal subject.

80. A method of Claim 79, wherein said compound selectively inhibits CSF-1R.

81. A method of Claim 79, wherein the CSF-1R mediated disorder is selected from the group consisting of cancer, osteoporosis, arthritis, atherosclerosis and chronic glomerular nephritis.

82. A method of Claim 79, wherein the CSF-1R mediated disorder is a cancer selected from the group consisting of myelocytic leukemia, idiopathic myelofibrosis, breast cancer, cervical cancer, ovarian cancer, endometrial cancer, prostate cancer, hepatocellular cancer, multiple myeloma, lung cancer, renal cancer, and bone cancer.

83. A method of Claim 79, wherein the CSF-1R mediated disorder is rheumatoid arthritis.

84. A method of Claim 79, wherein the composition further comprises at least one additional agent for treating the CSF-1R mediated disorder.

85. A method of inhibiting CSF-1R comprising contacting a cell with a compound of any one of Claims 1, 60, or 63.