

AMIDO-BENZYL SULFONE AND SULFOXIDE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to certain amido-benzyl sulfone and sulfoxide
5 compounds, pharmaceutical compositions comprising such compounds, and methods
of treating cancer, including leukemias and solid tumors, inflammatory diseases,
osteoporosis, atherosclerosis, irritable bowel syndrome, and other diseases and
medical conditions, with such compounds and pharmaceutical compositions. The
present invention also relates to certain amido-benzyl sulfone and sulfoxide
10 compounds for use in inhibiting nicotinamide phosphoribosyltransferase ("NAMPT").

BACKGROUND OF THE INVENTION

Nicotinamide adenine dinucleotide (NAD) plays a fundamental role in both
cellular energy metabolism and cellular signaling. NAD plays an important role in
15 energy metabolism, as the pyridine ring in the NAD molecule readily accepts and
donates electrons in hydride transfer reactions catalyzed by numerous
dehydrogenases. The enzyme nicotinamide phosphoribosyltransferase (NAMPT,
NMPRT, NMPRTase, or NAmPRTase, International nomenclature: E.C. 2.4.2.12),
promotes the condensation of nicotinamide with 5-phosphoribosyl-1-pyrophosphate
20 to generate nicotinamide mononucleotide, which is a precursor in the biosynthesis of
NAD.

NAMPT is implicated in a variety of functions, including the promotion of
vascular smooth muscle cell maturation, inhibition of neutrophil apoptosis, activation
of insulin receptors, development of T and B lymphocytes, and reduction of blood
25 glucose. Thus, small molecule NAMPT inhibitors have potential uses as therapies in
a variety of diseases or conditions, including cancers involving solid and liquid
tumors, non-small cell lung cancer, leukemia, lymphoma, ovarian cancer, glioma,
breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate
cancer, skin cancer, rhino-gastric tumors, colorectal cancer, central nervous system
30 (CNS) cancer, bladder cancer, pancreatic cancer and Hodgkin's disease. NAMPT

inhibitors also have potential uses as therapies for diseases or conditions such as cancer, rheumatoid arthritis, diabetes, atherosclerosis, sepsis, or aging.

Rongvaux et al. have demonstrated that NAMPT is implicated in the regulation of cell viability during genotoxic or oxidative stress, and NAMPT inhibitors may therefore be useful as treatments for inflammation. Rongvaux, A., et al. *J. Immunol.* 2008, 181, 4685-4695. NAMPT may also have effects on the reaction of endothelial cells to high glucose levels, oxidative stress, and aging. Thus, NAMPT inhibitors may enable proliferating endothelial cells to resist the oxidative stress of aging and of high glucose, and to productively use excess glucose to support replicative longevity and angiogenic activity.

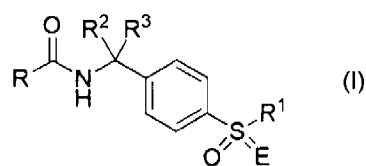
In particular, NAMPT inhibitors have been shown to interfere with NAD biosynthesis and to induce apoptotic cell death without any DNA damaging effects or primary effects on cellular energy metabolism, and thus have important anti-tumor effects. For example, the NAMPT inhibitor FK866 has these biochemical effects, and has also been shown to reduce NAD levels, induce a delay in tumor growth and enhance tumor radiosensitivity in a mouse mammary carcinoma model. *See, e.g.,* Hasmann M. and I. Schemainda, "FK866, a Highly Specific Noncompetitive Inhibitor of Nicotinamide Phosphoribosyltransferase, Represents a Novel Mechanism for Induction of Tumor Cell Apoptosis," *Cancer Res.* 2003, 63, 7436-7442; Dreves, J. et al., "Antiangiogenic potency of FK866/K22.175, a new inhibitor of intracellular NAD biosynthesis, in murine renal cell carcinoma," *Anticancer Res.* 2003, 23, 4853-4858.

More recently, another NAMPT inhibitor, CHS-828, has been shown to potently inhibit cell growth in a broad range of tumor cell lines. *See* Olesen, U.H. et al., "Anticancer agent CHS-828 inhibits cellular synthesis of NAD," *Biochem. Biophys. Res. Commun.* 2008, 367, 799-804; Ravaud, A. et al., "Phase I study and guanidine kinetics of CHS-828, a guanidine-containing compound, administered orally as a single dose every 3 weeks in solid tumors: an EORTC study," *Eur. J. Cancer* 2005, 41, 702-707. Both FK866 and CHS-828 are currently in clinical trials as cancer treatments.

There remains a need for potent NAMPT inhibitors with desirable pharmaceutical properties. Certain amido-benzyl sulfone and sulfoxide derivatives have been found in the context of this invention to have NAMPT-modulating activity.

5 SUMMARY OF THE INVENTION

In one aspect, the invention is directed to compounds of Formula I:



wherein:

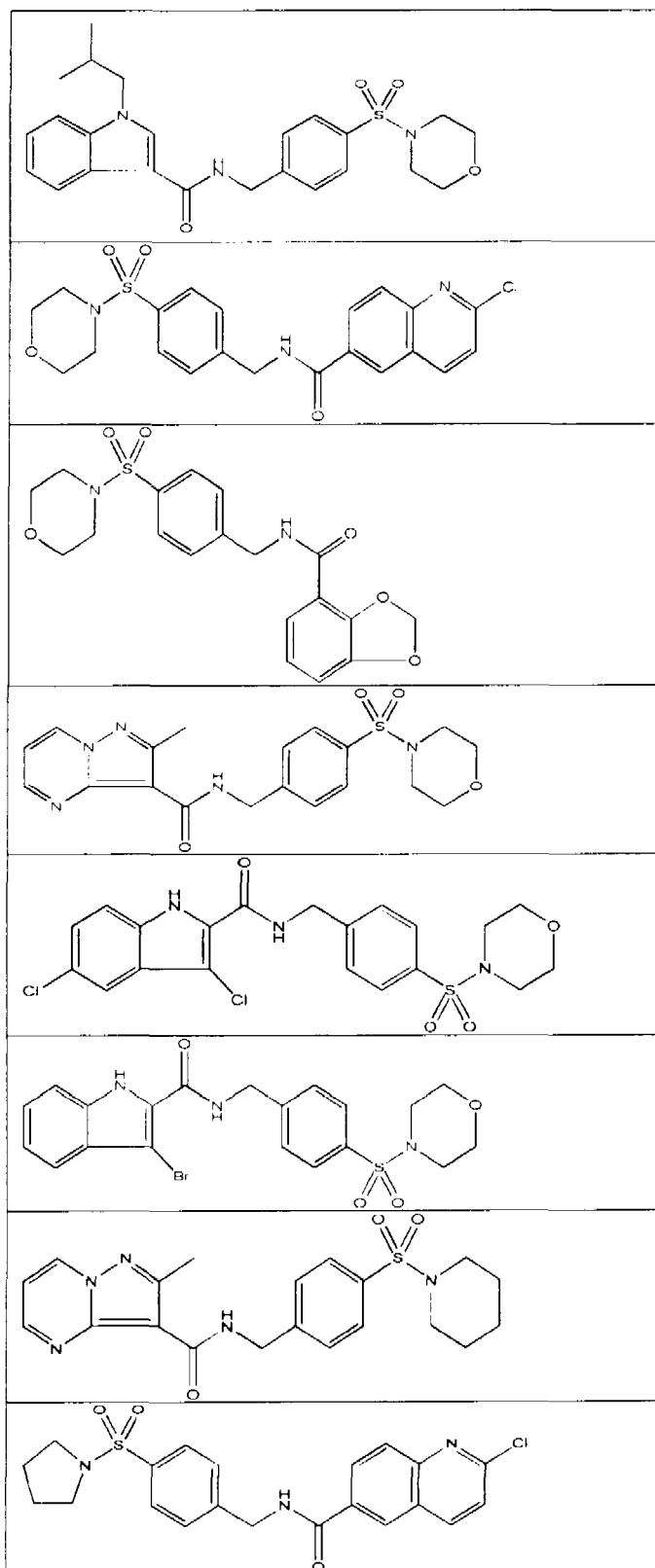
E is O or is absent;

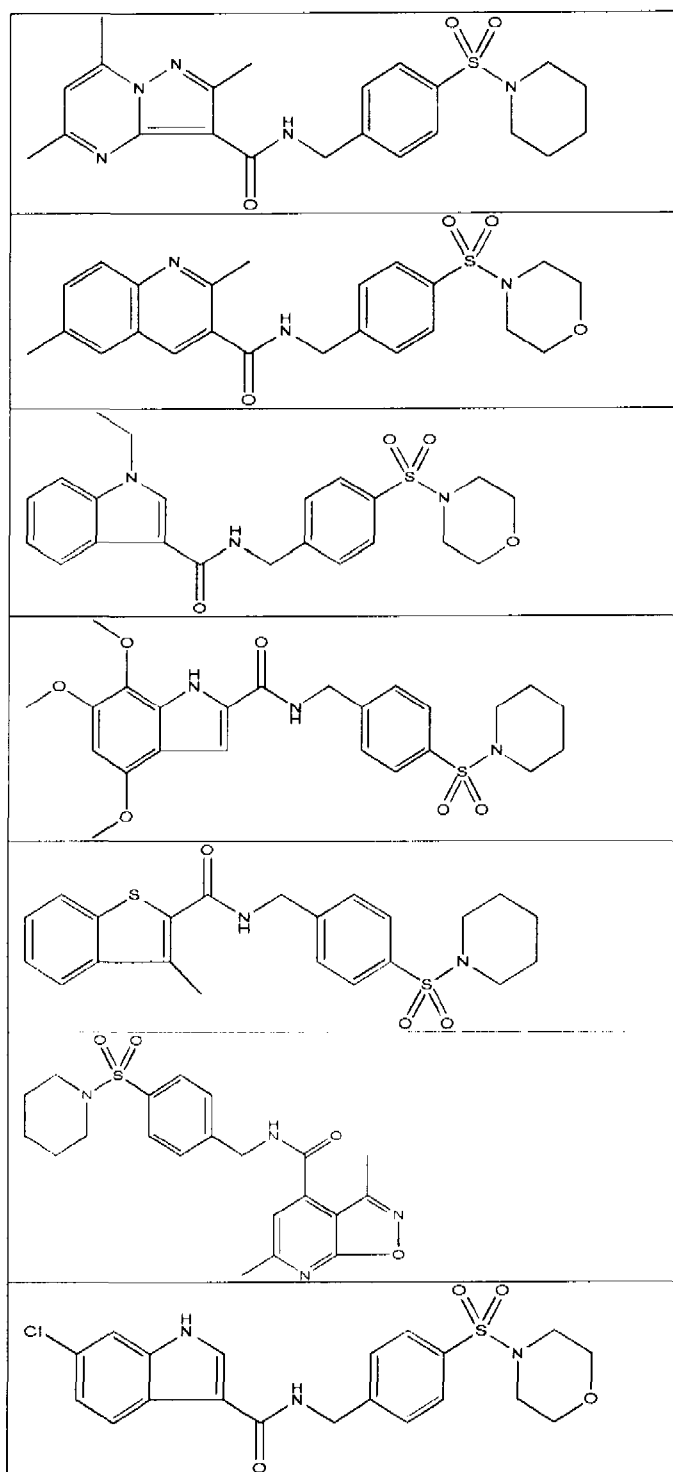
- 10 R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said
- 15 bicyclic heteroaryl is optionally an N-oxide; or

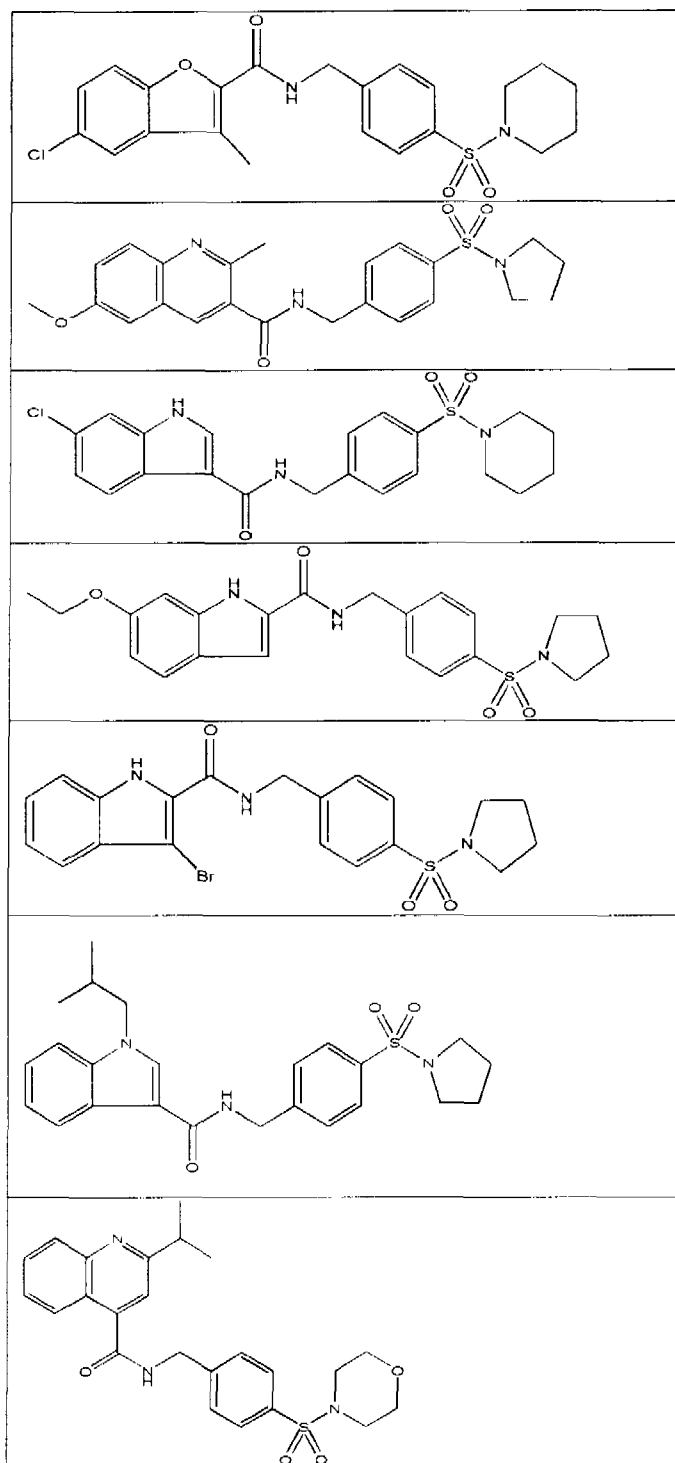
- (b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

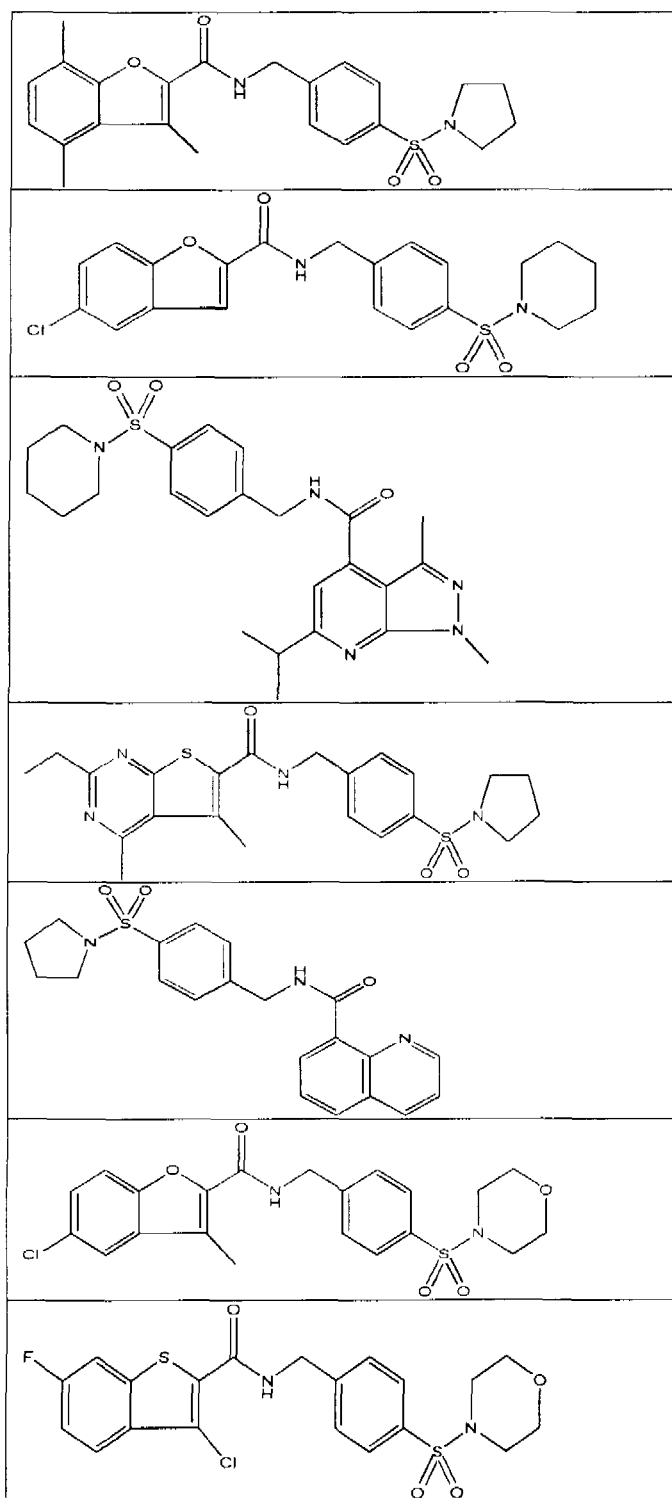
- 20 R¹ is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R^x;
- 25 wherein each R^x substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, cyano, -NR^aR^b, -alkylenyl-NR^aR^b, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl-, aryloxy-, arylalkoxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-,

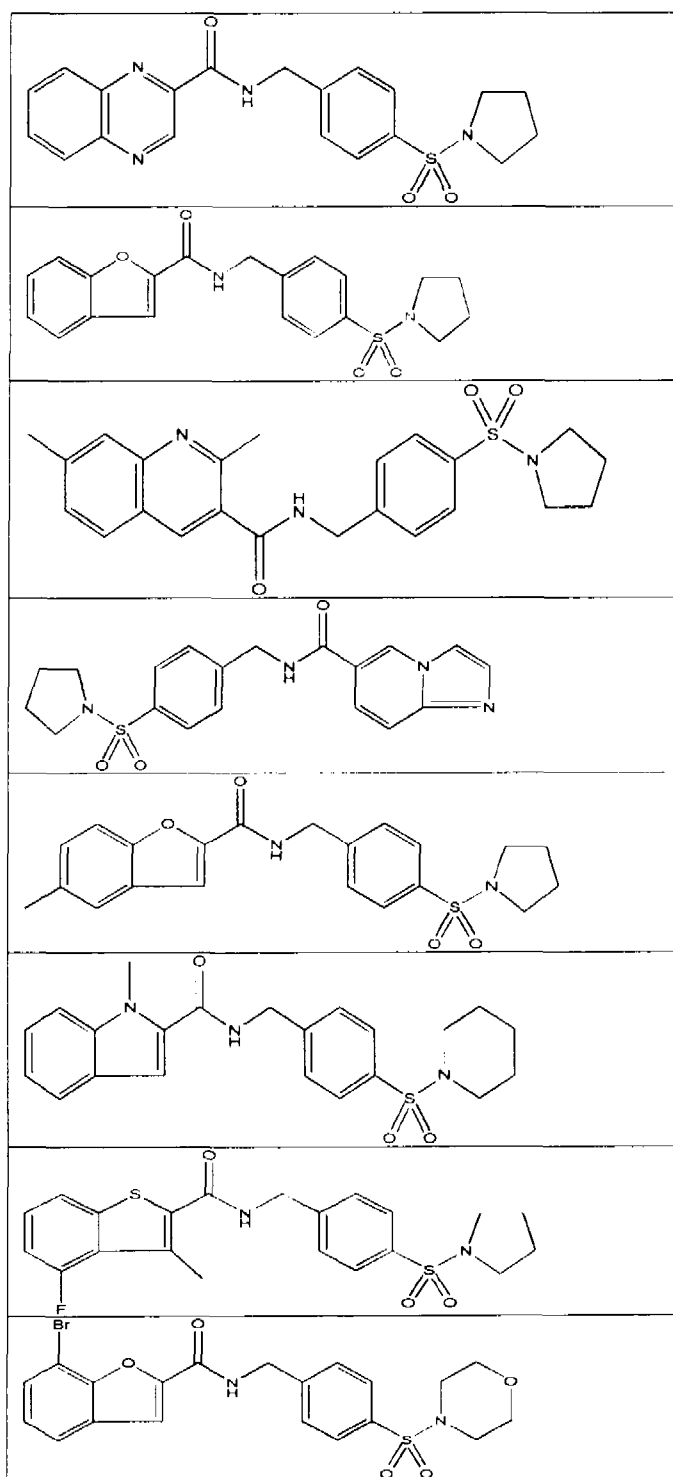
- heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-,
 -C(O)alkyl, -CO₂alkyl, -CO₂H, -C(O)cycloalkyl, -C(O)aryl,
 -C(O)heterocycloalkyl, -S(O)-alkyl, -SO₂-alkyl, -SO₂-aryl, -SO₂-
 (haloalkyl), -CONH₂, C(O)NH(alkyl), -C(O)NH(haloalkyl),
 5 -C(O)N(alkyl)₂, -C(O)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl-,
 -N(R^c)-C(O)-alkyl, -N(R^c)-C(O)-aryl, -N(R^c)-CO₂-alkyl, -SO₂NH₂,
 -SO₂NH(alkyl), -SO₂N(alkyl)₂, -SO₂NH(cycloalkyl), and
 -N(H)(SO₂alkyl), or two adjacent R^x substituents taken together form a
 phenyl ring,
 10 wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and
 phenyl substituents within R^x is independently unsubstituted or
 substituted with one or more substituents selected from the group
 consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,
 -NHCO₂alkyl, -C(O)alkyl, and -CO₂alkyl;
 15 wherein R^a and R^b are each independently H, alkyl, alkoxy,
 alkoxyalkyl, cyanoalkyl, or haloalkyl; and
 R^c is H or alkyl; or
 (2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein
 said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system,
 20 and said heterocycloalkyl is unsubstituted or substituted with one or more
 substituents independently selected from the group consisting of: alkyl,
 halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo,
 -NR^dR^e, -alkylenyl-NR^dR^e, -C(O)alkyl, -CO₂alkyl, and -SO₂alkyl;
 wherein R^d is H or alkyl; and
 25 R^e is H, alkyl, haloalkyl, -C(O)alkyl, -CO₂alkyl, or -SO₂alkyl; and
 R² and R³ are each independently H or deuterium;
 and pharmaceutically acceptable salts thereof,
 with the proviso that the compound of Formula I is not one of the following
 compounds:

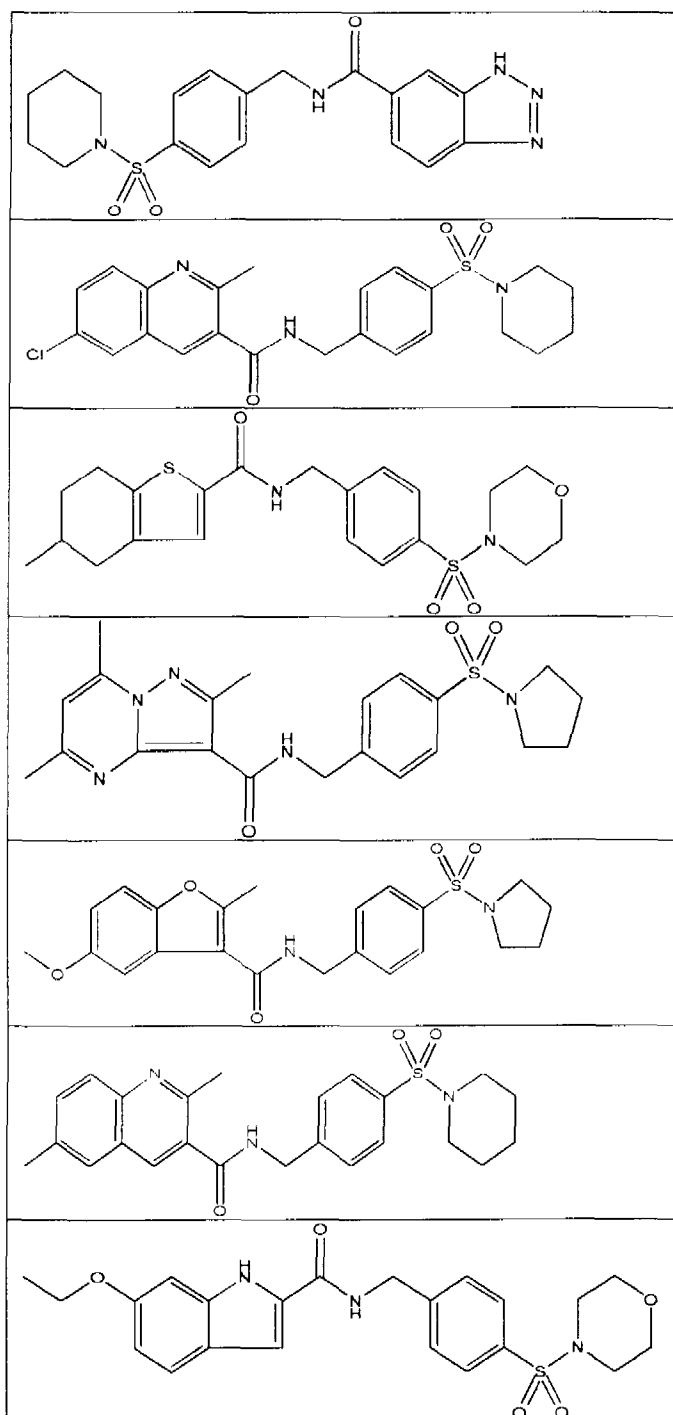


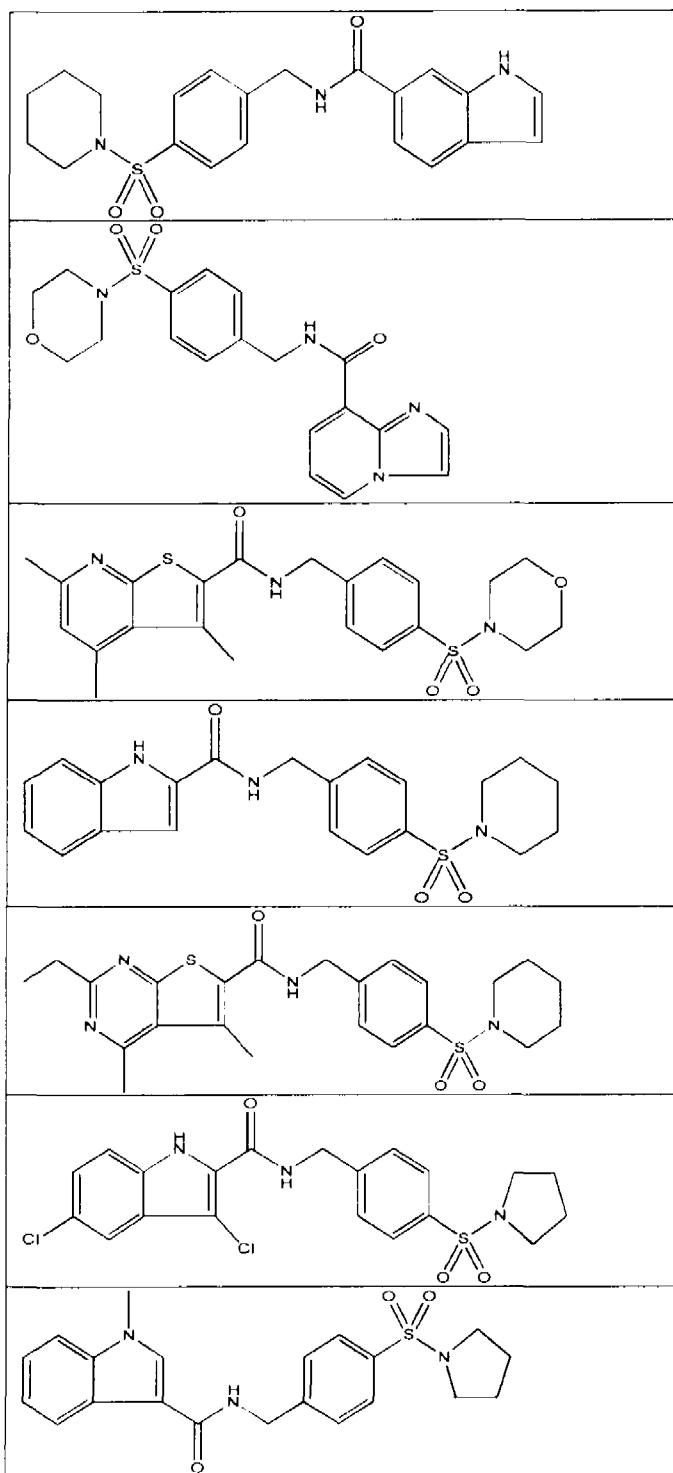


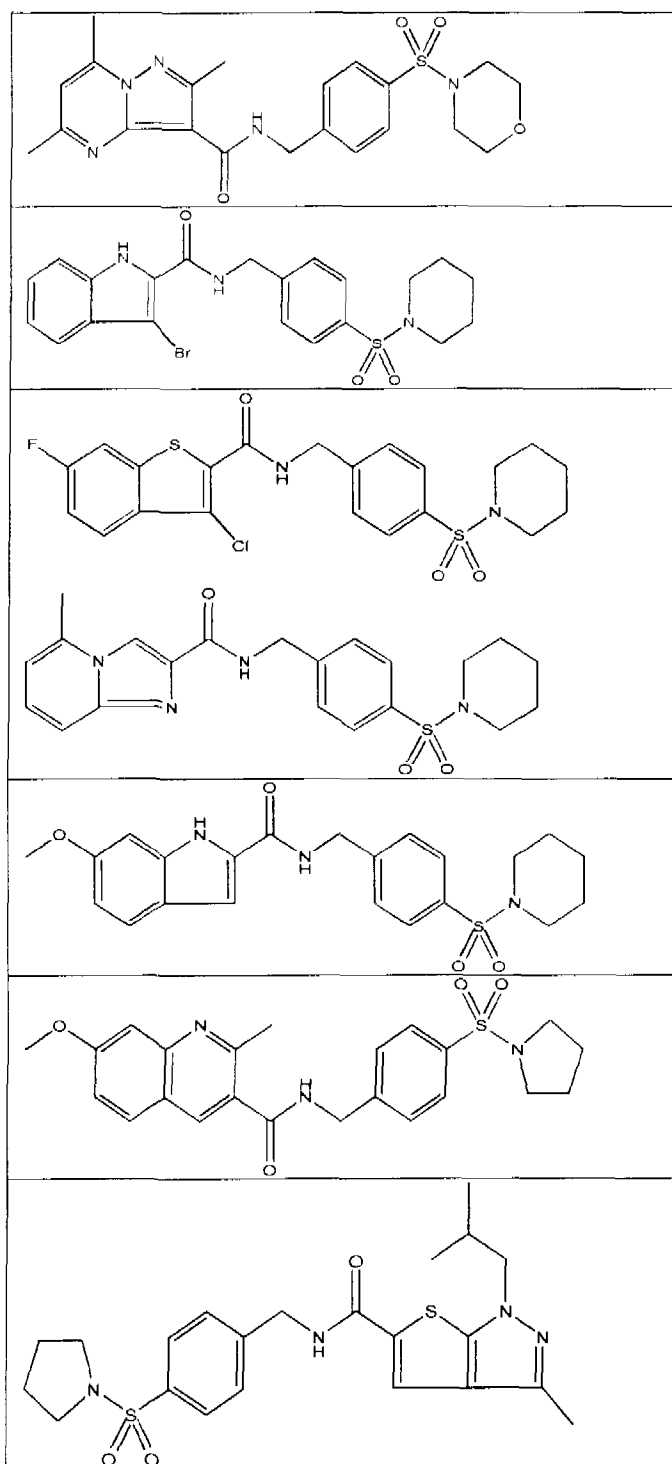


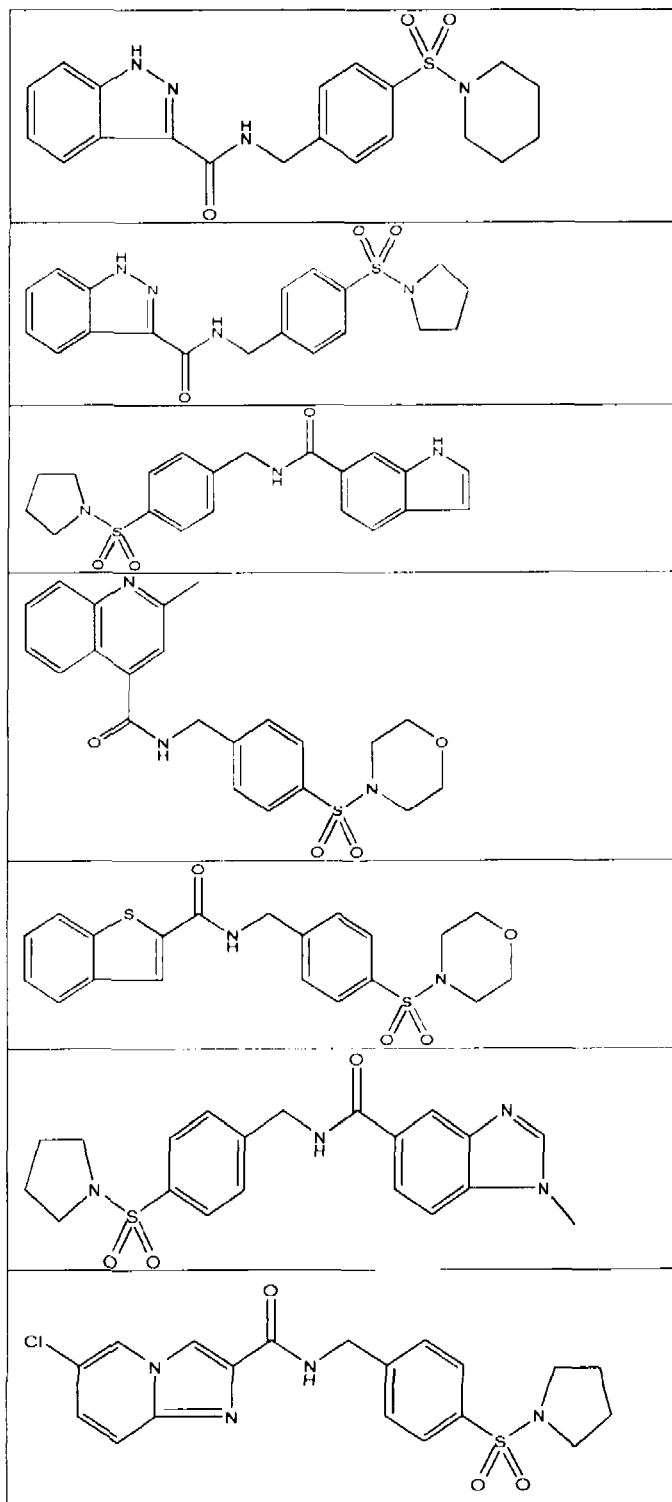


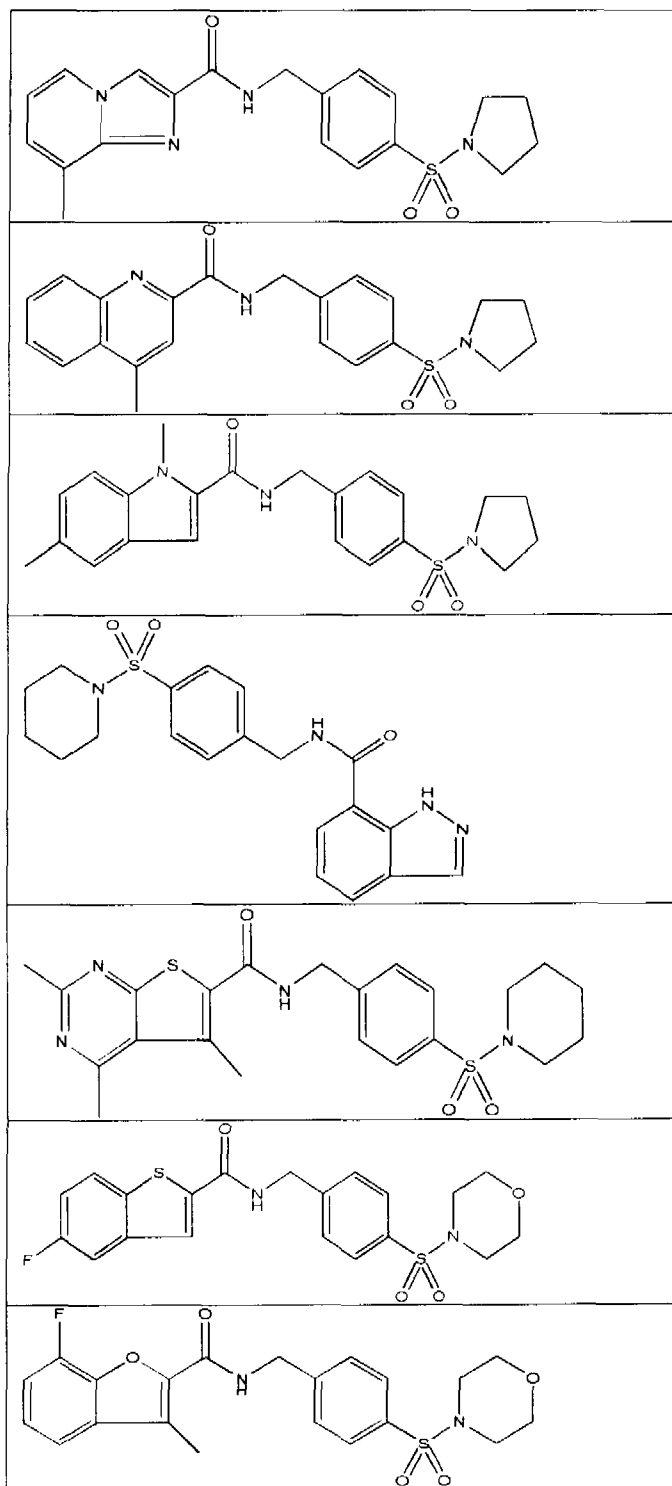


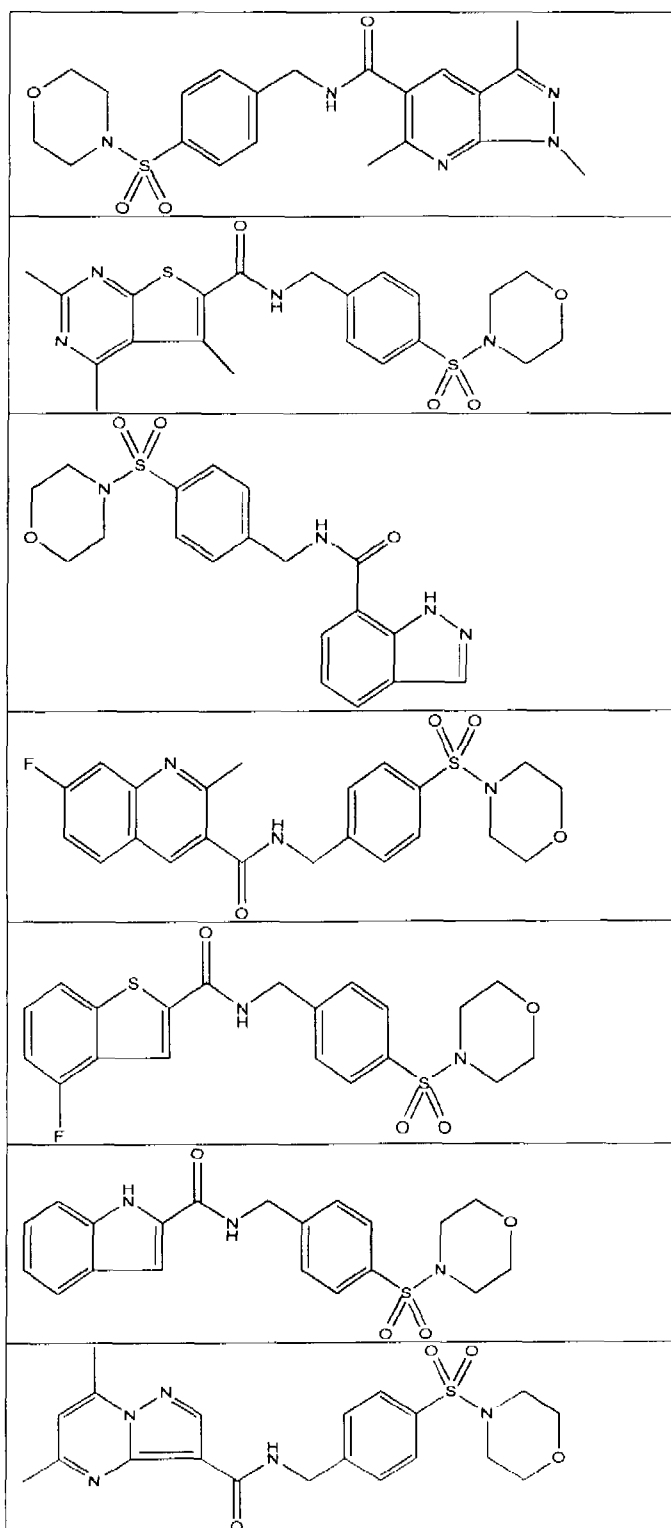


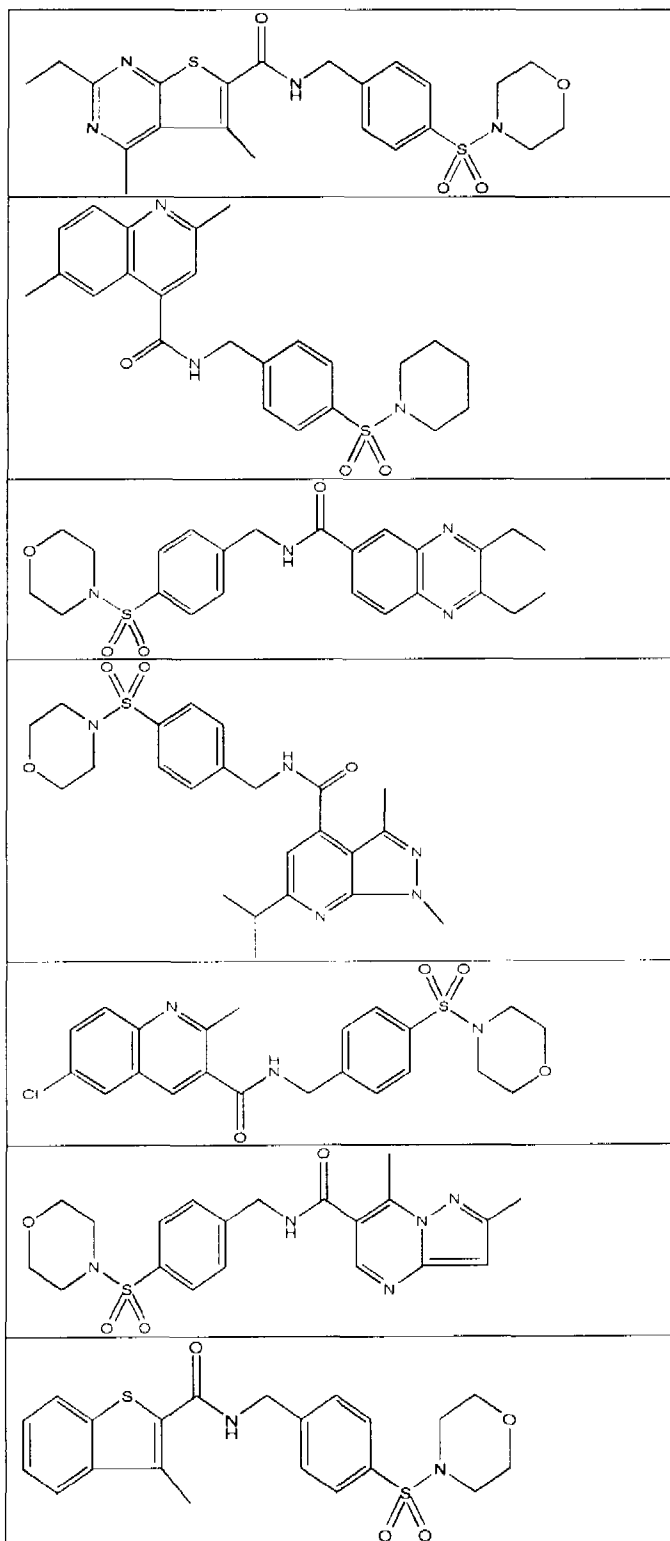


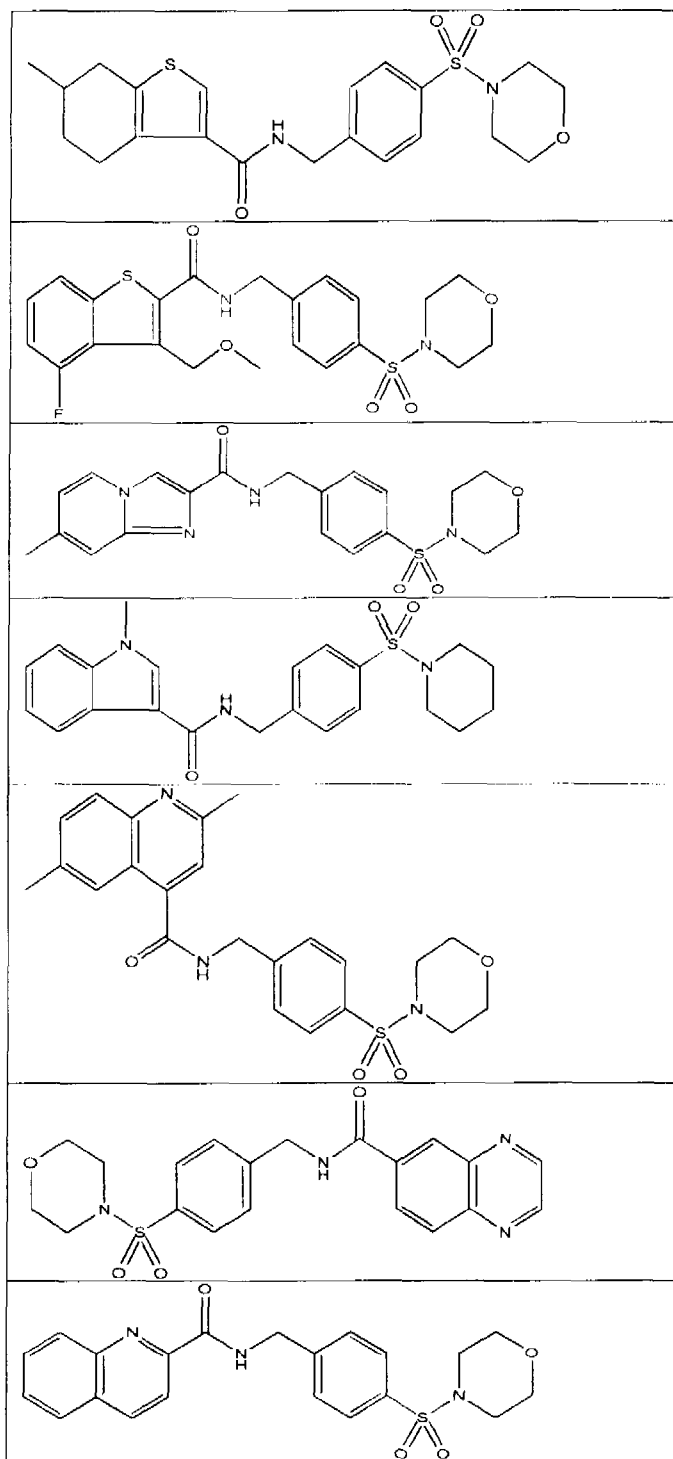


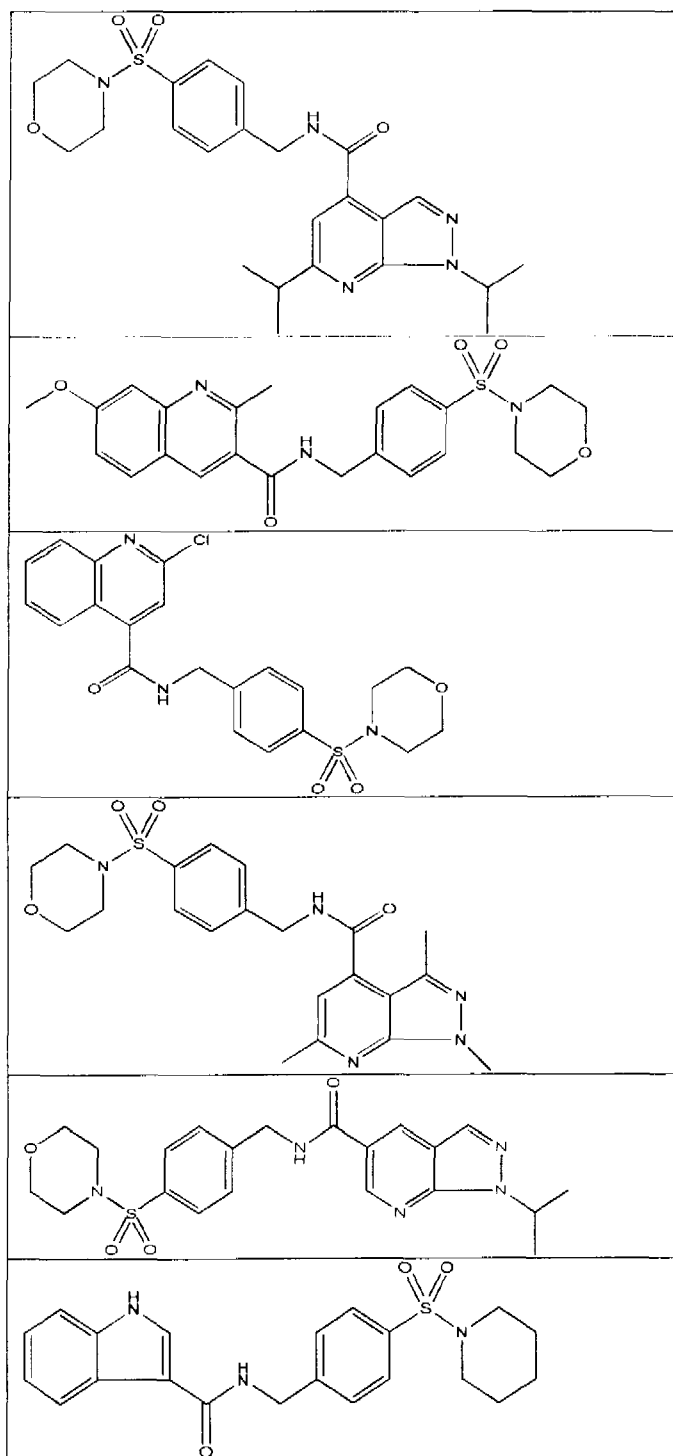


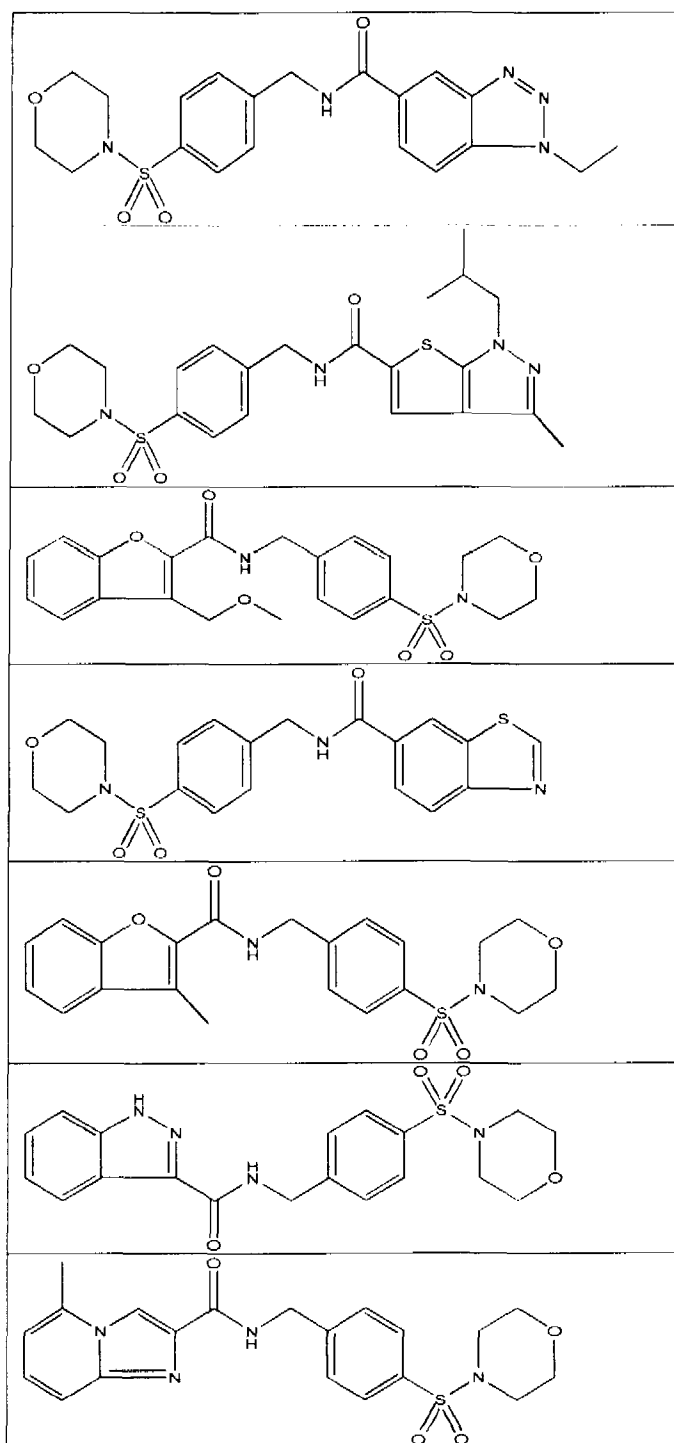


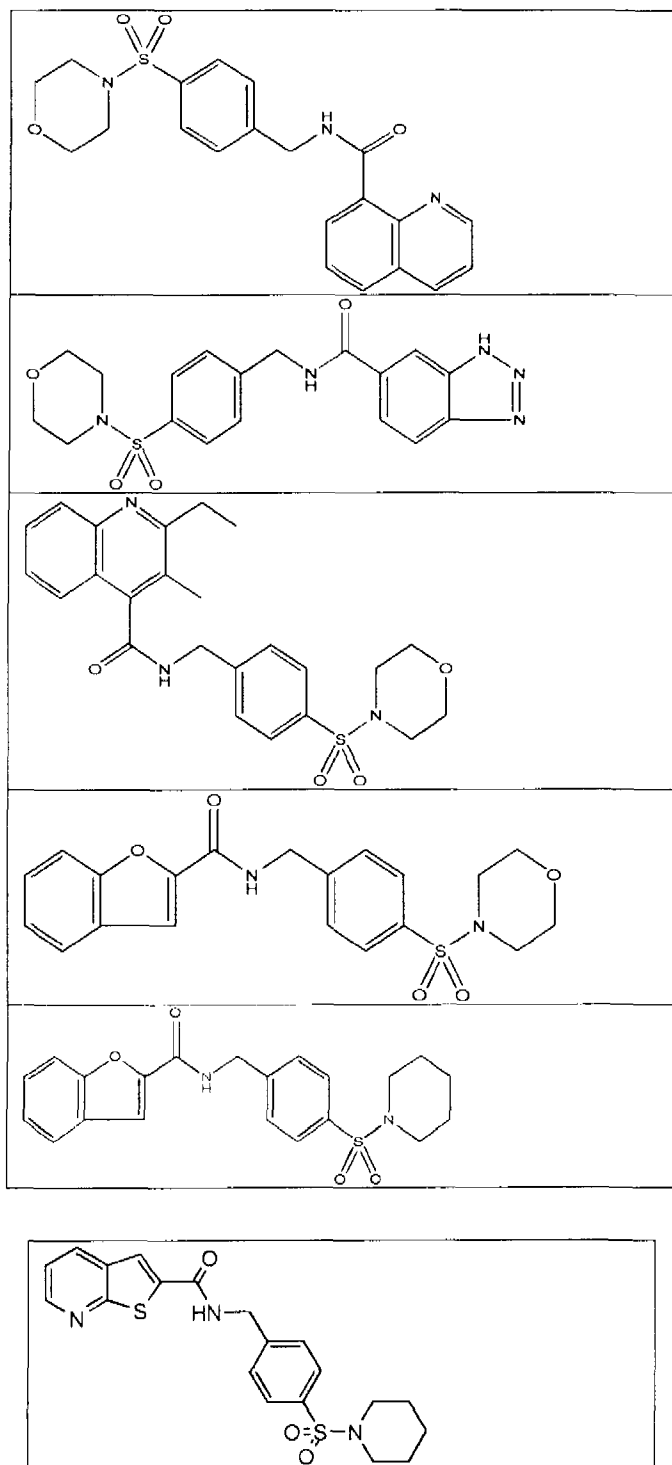


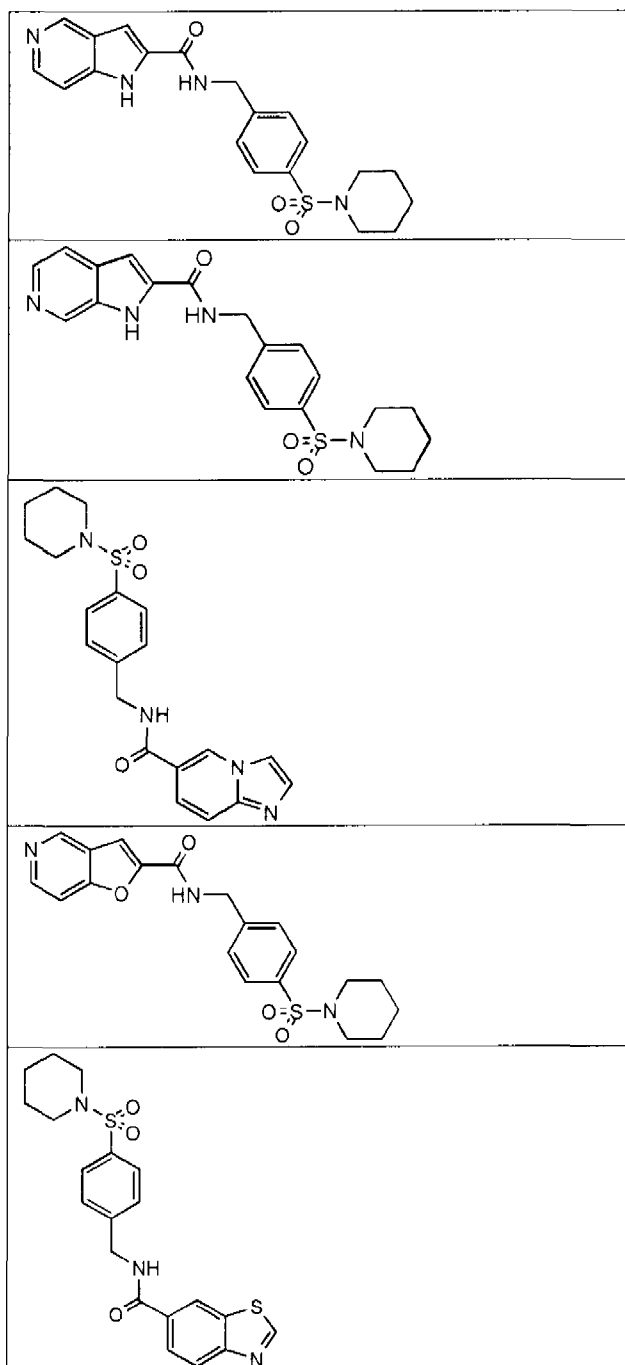


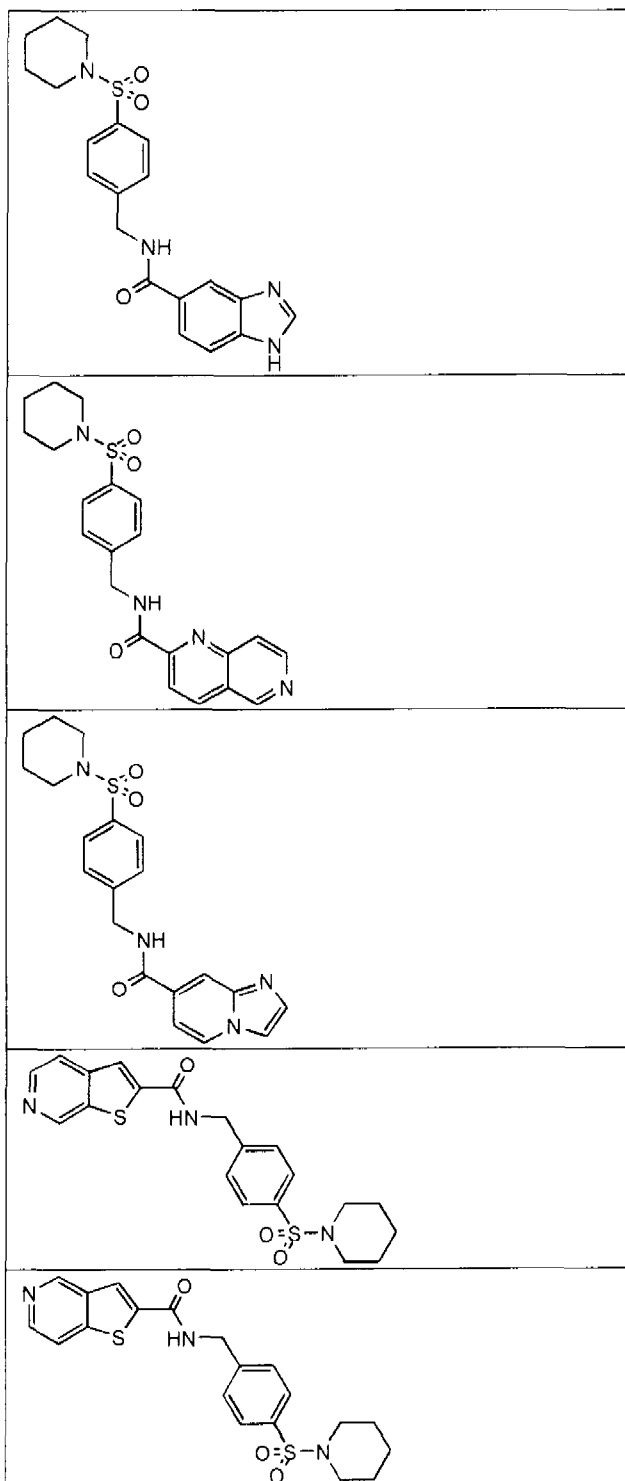


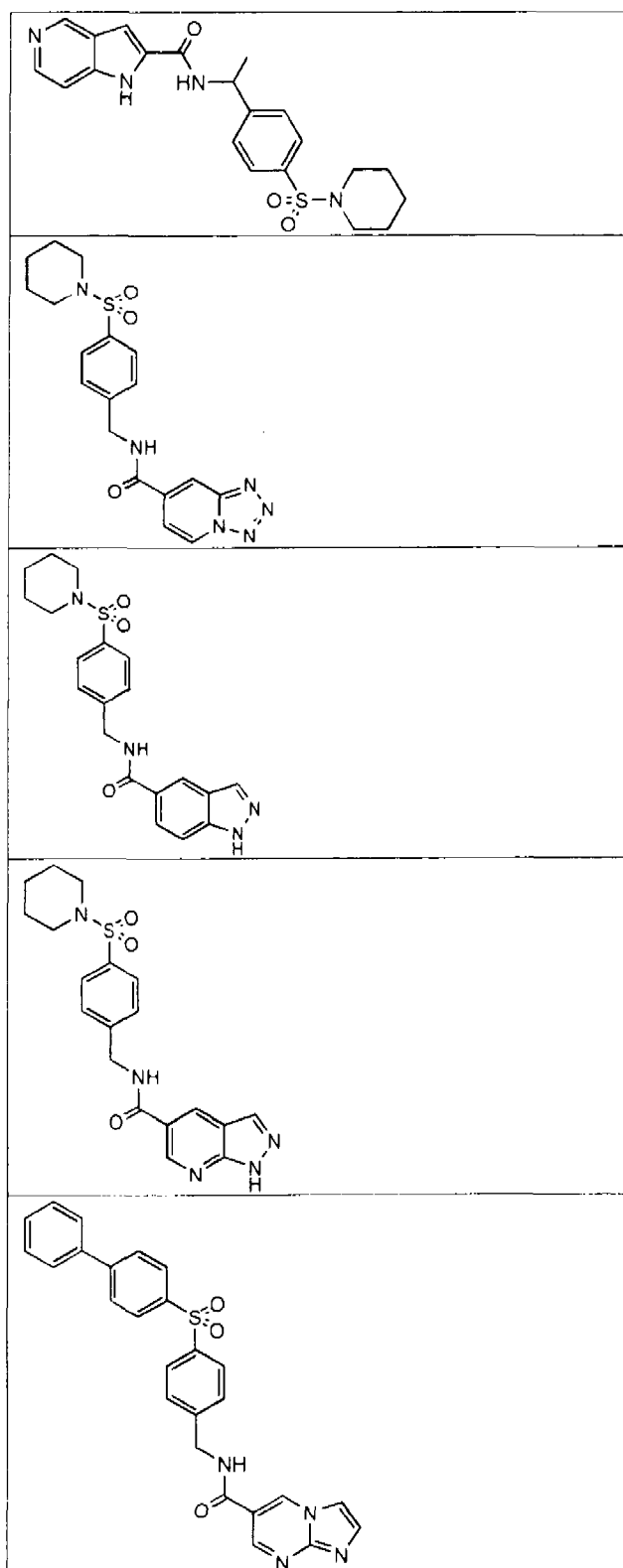


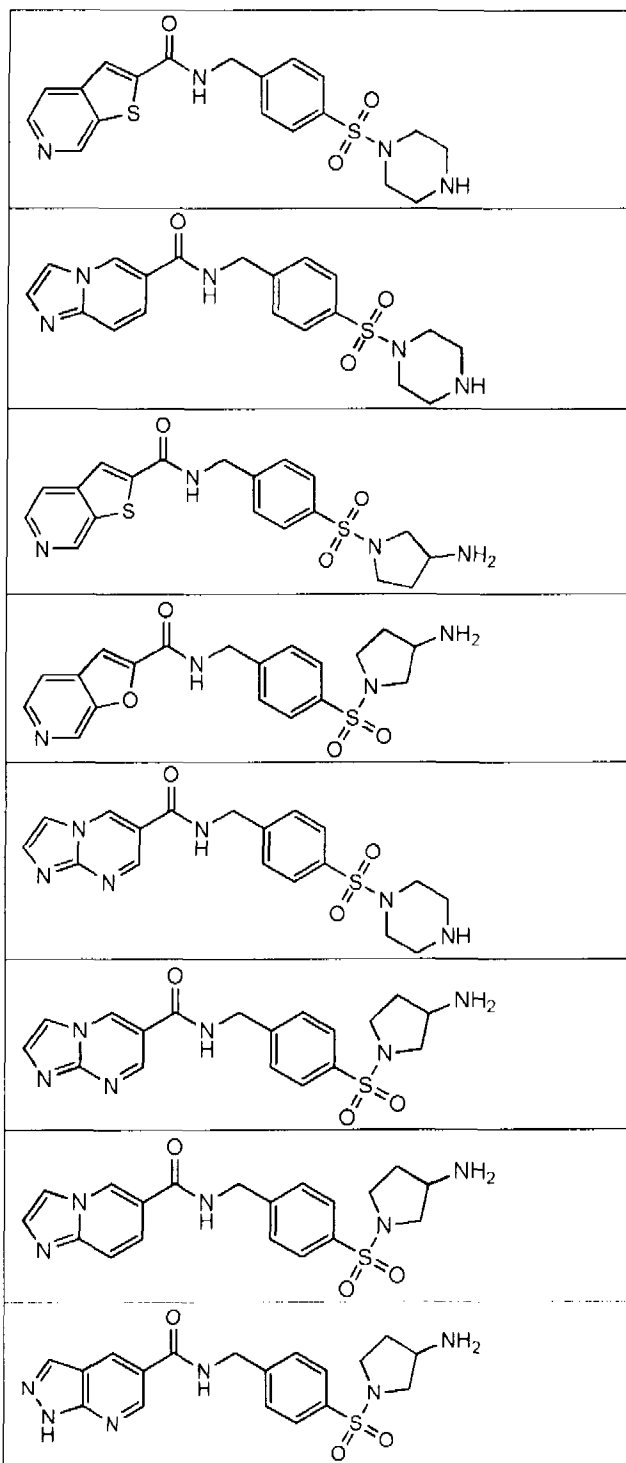


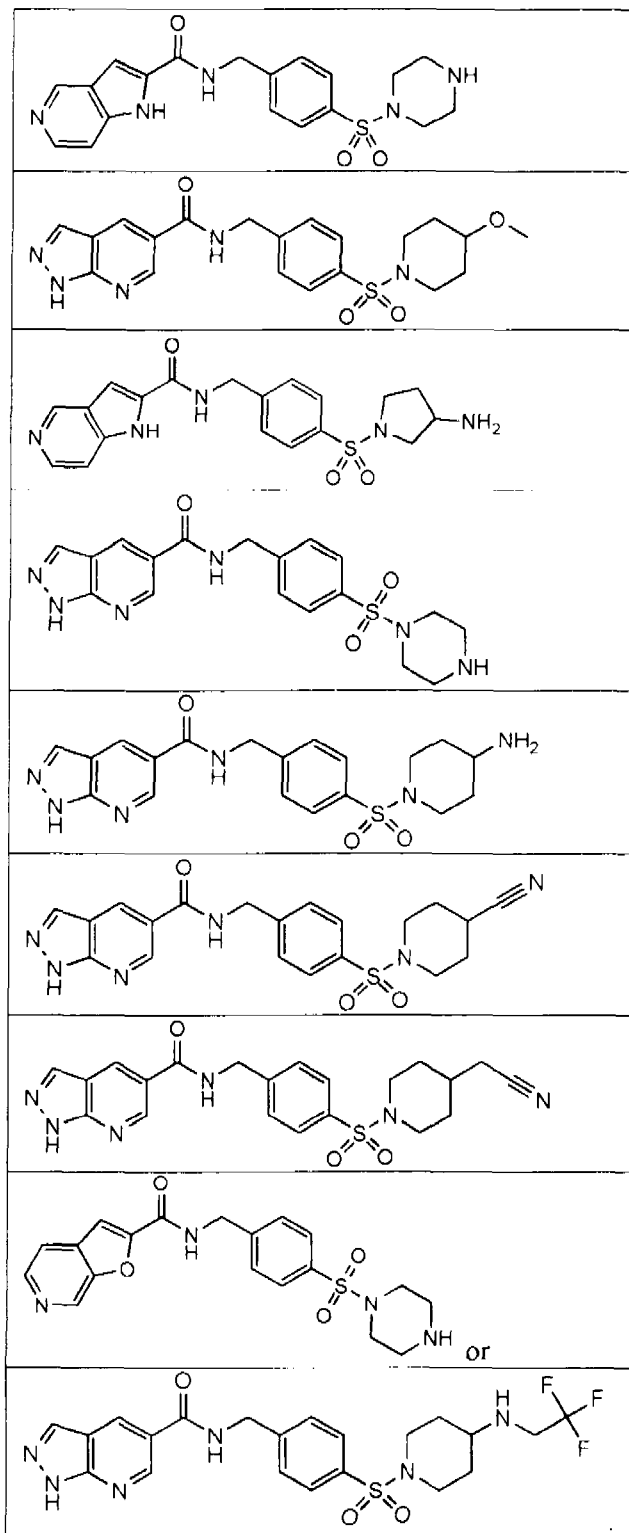












In a further aspect, the invention relates to pharmaceutical compositions each comprising an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt of a compound of Formula I. Pharmaceutical compositions according to the invention may further comprise at least one
5 pharmaceutically acceptable excipient.

In another aspect, the invention is directed to a method of treating a subject suffering from a disease or medical condition mediated by NAMPT activity, comprising administering to the subject in need of such treatment an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt of a
10 compound of Formula I, or comprising administering to the subject in need of such treatment an effective amount of a pharmaceutical composition comprising an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt of a compound of Formula I.

An aspect of the present invention concerns the use of compound of Formula I
15 for the preparation of a medicament used in the treatment, prevention, inhibition or elimination of cancer.

An aspect of the present invention concerns the use of a compound of Formula I for the preparation of a medicament used in the treatment, prevention, inhibition or elimination of cancer, where the cancer can be selected from leukemia,
20 lymphoma, ovarian cancer, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, CNS cancer, bladder cancer, pancreatic cancer and Hodgkin's disease.

An aspect of the present invention concerns the use of a compound of Formula I for the preparation of a medicament used in the treatment, prevention,
25 inhibition or elimination of cancer, where the cancer can be selected from cancers with solid and liquid tumors, non-small cell lung cancer, leukemia, lymphoma, ovarian cancer, glioma, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, rhino-gastric tumors, colorectal cancer, CNS cancer, bladder cancer, pancreatic cancer and Hodgkin's disease.

30 In another aspect, the compounds of Formula I and pharmaceutically acceptable salts thereof are useful as NAMPT modulators. Thus, the invention is

directed to a method for modulating NAMPT activity, including when NAMPT is in a subject, comprising exposing NAMPT to an effective amount of at least one compound of Formula I or a pharmaceutically acceptable salt of a compound of Formula I.

5 In yet another aspect, the present invention is directed to methods of making compounds of Formula I and pharmaceutically acceptable salts thereof.

 In certain embodiments of the compounds, pharmaceutical compositions, and methods of the invention, the compound of Formula I is a compound selected from those species described or exemplified in the detailed description below, or is a
10 pharmaceutically acceptable salt of such a compound.

 Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

DETAILED DESCRIPTION AND PARTICULAR EMBODIMENTS

15 For the sake of brevity, the disclosures of the publications cited in this specification, including patents and patent applications, are herein incorporated by reference in their entirety.

 Most chemical names were generated using IUPAC nomenclature herein. Some chemical names were generated using different nomenclatures or alternative or
20 commercial names known in the art. In the case of conflict between names and structures, the structures prevail.

General Definitions

 As used above, and throughout this disclosure, the following terms, unless
25 otherwise indicated, shall be understood to have the following meanings. If a definition is missing, the conventional definition as known to one skilled in the art controls. If a definition provided herein conflicts or is different from a definition provided in any cited publication, the definition provided herein controls.

 As used herein, the terms “including”, “containing”, and “comprising” are
30 used in their open, non-limiting sense.

As used herein, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term “about”. It is understood that, whether
5 the term “about” is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including equivalents and approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a
10 percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

15 Chemical Definitions

As used herein, “alkyl” refers to a saturated, straight- or branched-chain hydrocarbon group having from 1 to 10 carbon atoms. Representative alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-
20 dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, and the like, and longer alkyl groups, such as heptyl, octyl, and the like. As used herein, “lower alkyl” means an alkyl having from 1 to 6 carbon
25 atoms.

The term “alkylamino” as used herein denotes an amino group as defined herein wherein one hydrogen atom of the amino group is replaced by an alkyl group as defined herein. Aminoalkyl groups can be defined by the following general formula -NH-alkyl. This general formula includes groups of the following general
30 formulae: -NH-C₁-C₁₀-alkyl and -NH-C₁-C₆-alkyl. Examples of aminoalkyl groups include, but are not limited to aminomethyl, aminoethyl, aminopropyl, aminobutyl.

The term “dialkylamino” as used herein denotes an amino group as defined herein wherein two hydrogen atoms of the amino group are replaced by alkyl groups as defined herein. Diaminoalkyl groups can be defined by the following general formula $-N(\text{alkyl})_2$, wherein the alkyl groups can be the same or can be different and
5 can be selected from alkyls as defined herein, for example C_1 - C_{10} -alkyl or C_1 - C_6 -alkyl.

The term “alkylenyl” refers to a divalent alkyl group.

The term “alkoxy” as used herein includes $-O(\text{alkyl})$, wherein alkyl is defined
10 above.

As used herein, “alkoxyalkyl” means $-(\text{alkylenyl})-O(\text{alkyl})$, wherein each “alkyl” is independently an alkyl group defined above.

As used herein, an “alkenyl” refers to a straight- or branched-chain hydrocarbon group having one or more double bonds therein and having from 2 to 10
15 carbon atoms. Illustrative alkenyl groups include, but are not limited to, ethylenyl, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, and the like. As used herein, “lower alkenyl” means an alkenyl having from 2 to 6 carbon atoms.

As used herein, “alkynyl” refers to a straight- or branched-chain hydrocarbon
20 group having one or more triple bonds therein and having from 2 to 10 carbon atoms. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butyne, 4-propyl-2-pentyne, 4-butyl-2-hexynyl, and the like.

The term “amino” as used herein refers to an $-NH_2$ group.

25 “Aryl” means a mono-, bi-, or tricyclic aromatic group, wherein all rings of the group are aromatic. For bi- or tricyclic systems, the individual aromatic rings are fused to one another. Exemplary aryl groups include, but are not limited to, phenyl, naphthalene, and anthracene.

“Aryloxy” as used herein refers to an $-O(\text{aryl})$ group, wherein aryl is defined
30 as above.

“Arylalkyl” as used herein refers to an $-(\text{alkylenyl})-(\text{aryl})$ group, wherein alkylenyl and aryl are as defined above. Non-limiting examples of arylalkyls comprise a lower alkyl group. Non-limiting examples of suitable arylalkyl groups include benzyl, 2-phenethyl, and naphthalenylmethyl.

5 “Arylalkoxy” as used herein refers to an $-O-(\text{alkylenyl})-\text{aryl}$ group wherein alkylenyl and aryl are as defined above.

The term “cyano” as used herein means a substituent having a carbon atom joined to a nitrogen atom by a triple bond.

The term “cyanoalkyl” denotes an alkyl group as defined above wherein a
10 hydrogen atom of the alkyl group is replaced by a cyano ($-\text{CN}$) group. The alkyl portion of the cyanoalkyl group provides the connection point to the remainder of the molecule.

The term “deuterium” as used herein means a stable isotope of hydrogen having one proton and one neutron.

15 The term “halogen” as used herein refers to fluorine, chlorine, bromine, or iodine. The term “halo” represents chloro, fluoro, bromo, or iodo. Halo can also denote chloro, fluoro, or bromo.

The term “haloalkyl” denotes an alkyl group as defined above wherein one or more, for example one, two, or three of the hydrogen atoms of the alkyl group are
20 replaced by a halogen atom, for example fluoro, bromo, or chloro, in particular fluoro. Examples of haloalkyl include, but are not limited to, monofluoro-, difluoro-, or trifluoro-methyl, -ethyl or -propyl, for example, 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl, or trifluoromethyl, or bromoethyl or chloroethyl. Similarly, the term “fluoroalkyl” refers to an alkyl group as defined
25 above substituted with one or more, for example one, two, or three fluorine atoms.

The term “haloalkoxy” as used herein refers to an $-O-(\text{haloalkyl})$ group wherein haloalkyl is defined as above. Exemplary haloalkoxy groups are bromoethoxy, chloroethoxy, trifluoromethoxy and 2,2,2-trifluoroethoxy.

The term “hydroxy” means an $-\text{OH}$ group.

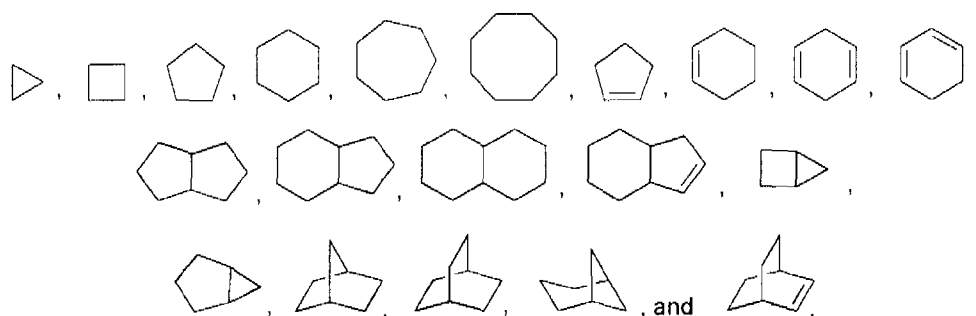
30 The term “hydroxyalkyl” denotes an alkyl group that is substituted by at least one hydroxy group, for example, one, two or three hydroxy group(s). The alkyl

portion of the hydroxyalkyl group provides the connection point to the remainder of a molecule. Examples of hydroxyalkyl groups include, but are not limited to, hydroxymethyl, hydroxyethyl, 1-hydroxypropyl, 2-hydroxyisopropyl, 1,4-dihydroxybutyl, and the like.

- 5 The term “methylenedioxy” as used herein means a functional group with the structural formula $-O-CH_2-O-$ which is connected to the molecule by two chemical bonds via the oxygens.

The term “oxo” means an $=O$ group and may be attached to a carbon atom or a sulfur atom. The term “N-oxide” refers to the oxidized form of a nitrogen atom.

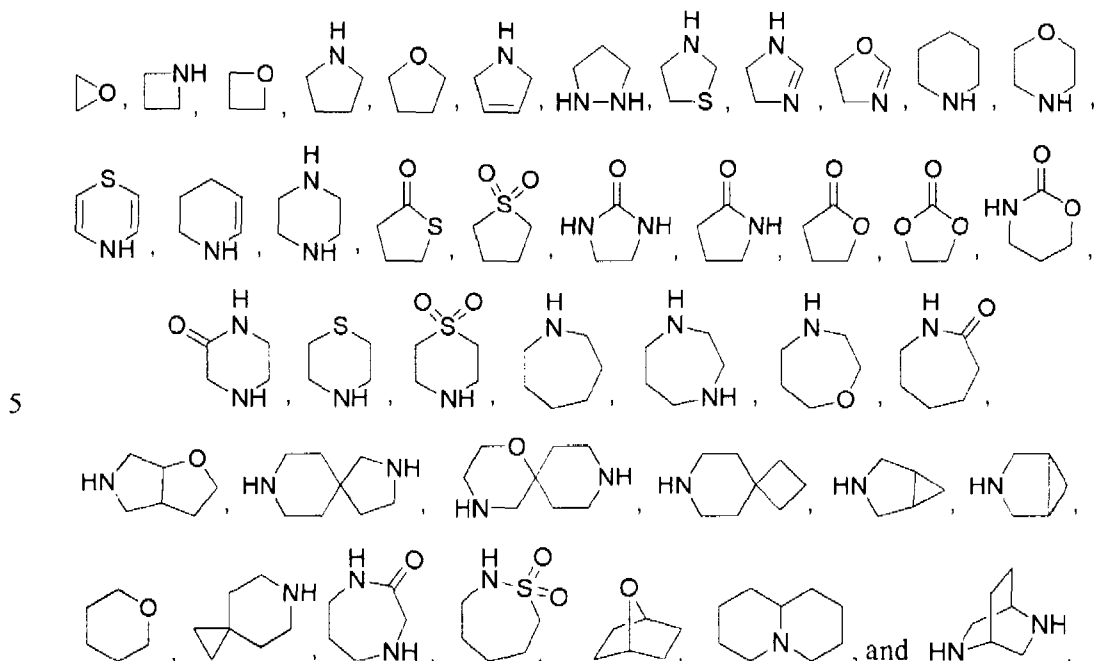
- 10 As used herein, the term “cycloalkyl” refers to a saturated or partially saturated, monocyclic, fused polycyclic, bridged polycyclic, or spiro polycyclic carbocycle having from 3 to 15 ring carbon atoms. A non limiting category of cycloalkyl groups are saturated or partially saturated, monocyclic carbocycles having from 3 to 6 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to, the following moieties:



The term “cycloalkoxy” refers to a $-O-(\text{cycloalkyl})$ group.

- 20 “Heterocycloalkyl” as used herein refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms selected from carbon atoms and up to three heteroatoms selected from nitrogen, oxygen, and sulfur. The ring structure may optionally contain up to two oxo groups on carbon or sulfur ring members. Heterocycloalkyl groups also include
- 25 monocyclic rings having 5 to 6 atoms as ring members, of which 1, 2, or 3 ring members are selected from N, S, or O and the rest are carbon atoms. A “nitrogen-linked” heterocycloalkyl is attached to the parent moiety via a nitrogen ring atom. A

“carbon-linked” heterocycloalkyl is attached to the parent moiety via a carbon ring atom. Illustrative heterocycloalkyl entities include, but are not limited to:



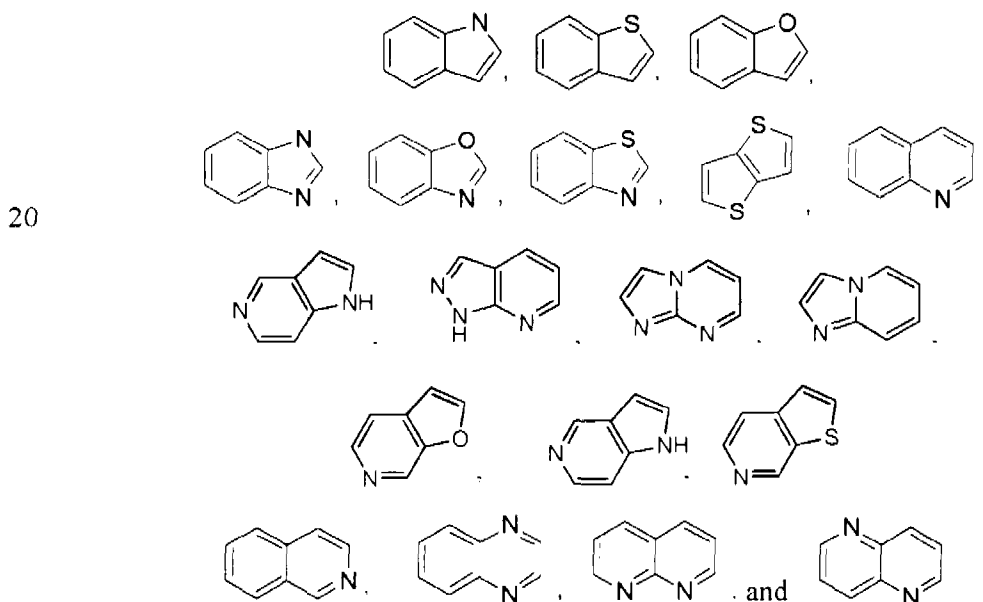
“(Heterocycloalkyl)alkyl-” refers to a heterocycloalkyl group as defined above, substituted with an alkylenyl group as defined above, wherein the alkylenyl group provides for the attachment to the parent moiety.

The term “(heterocycloalkyl)alkoxy-” refers to a (heterocycloalkyl)-(alkylenyl)-O- group, wherein heterocycloalkyl and alkylenyl are as defined above.

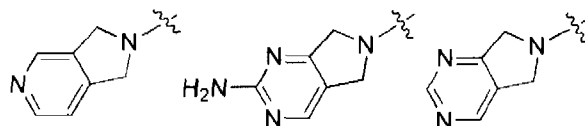
As used herein, the term “heteroaryl” refers to a monocyclic, or fused polycyclic, aromatic heterocycle having from three to 15 ring atoms that are selected from carbon, oxygen, nitrogen, and sulfur. Suitable heteroaryl groups do not include ring systems that must be charged to be aromatic, such as pyrylium. Some suitable 5-membered heteroaryl rings (as a monocyclic heteroaryl or as part of a polycyclic heteroaryl) have one oxygen, sulfur, or nitrogen atom, or one nitrogen plus one oxygen or sulfur, or 2, 3, or 4 nitrogen atoms. Some suitable 6-membered heteroaryl rings (as a monocyclic heteroaryl or as part of a polycyclic heteroaryl) have 1, 2, or 3 nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl,

quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and
 5 furopyridinyl.

The term "bicyclic heteroaryl" refers to a heteroaryl as defined above, having two constituent aromatic rings, wherein the two rings are fused to one another and at least one of the rings is a heteroaryl as defined above. Bicyclic heteroaryls include bicyclic heteroaryl groups comprising 1, 2, 3, or 4 heteroatom ring members and are
 10 unsubstituted or substituted with one or more substituents selected from the group consisting of amino and halo; and wherein one or more N ring members of said heteroaryl is optionally an N-oxide. Bicyclic heteroaryls also include 8-, 9-, or 10-membered bicyclic heteroaryl groups. Bicyclic heteroaryls also include 8-, 9-, or 10-membered bicyclic heteroaryl groups that have 1, 2, 3 or 4 heteroatom ring members
 15 and that are unsubstituted or substituted with one or more substituents selected from the group consisting of amino and halo; and wherein one or more N ring members of said heteroaryl is optionally an N-oxide. Illustrative examples of bicyclic heteroaryls include, but are not limited to:



The term “five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with amino” include, but are not limited to, the following groups:



Those skilled in the art will recognize that the species of heteroaryl, cycloalkyl, and heterocycloalkyl groups listed or illustrated above are not exhaustive, and that additional species within the scope of these defined terms may also be selected.

As used herein, the term “substituted” means that the specified group or moiety bears one or more suitable substituents. As used herein, the term “unsubstituted” means that the specified group bears no substituents. As used herein, the term “optionally substituted” means that the specified group is unsubstituted or substituted by the specified number of substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system.

As used herein, the expression “one or more substituents” denotes one to maximum possible number of substitution(s) that can occur at any valency-allowed position on the system. In a certain embodiment, one or more substituent means 1, 2, 3, 4, or 5 substituents. In another embodiment, one or more substituent means 1, 2, or 3 substituents.

Any atom that is represented herein with an unsatisfied valence is assumed to have the sufficient number of hydrogen atoms to satisfy the atom’s valence.

When any variable (e.g., alkyl, alkylenyl, heteroaryl, R^1 , R^2 , or R^a) appears in more than one place in any formula or description provided herein, the definition of that variable on each occurrence is independent of its definition at every other occurrence.

Numerical ranges, as used herein, are intended to include sequential whole numbers. For example, a range expressed as “from 0 to 4” or “0-4” includes 0, 1, 2, 3 and 4.

When a multifunctional moiety is shown, the point of attachment to the core is indicated by a line or hyphen. For example, aryloxy- refers to a moiety in which an oxygen atom is the point of attachment to the core molecule while aryl is attached to the oxygen atom.

Additional Definitions

As used herein, the term “subject” encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans; non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; and laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. In one embodiment of the present invention, the mammal is a human.

“Patient” includes both human and animals.

The term “inhibitor” refers to a molecule such as a compound, a drug, an enzyme activator, or a hormone that blocks or otherwise interferes with a particular biologic activity.

The term “modulator” refers to a molecule, such as a compound of the present invention, that increases or decreases, or otherwise affects the activity of a given enzyme or protein.

The terms “effective amount” or “therapeutically effective amount” refer to a sufficient amount of the agent to provide the desired biological result. That result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease or medical condition, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic use is the amount of a compound, or of a composition comprising the compound, that is required to provide a clinically relevant change in a disease state, symptom, or medical condition. An appropriate

“effective” amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation. Thus, the expression “effective amount” generally refers to the quantity for which the active substance has a therapeutically desired effect.

5 As used herein, the terms “treat” or “treatment” encompass both “preventative” and “curative” treatment. “Preventative” treatment is meant to indicate a postponement of development of a disease, a symptom of a disease, or medical condition, suppressing symptoms that may appear, or reducing the risk of developing or recurrence of a disease or symptom. “Curative” treatment includes
10 reducing the severity of or suppressing the worsening of an existing disease, symptom, or condition. Thus, treatment includes ameliorating or preventing the worsening of existing disease symptoms, preventing additional symptoms from occurring, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disorder or disease, e.g., arresting the development of the disorder or disease,
15 relieving the disorder or disease, causing regression of the disorder or disease, relieving a condition caused by the disease or disorder, or stopping the symptoms of the disease or disorder.

Additional Chemical Descriptions

20 Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. For example, compounds of any formula given herein may have asymmetric or chiral centers and therefore exist in different stereoisomeric forms. All stereoisomers, including optical isomers, enantiomers, and diastereomers, of the compounds of the
25 general formula, and mixtures thereof, are considered to fall within the scope of the formula. Furthermore, certain structures may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers, or as atropisomers. All such isomeric forms, and mixtures thereof, are contemplated herein as part of the present invention. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric
30 forms, one or more diastereomeric forms, one or more tautomeric or atropisomeric forms, and mixtures thereof.

Diastereomeric mixtures may be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers may be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride, or formation of a mixture of diastereomeric salts), separating the diastereomers and converting (e.g., hydrolyzing or de-salting) the individual diastereomers to the corresponding pure enantiomers. Enantiomers may also be separated by use of chiral HPLC column. The chiral centers of compounds of the present invention may be designated as "R" or "S" as defined by the IUPAC 1974 Recommendations.

The compounds of the invention can form pharmaceutically acceptable salts, which are also within the scope of this invention. A "pharmaceutically acceptable salt" refers to a salt of a free acid or base of a compound of Formula I that is non-toxic, is physiologically tolerable, is compatible with the pharmaceutical composition in which it is formulated, and is otherwise suitable for formulation and/or administration to a subject. Reference to a compound herein is understood to include reference to a pharmaceutically acceptable salt of said compound unless otherwise indicated.

Compound salts include acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, where a given compound contains both a basic moiety, such as, but not limited to, a pyridine or imidazole, and an acidic moiety, such as, but not limited to, a carboxylic acid, one of skill in the art will recognize that the compound may exist as a zwitterion ("inner salt"); such salts are included within the term "salt" as used herein. Salts of the compounds of the invention may be prepared, for example, by reacting a compound with an amount of a suitable acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate,

lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate ("mesylate"), ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counterion. The counterion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counterions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, *t*-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Additionally, acids and bases which are generally considered suitable for the formation of pharmaceutically useful salts from pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S.

Berge et al, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson et al, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, MD, available from FDA). These disclosures are
5 incorporated herein by reference thereto.

Additionally, any compound described herein is intended to refer also to any unsolvated form, or a hydrate, solvate, or polymorph of such a compound, and mixtures thereof, even if such forms are not listed explicitly. "Solvate" means a physical association of a compound of the invention with one or more solvent
10 molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Suitable solvates include those formed with pharmaceutically
15 acceptable solvents such as water, ethanol, and the like. In some embodiments, the solvent is water and the solvates are hydrates.

One or more compounds of the invention may optionally be converted to a solvate. Methods for the preparation of solvates are generally known. Thus, for example, M. Caira et al., *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004), describes the
20 preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates, and the like are described by E. C. van Tonder et al, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham et al, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting process involves dissolving the compound of the invention in a suitable amounts of
25 the solvent (organic solvent or water or a mixture thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example, infrared spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

30 The invention also relates to pharmaceutically acceptable prodrugs of the compounds of Formula I, and treatment methods employing such pharmaceutically

acceptable prodrugs. The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula I). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise suitable for formulation and/or administration to the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Examples of prodrugs include pharmaceutically acceptable esters of the compounds of the invention, which are also considered to be part of the invention. Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di(C₆₋₂₄)acyl glycerol. Additional discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press.

For example, if a compound of Formula I contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms,

- alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholine (C₂-C₃)alkyl, and the like.
- 10 Similarly, if a compound of Formula I contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.
- 20 If a compound of Formula I incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R^{''}-carbonyl, R^{''}O-carbonyl, NR^{''}R'-carbonyl where R^{''} and R' are each independently (C₁-C₁₀)alkyl, (C₃-C₇) cycloalkyl, benzyl, or R^{''}-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, -C(OH)C(O)OY¹ wherein
- 25 Y¹ is H, (C₁-C₆)alkyl or benzyl, -C(OY²)Y³ wherein Y² is (C₁-C₄) alkyl and Y³ is (C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl, -C(Y⁴)Y⁵ wherein Y⁴ is H or methyl and Y⁵ is mono-N- or di-N,N-(C₁-C₆)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

The present invention also relates to pharmaceutically active metabolites of compounds of Formula I, and uses of such metabolites in the methods of the invention. A "pharmaceutically active metabolite" means a pharmacologically active

product of metabolism in the body of a compound of Formula I or salt thereof.

Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labelled compounds are useful in metabolic studies (for example with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or ^{11}C labeled compound may be particularly suitable for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The use of the terms "salt," "solvate," "polymorph," "prodrug," and the like, with respect to the compounds described herein is intended to apply equally to the salt,

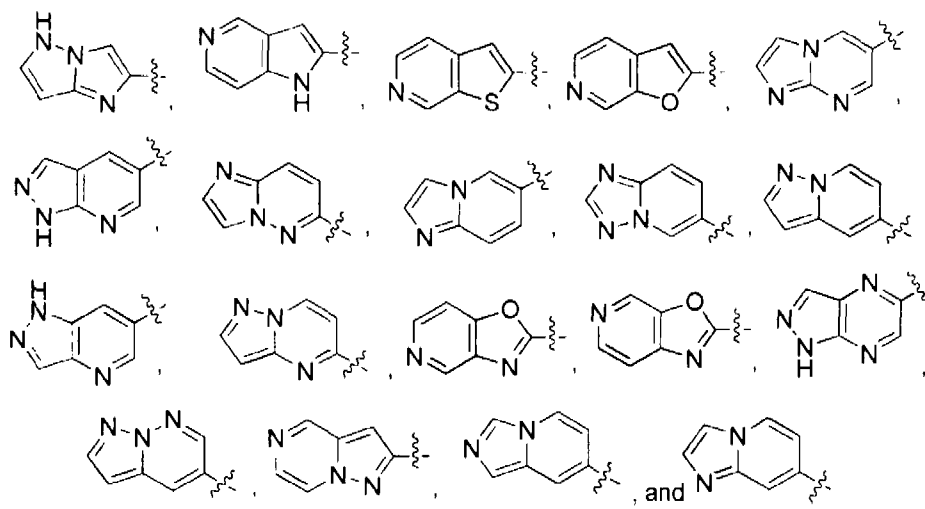
solvate, polymorph, and prodrug forms of enantiomers, stereoisomers, rotamers, tautomers, atropisomers, and racemates of the compounds of the invention.

Compounds of the Invention

- 5 In some embodiments of Formula I, E is O. In other embodiments, E is absent.

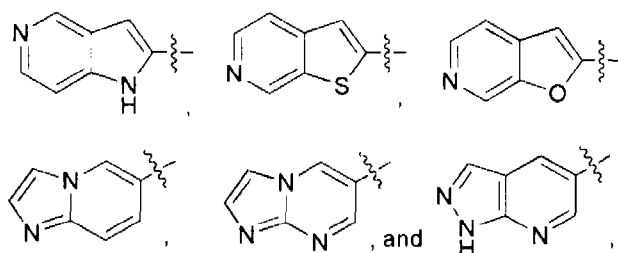
In some embodiments, R is an unsubstituted or substituted bicyclic heteroaryl as defined for Formula I. In some embodiments, the bicyclic heteroaryl has 1, 2, or 3 nitrogen ring atoms. In other embodiments, the bicyclic heteroaryl is a 9- or 10-membered bicyclic heteroaryl, unsubstituted or substituted as described for Formula I.

- 10 In other embodiments, the bicyclic heteroaryl is a 8- or 9-membered heteroaryl, unsubstituted or substituted as described for Formula I. In other embodiments, R is a bicyclic heteroaryl selected from the group consisting of:

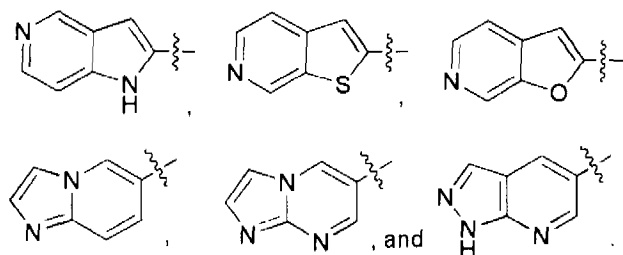


each unsubstituted or substituted as described for Formula I. In further embodiments,

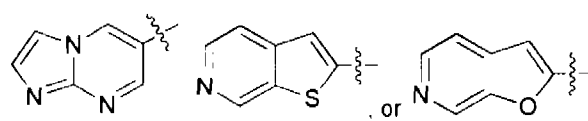
- 15 R is selected from the group consisting of:



each unsubstituted or substituted as described for Formula I. In further embodiments, R is selected from the group consisting of:

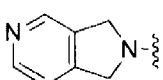
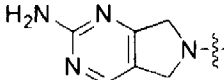


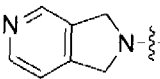
In further embodiments, R is



In other embodiments, R is a five- or six-membered nitrogen-linked

- 5 heterocycloalkyl ring fused to an unsubstituted or substituted phenyl or monocyclic heteroaryl, for examples a 6 membered heteroaryl, as defined in Formula I. In further

embodiments, R is  or . In still other embodiments,

R is .

- In other embodiments, R is substituted with one or more substituents selected
- 10 from the group consisting of amino and halo. In some embodiments, R¹ is a saturated, monocyclic, nitrogen-linked heterocycloalkyl, unsubstituted or substituted as described for Formula I. In some embodiments, the saturated, monocyclic, nitrogen-linked heterocycloalkyl is azetidiny, pyrrolidiny, piperidiny, morpholinyl, piperazinyl, azepanyl, or diazepanyl, unsubstituted or substituted as described for
- 15 Formula I. In certain embodiments, the saturated, monocyclic, nitrogen-linked heterocycloalkyl is unsubstituted. In other embodiments, the saturated, monocyclic, nitrogen-linked heterocycloalkyl is substituted with one or more R^x groups as defined above. In other embodiments, the one or more R^x groups are independently selected from the group consisting of: hydroxy, methoxy, cyano, cyanomethyl, amino,
- 20 difluoroethylamino, methoxyethylamino, cyanoethylamino, hydroxymethyl, pyrrolidiny, methyl, ethyl, isopropyl, isobutyl, trifluoroethyl, trifluoromethyl, cyclohexyl, tetrahydropyranyl, pyrrolidiny, oxetanyl, fluoro, -C(O)(4-methyl-piperazin-1-yl), 4-methylpiperazinyl, -NH(Boc), acetyl, hydroxyethyl,

dimethylaminoethyl, cyanoethyl, methoxyethyl, -N(Me)(acetyl), dimethylamino, -C(O)(dimethylamino), and oxo, and where two adjacent substituents taken together form a phenyl ring. In other embodiments, the saturated, monocyclic, nitrogen-linked heterocycloalkyl is substituted with 1, 2, or 3 R^x groups independently selected from the group consisting of: methyl, ethyl, isopropyl, hydroxy, methoxy, amino, cyano, fluoro, and trifluoromethyl.

In other embodiments, R¹ is a saturated, monocyclic, carbon-linked heterocycloalkyl, unsubstituted or substituted as described for Formula I. In other embodiments, the saturated, monocyclic, carbon-linked heterocycloalkyl is tetrahydropyranyl, piperidinyl, pyrrolidinyl, or tetrahydrofuranyl, unsubstituted or substituted as described for Formula I. In still other embodiments, the saturated, monocyclic, carbon-linked heterocycloalkyl is pyrrolidin-3-yl, tetrahydropyran-4-yl, tetrahydropyran-3-yl, piperidin-3-yl, piperidin-4-yl, or tetrahydrofuran-3-yl, unsubstituted or substituted as described for Formula I. In certain embodiments, the saturated, monocyclic, carbon-linked heterocycloalkyl is unsubstituted. In some embodiments, the substituents R^x on the saturated, monocyclic, carbon-linked heterocycloalkyl are as defined above. In other embodiments, the saturated, monocyclic, carbon-linked heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, trifluoroethyl, acetyl, propionyl, butyryl, isobutyryl, benzoyl, methylsulfonyl, phenylsulfonyl, tert-butoxycarbonyl, tetrahydropyranyl, and oxetanyl.

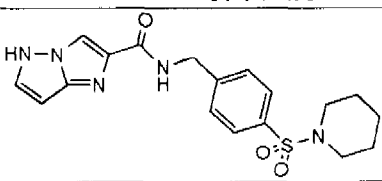
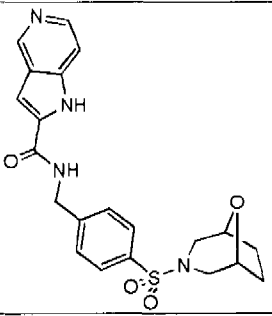
In some embodiments, R¹ is a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and is unsubstituted or substituted as described for Formula I. In some embodiments, the heterocycloalkyl is a bridged, bicyclic, nitrogen-linked heterocycloalkyl, unsubstituted or substituted as described for Formula I. In certain embodiments, the saturated, bicyclic, nitrogen-linked heterocycloalkyl is an azetidine, pyrrolidine, piperidine, morpholine, azepane, 1,4-diazepane, or azocane ring, substituted with two substituents on the same or different carbons that together form a C₁₋₆alkenyl group, wherein one carbon atom of the alkenyl group is optionally

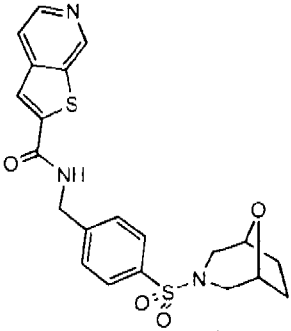
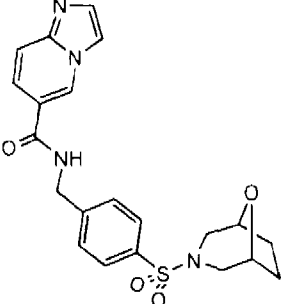
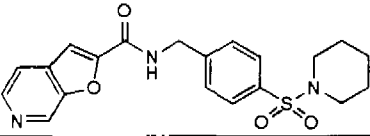
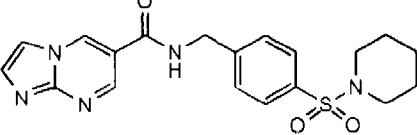
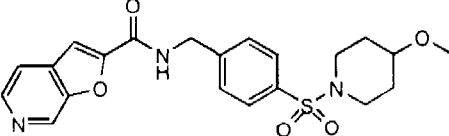
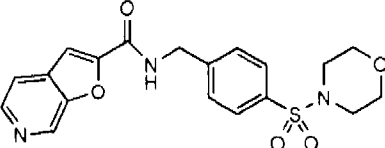
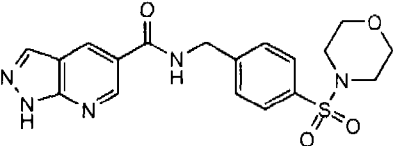
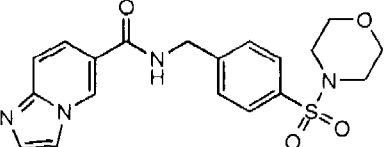
replaced with one or two O, S, or NH groups, and the resulting bicyclic heterocycloalkyl is optionally further substituted as described for Formula I. In some embodiments, the saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl is unsubstituted. In other embodiments, the saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of: methyl, ethyl, isopropyl, acetyl, fluoro, oxo, hydroxy, tert-butoxycarbonyl, amino, aminomethyl, tert-butoxycarbonylamino, and tert-butoxycarbonyl-aminomethyl. In other embodiments, the saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of: methyl, fluoro, hydroxy, tert-butoxycarbonyl, methoxycarbonyl, and amino.

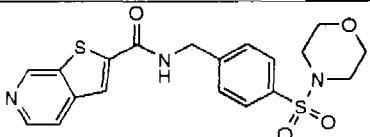
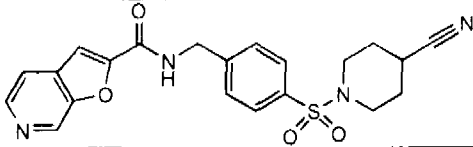
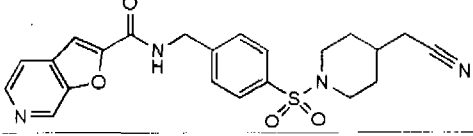
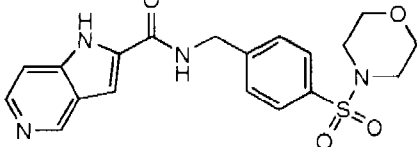
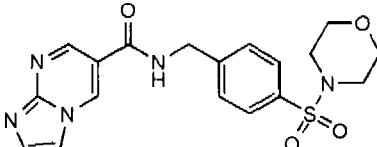
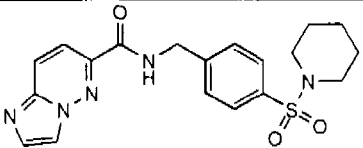
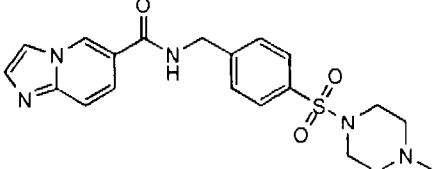
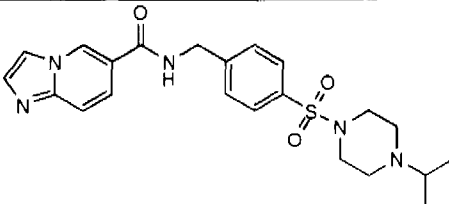
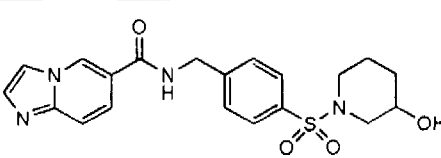
In some embodiments, one of R^2 and R^3 is deuterium and the other is H. In other embodiments, both R^2 and R^3 are H.

In some embodiments, each alkyl or alkylene described above is independently a C_{1-10} alkyl. In other embodiments, each alkyl or alkylene in Formula I is independently a C_{1-6} alkyl. In still other embodiments, each alkyl or alkylene in Formula I is independently a C_{1-4} alkyl.

In certain embodiments, the compound of Formula I is chosen from the following table:

Ex.	Structure	Chemical Name
1		5H-Imidazo[1,2-b]pyrazole-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
2		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide

3		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide
4		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide
5		Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
6		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
7		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-methoxy-piperidine-1-sulfonyl)-benzylamide
8		Furo[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide
9		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide
10		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide

11		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide
12		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide
13		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyanomethyl-piperidine-1-sulfonyl)-benzylamide
14		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide
15		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide
16		Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
17		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-methyl-piperazine-1-sulfonyl)-benzylamide
18		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-isopropyl-piperazine-1-sulfonyl)-benzylamide
19		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic)

20		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide
21		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide
22		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide
23		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide
24		Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide
25		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide
26		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide
27		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(8-oxa-3-aza-bicyclo[3.2.1]octane-3-sulfonyl)-benzylamide
28		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide

29		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide
30		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide
31		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide
32		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic)
33		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic)
34		Furo[2,3-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic)
35		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic)
36		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-piperidine-1-sulfonyl)-benzylamide
37		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2,2-difluoroethylamino)-piperidine-1-sulfonyl]-benzylamide

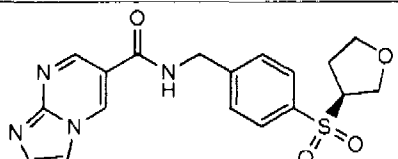
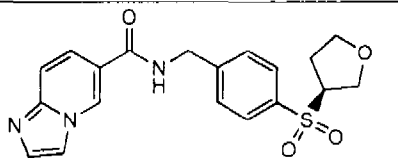
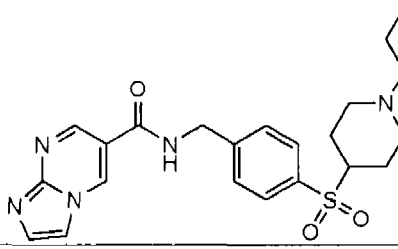
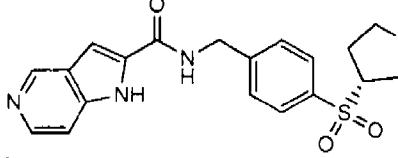
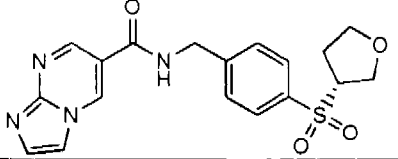
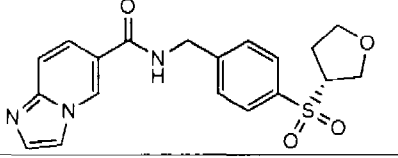
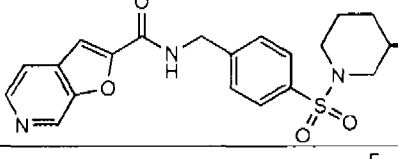
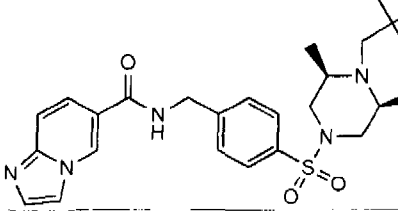
38		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide
39		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-methoxyethylamino)-piperidine-1-sulfonyl]-benzylamide
40		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-cyclohexyl-piperazine-1-sulfonyl)-benzylamide
41		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide
42		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide
43		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-isobutyl-piperazine-1-sulfonyl)-benzylamide
44		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(((1R,3R,5S)-3-amino-8-aza-bicyclo[3.2.1]octane-8-sulfonyl)-benzylamide
45		[1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
46		Thieno[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide

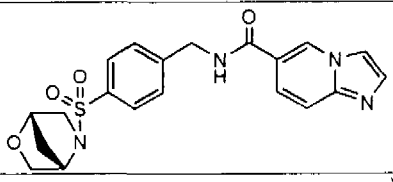
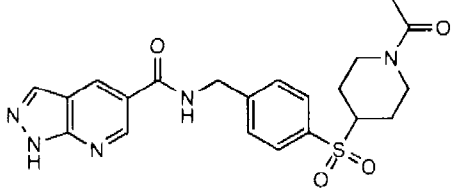
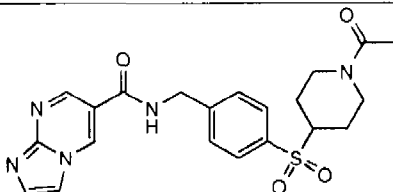
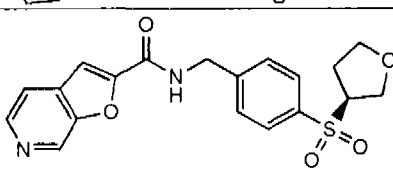
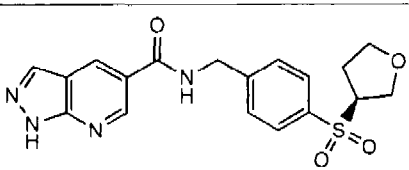
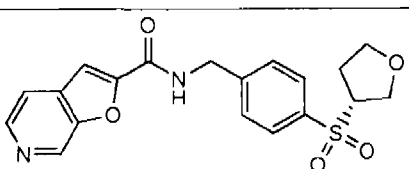
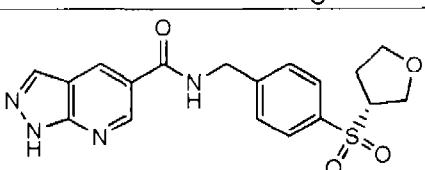
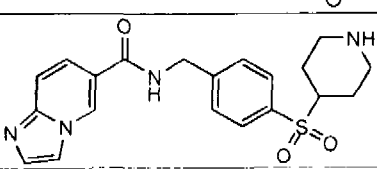
47		Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide
48		Pyrazolo[1,5-a]pyridine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
49		1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
50		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
51		Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
52		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
53		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
54		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide

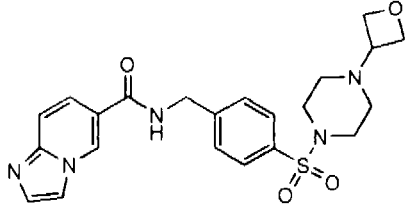
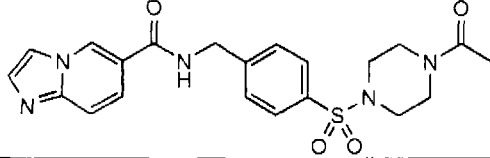
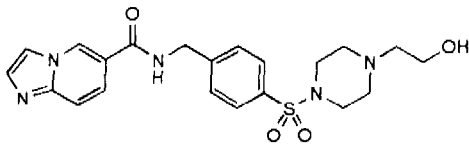
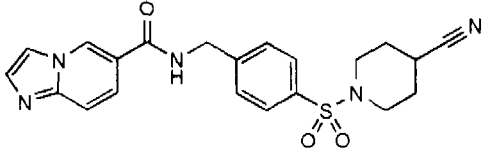
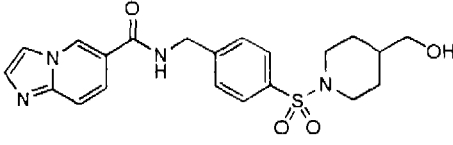
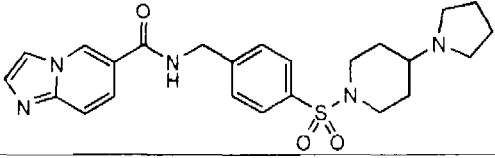
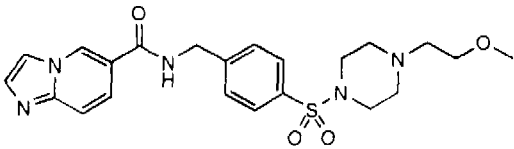
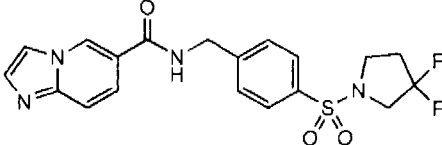
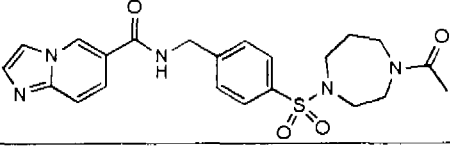
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56		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide
57		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-cyanoethylamino)-piperidine-1-sulfonyl]-benzylamide
58		Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
59		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(tetrahydro-pyran-4-yl)-piperazine-1-sulfonyl]-benzylamide
60		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide
61		cis-Furo[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide

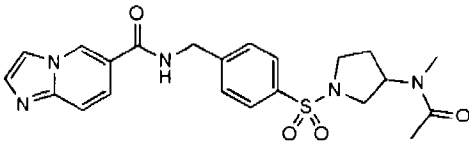
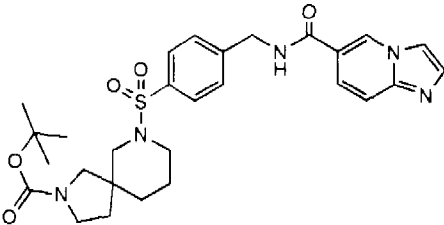
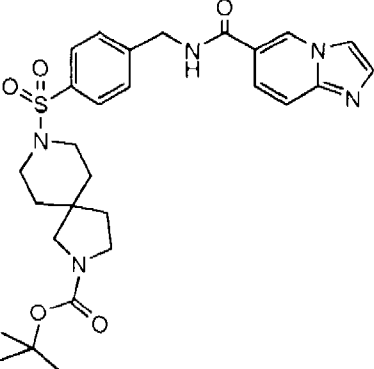
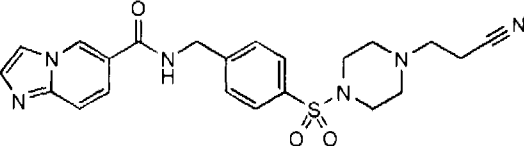
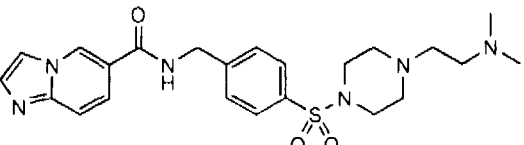
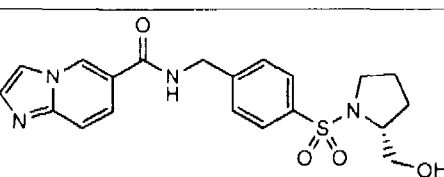
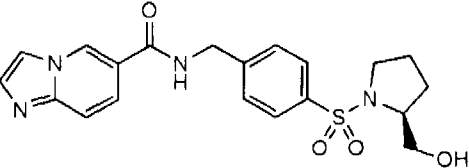
62		Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide
63		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[1-(2,2,2-trifluoroethyl)-piperidine-4-sulfonyl]-benzylamide
64		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(2,2,2-trifluoroethyl)-piperidine-4-sulfonyl]-benzylamide
65		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[1-(2,2,2-trifluoroethyl)-piperidine-4-sulfonyl]-benzylamide
66		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[1-(2,2,2-trifluoroethyl)-piperidine-4-sulfonyl]-benzylamide
67		Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(2,2,2-trifluoroethyl)-piperidine-4-sulfonyl]-benzylamide
68		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[1-(tetrahydropyran-4-yl)-piperidine-4-sulfonyl]-benzylamide

69		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide
70		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3aR,6aS)-5,5-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide
71		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3aR,6aS)-(tetrahydro-furo[3,4-c]pyrrol-5-yl)sulfonyl]-benzylamide
72		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[2,3-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers)
73		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (isomer A)
74		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (isomer B)
75		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide

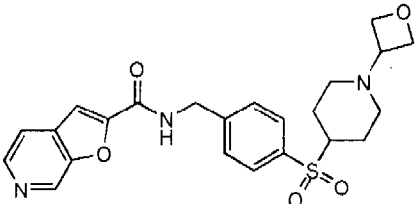
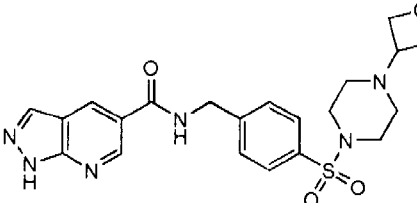
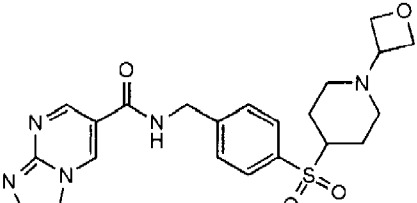
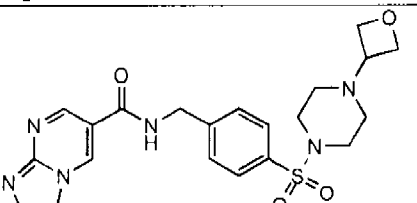
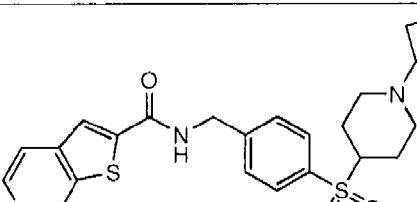
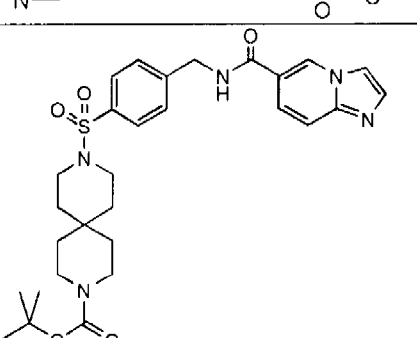
76		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
77		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
78		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide
79		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
80		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
81		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
82		Furo[2,3-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
83		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide

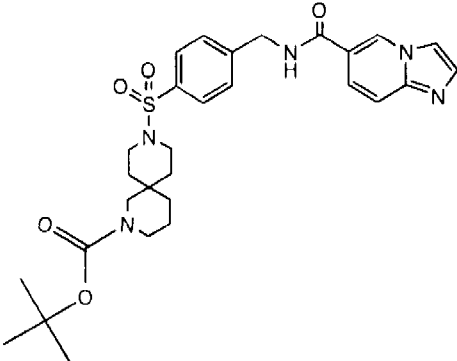
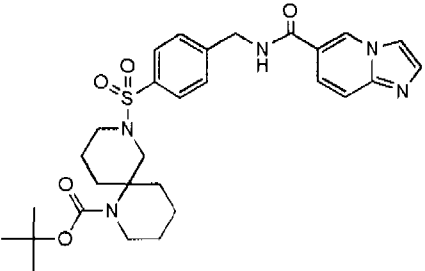
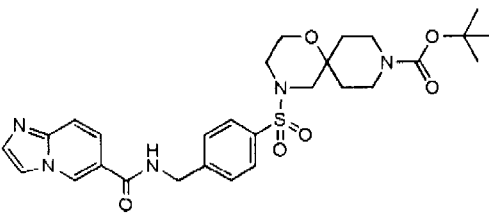
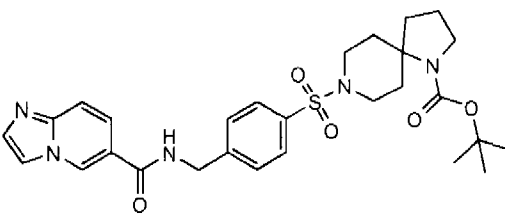
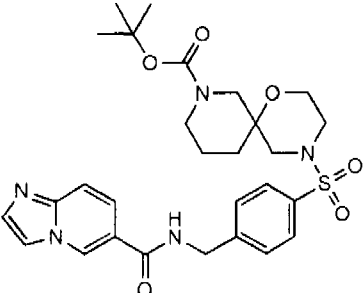
84		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(1S,4S)-(2-oxa-5-azabicyclo[2.2.1]hept-5-yl)sulfonyl]-benzylamide
85		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide
86		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide
87		Furo[2,3-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
88		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
89		Furo[2,3-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
90		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide
91		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide

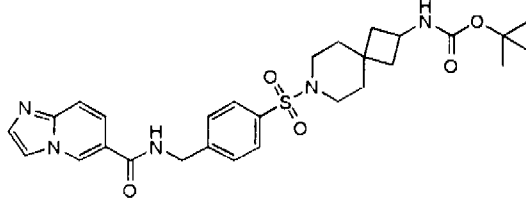
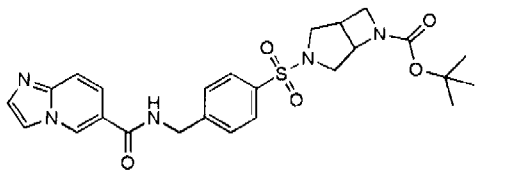
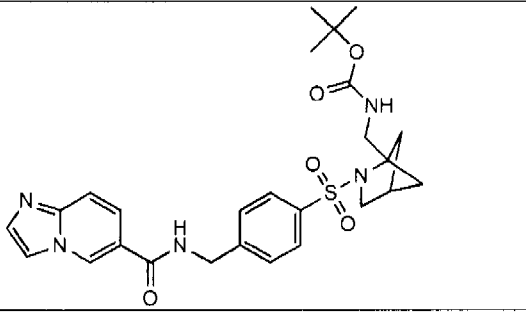
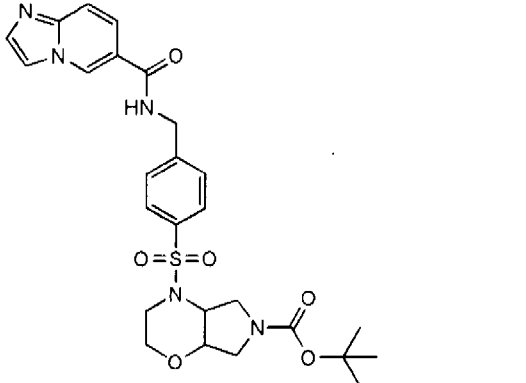
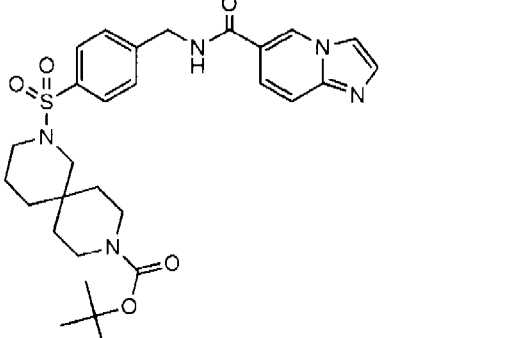
92		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide
93		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-acetyl-piperazine-1-sulfonyl)-benzylamide
94		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-hydroxy-ethyl)-piperazine-1-sulfonyl]-benzylamide
95		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide
96		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide
97		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide
98		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-methoxy-ethyl)-piperazine-1-sulfonyl]-benzylamide
99		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3,3-difluoro-pyrrolidine-1-sulfonyl)-benzylamide
100		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-acetyl-[1,4]diazepane-1-sulfonyl)-benzylamide

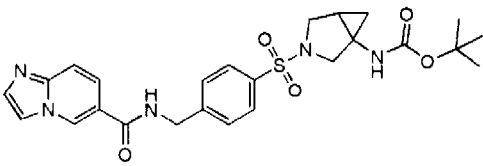
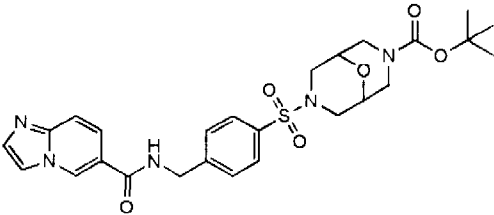
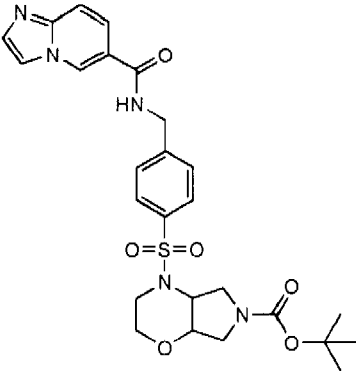
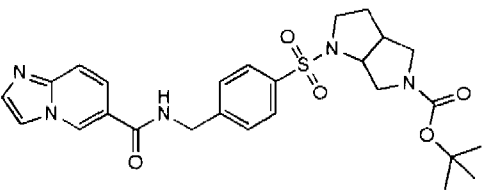
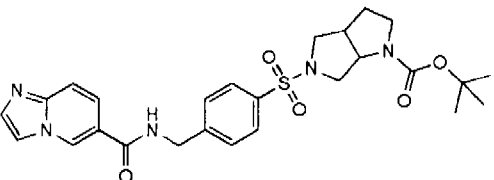
101		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[3-(acetyl-methyl-amino)-pyrrolidine-1-sulfonyl]-benzylamide (racemic)
102		7-(4-{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,7-diaza-spiro[4.5]decane-2-carboxylic acid tert-butyl ester (racemic)
103		8-(4-{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,8-diaza-spiro[4.5]decane-2-carboxylic acid tert-butyl ester
104		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-cyano-ethyl)-piperazine-1-sulfonyl]-benzylamide
105		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-dimethylamino-ethyl)-piperazine-1-sulfonyl]-benzylamide
106		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide
107		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide

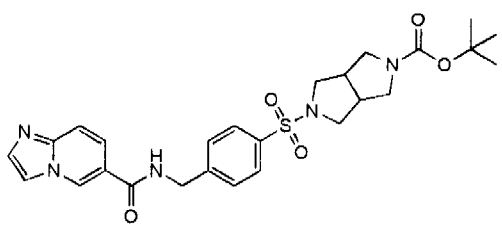
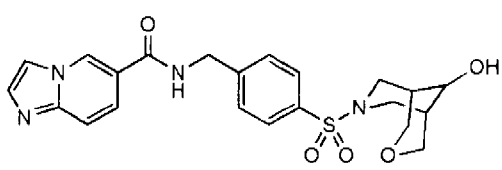
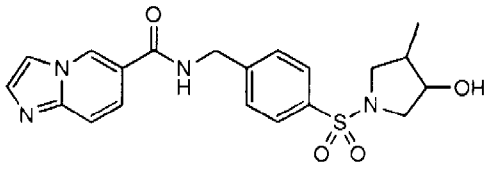
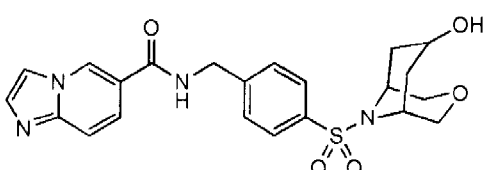
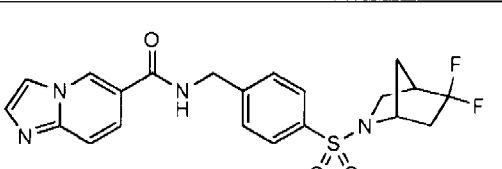
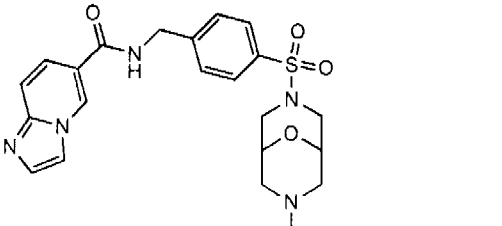
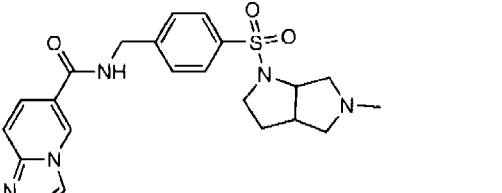
108		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-dimethylamino-pyrrolidine-1-sulfonyl)-benzylamide
109		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-benzylamide
110		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methyl-piperazin-1-yl)-piperidine-1-sulfonyl]-benzylamide
111		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-trifluoromethyl-pyrrolidine-1-sulfonyl)-benzylamide (racemic)
112		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-piperidine-1-sulfonyl)-benzylamide
113		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide
114		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide
115		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide

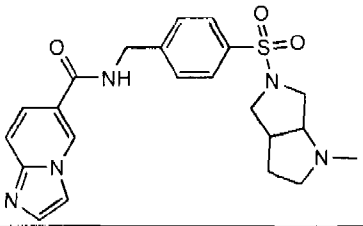
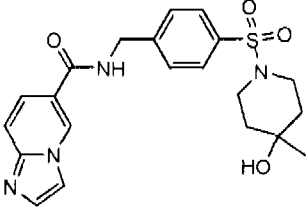
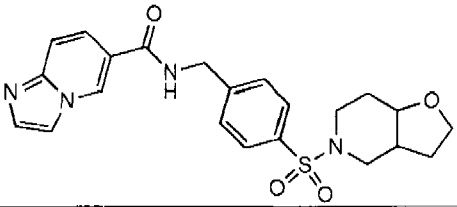
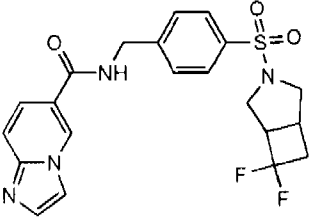
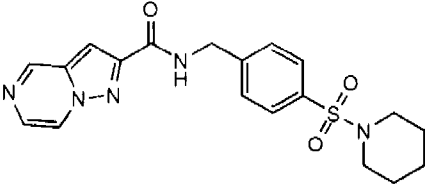
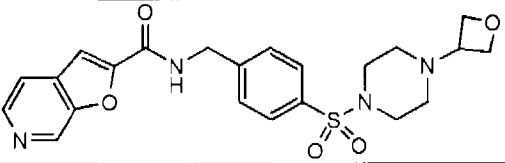
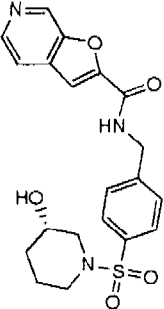
116		Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide
117		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide
118		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide
119		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide
120		Thieno[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide
121		9-(4-((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester

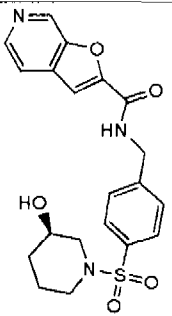
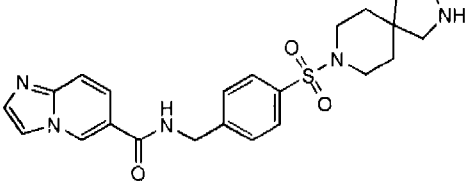
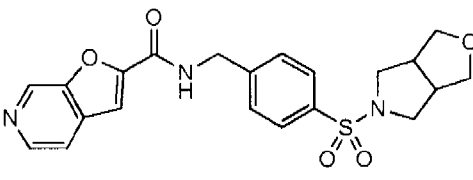
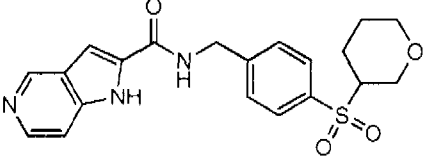
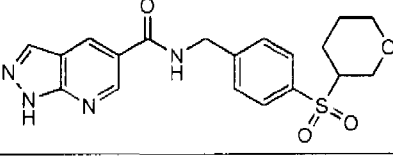
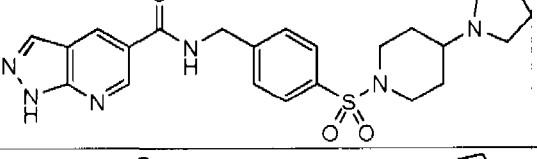
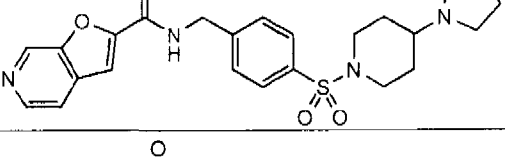
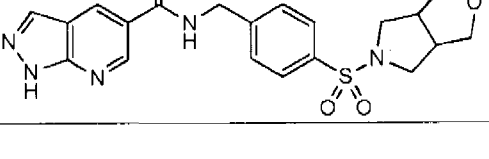
122		9-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-2,9-diaza-spiro[5.5]undecane-2-carboxylic acid tert-butyl ester
123		8-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1,8-diaza-spiro[5.5]undecane-1-carboxylic acid tert-butyl ester (racemic)
124		4-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1-oxa-4,9-diaza-spiro[5.5]undecane-9-carboxylic acid tert-butyl ester
125		8-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1,8-diaza-spiro[4.5]decane-1-carboxylic acid tert-butyl ester
126		4-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1-oxa-4,8-diaza-spiro[5.5]undecane-8-carboxylic acid tert-butyl ester (racemic)

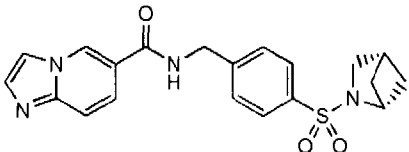
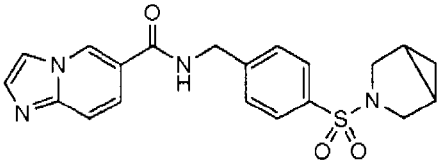
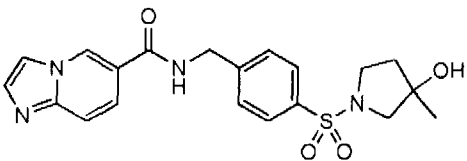
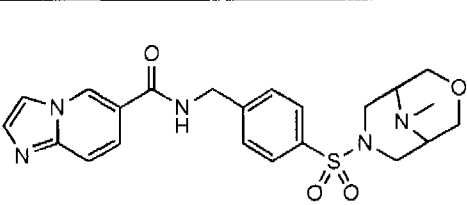
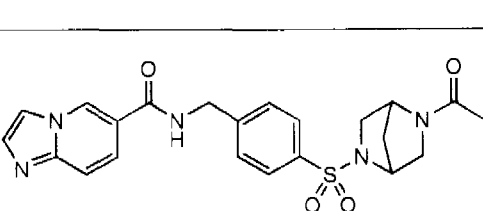
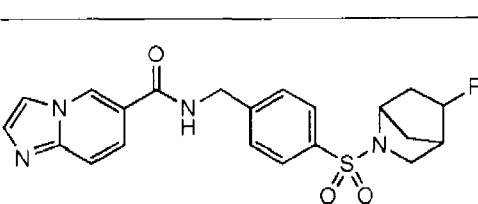
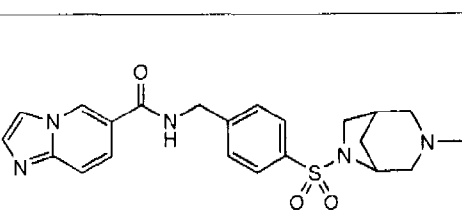
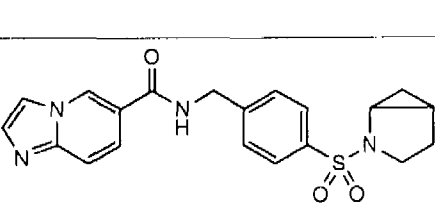
127		[7-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-7-azaspiro[3.5]non-2-yl)-carbamic acid tert-butyl ester
128		cis-3-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-3,6-diazabicyclo[3.2.0]heptane-6-carboxylic acid tert-butyl ester (racemic)
129		[2-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2-azabicyclo[2.1.1]hex-1-ylmethyl]-carbamic acid tert-butyl ester
130		cis-4-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic)
131		2-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,9-diaza-spiro[5.5]undecane-9-carboxylic acid tert-butyl ester

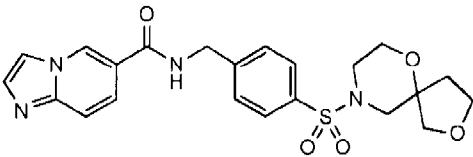
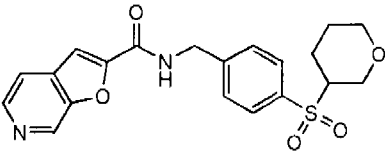
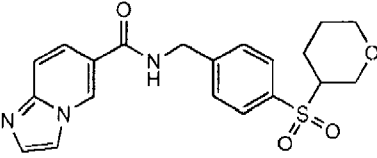
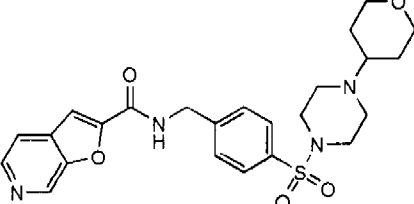
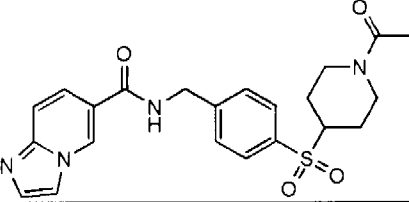
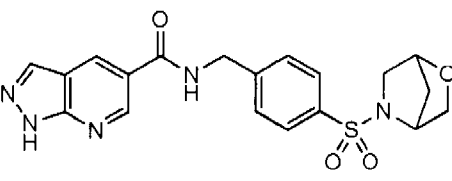
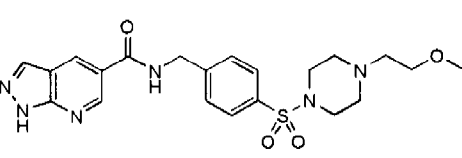
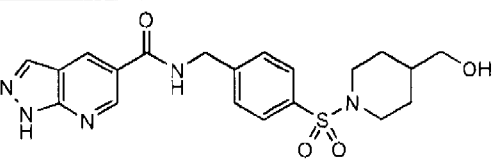
132		cis-[3-(4-{{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}}-benzenesulfonyl)-3-aza-bicyclo[3.1.0]hex-1-yl]-carbamic acid tert-butyl ester (racemic)
133		cis-7-(4-{{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}}-benzenesulfonyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (racemic)
134		cis-4-(4-{{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic)
135		cis-1-(4-{{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-5-carboxylic acid tert-butyl ester (racemic)
136		cis-5-(4-{{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}}-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-1-carboxylic acid tert-butyl ester (racemic)

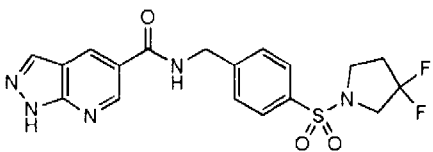
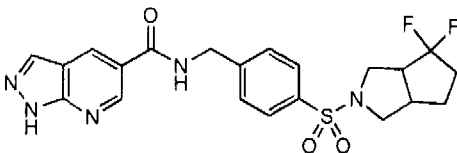
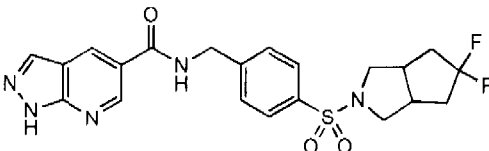
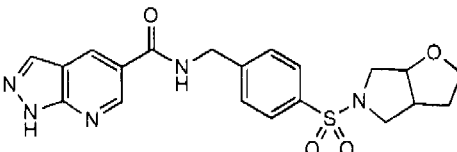
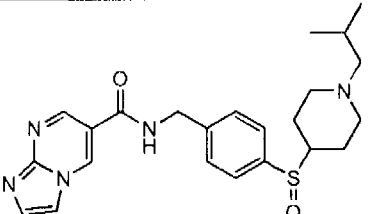
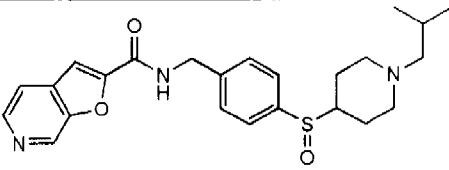
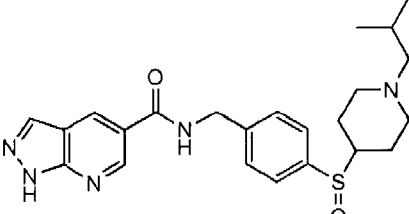
137		cis-5-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester (racemic)
138		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-hydroxy-3-oxa-7-aza-bicyclo[3.3.1]nonane-7-sulfonyl)-benzylamide (mixture of diastereomers)
139		trans-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-4-methyl-pyrrolidine-1-sulfonyl)-benzylamide (racemic)
140		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-sulfonyl)-benzylamide (racemic)
141		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5,5-difluoro-2-aza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic)
142		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-methyl-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-sulfonyl)-benzylamide (racemic)
143		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-1-sulfonyl)-benzylamide (racemic)

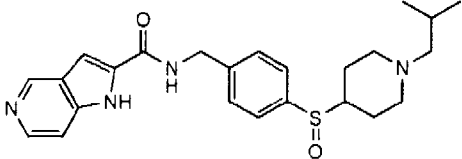
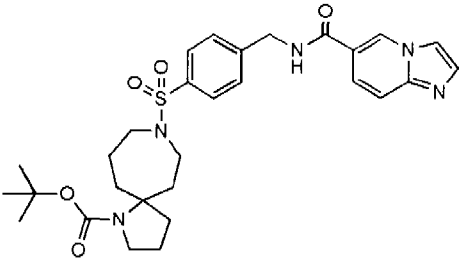
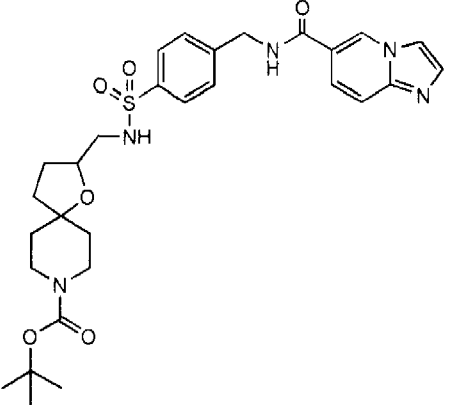
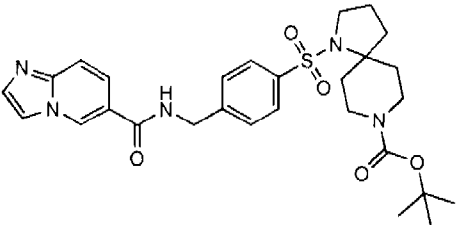
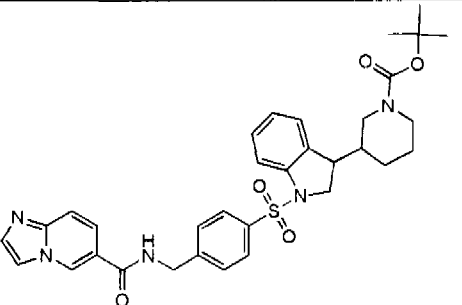
144		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-benzylamide (racemic)
145		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-4-methyl-piperidine-1-sulfonyl)-benzylamide
146		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[3,2-c]pyridine-5-sulfonyl)-benzylamide (mixture of diastereomers)
147		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(6,6-difluoro-3-azabicyclo[3.2.0]heptane-3-sulfonyl)-benzylamide (racemic)
148		Pyrazolo[1,5-a]pyrazine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide
149		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide
150		Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide

151		Furo[2,3-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide
152		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,8-diaza-spiro[4.5]decane-8-sulfonyl)-benzylamide
153		Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-furo[3,4-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers)
154		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic)
155		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic)
156		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide
157		Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide
158		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydro-furo[3,4-c]pyrrole-5-sulfonyl)-benzylamide

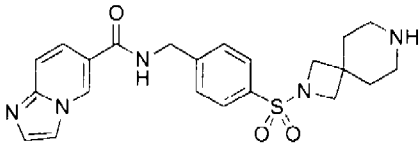
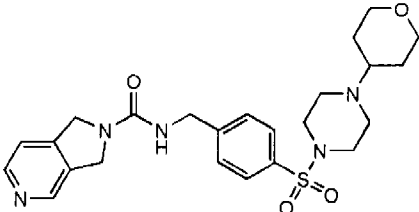
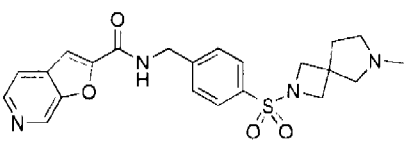
		(mixture of diastereomers)
159		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-azabicyclo[2.1.1]hexane-2-sulfonyl)-benzylamide
160		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-azabicyclo[3.1.0]hexane-3-sulfonyl)-benzylamide
161		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-3-methylpyrrolidine-1-sulfonyl)-benzylamide (racemic)
162		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-methyl-3-oxa-7,9-diazabicyclo[3.3.1]nonane-7-sulfonyl)-benzylamide (racemic)
163		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-acetyl-2,5-diazabicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic)
164		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-fluoro-2-azabicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic)
165		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-methyl-3,6-diazabicyclo[3.2.1]octane-6-sulfonyl)-benzylamide (racemic)
166		cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-azabicyclo[3.1.0]hexane-2-sulfonyl)-benzylamide

		(racemic)
167		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,6-dioxo-9-aza-spiro[4.5]decane-9-sulfonyl)-benzylamide (racemic)
168		Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic)
169		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic)
170		Furo[2,3-c]pyridine-2-carboxylic acid 4-[4-(tetrahydro-pyran-4-yl)-piperazine-1-sulfonyl]-benzylamide
171		Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide
172		cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(2-oxa-5-aza-bicyclo[2.2.1]heptane-5-sulfonyl)-benzylamide (racemic)
173		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-methoxy-ethyl)-piperazine-1-sulfonyl]-benzylamide
174		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide

175		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3,3-difluoropyrrolidine-1-sulfonyl)-benzylamide
176		cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4,4-difluorohexahydrocyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic)
177		cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(5,5-difluorohexahydrocyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic)
178		cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(hexahydrofuro[2,3-c]pyrrole-5-sulfonyl)-benzylamide (racemic)
179		Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic)
180		Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic)
181		1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic)

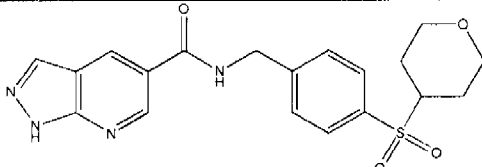
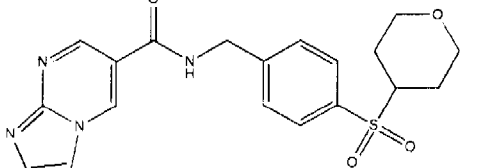
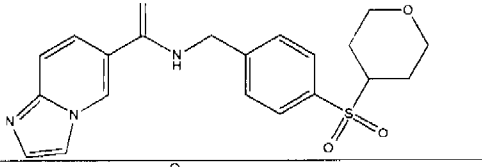
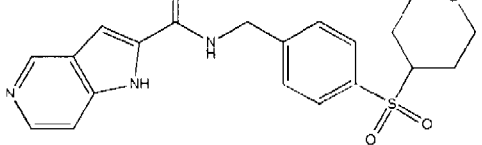
182		1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide (racemic)
183		8-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1,8-diaza-spiro[4.6]undecane-1-carboxylic acid tert-butyl ester (racemic)
184		3-[(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonylamino)-methyl]-1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester (racemic)
185		1-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-1,8-diaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester
186		3-[1-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl} - benzenesulfonyl)-2,3-dihydro-1H-indol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (mixture of diastereomers)

187		N-(4-(1-isobutylpiperidin-4-ylsulfinyl)benzyl)H-imidazo[1,2-a]pyridine-6-carboxamide (racemic)
188		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
189		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
190		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
191		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
192		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer)
193		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer)
194		N-[[4-(8-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

195		N-[[4-(2,8-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
196		N-[[4-(4-tetrahydropyran-4-yl)piperazin-1-yl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide or N-[[4-[(6-methyl-2,6-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
197		N-[[4-[(6-methyl-2,6-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide

or a stereoisomer thereof, or a pharmaceutically acceptable salt of such a compound or stereoisomer.

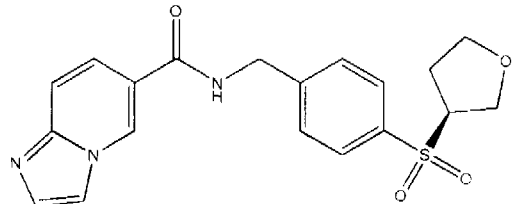
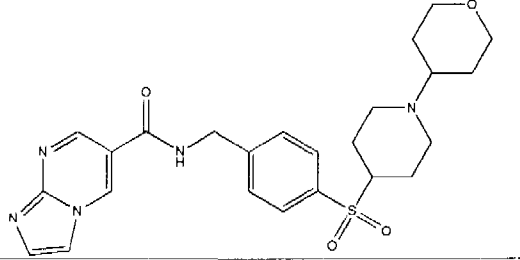
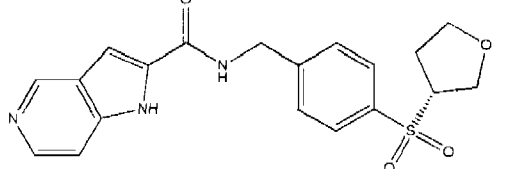
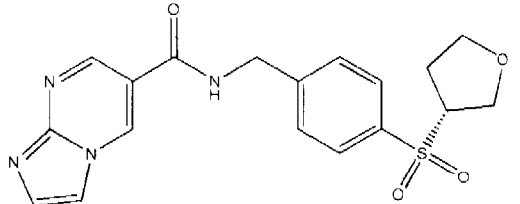
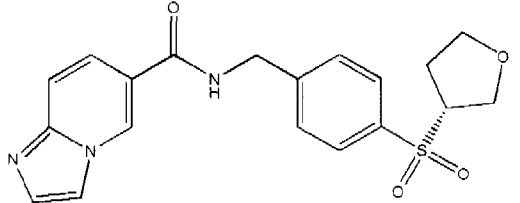
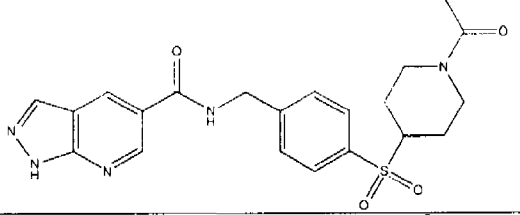
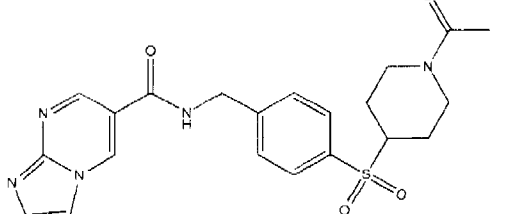
In certain embodiments, the compound of Formula I is chosen from the following table:

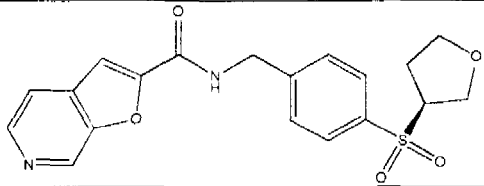
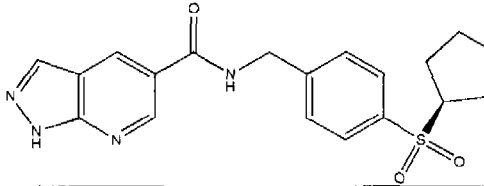
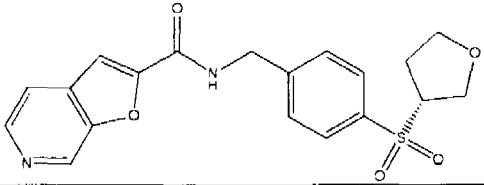
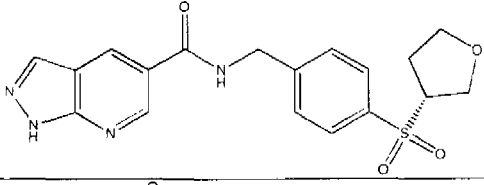
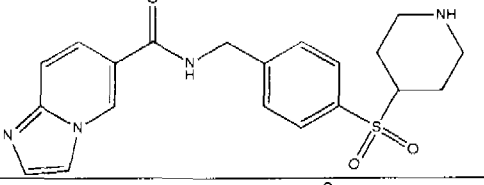
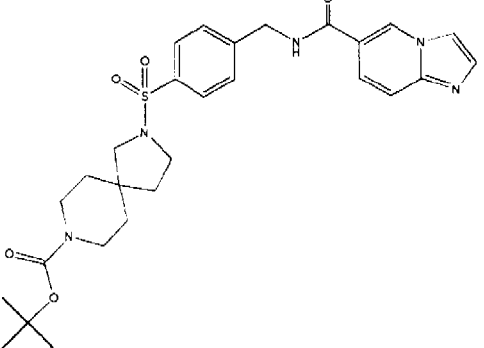
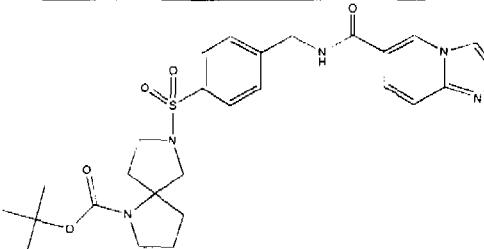
Ex.	Structure	Chemical Name
198		N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
199		N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
200		N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
201		N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

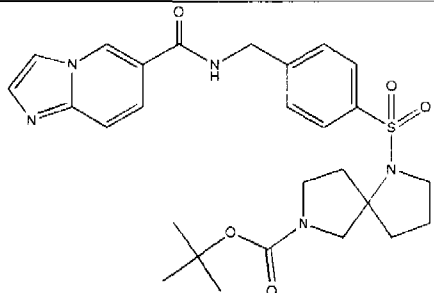
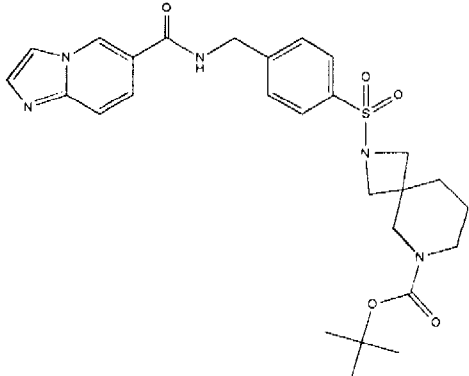
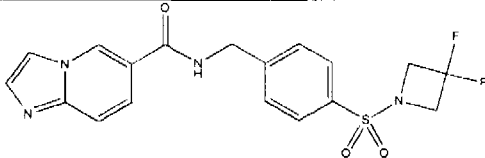
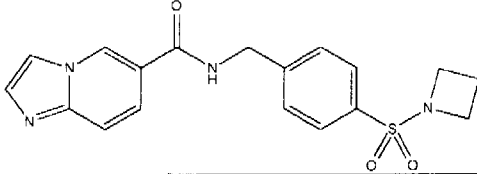
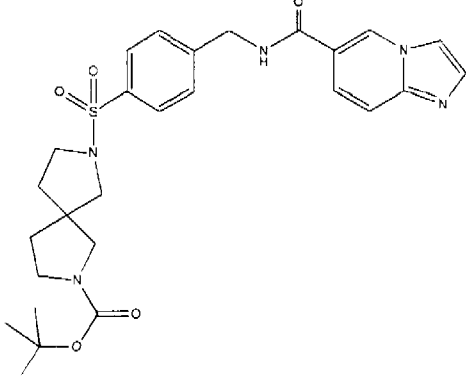
202		N-[(4-(4-(4-(2-furo[2,3-c]pyridin-2-yl)sulfonyl)phenyl)methyl)furo[2,3-c]pyridine-2-carboxamide
203		N-[[4-(4-(4-(1H-pyrazolo[3,4-b]pyridine-5-carboxamide)sulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
204		N-[[4-(4-(4-(thieno[2,3-c]pyridine-2-carboxamide)sulfonyl)phenyl)methyl]thieno[2,3-c]pyridine-2-carboxamide
205		N-[[4-[(1-(4-(4-(4-(2-furo[2,3-c]pyridin-2-yl)sulfonyl)phenyl)methyl)-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
206		N-[[4-[(1-(4-(4-(4-(1H-pyrazolo[3,4-b]pyridine-5-carboxamide)sulfonyl)phenyl)methyl)-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
207		N-[[4-[(1-(4-(4-(4-(2-furo[2,3-c]pyridin-2-yl)sulfonyl)phenyl)methyl)-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
208		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

209		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
210		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
211		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
212		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
213		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
214		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

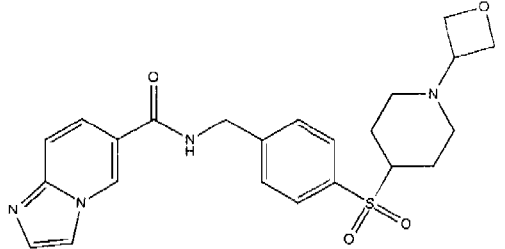
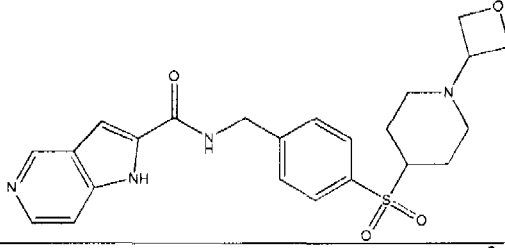
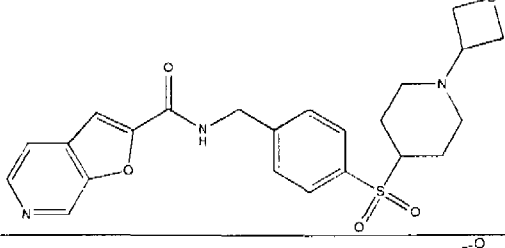
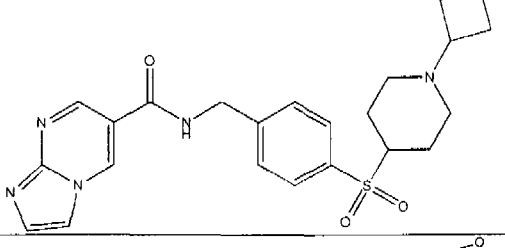
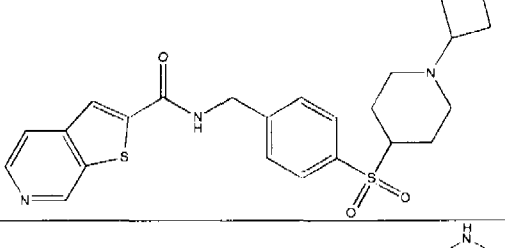
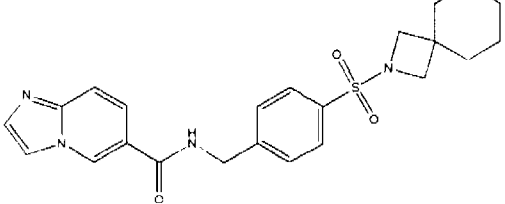
215		N-[[4-(2,6-diazaspiro[3.4]octan-6-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
216		N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
217		N-[[4-[(1-oxo-2,7-diazaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
218		N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
219		N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
220		N-[[4-(6-oxa-2-azaspiro[3.4]octan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
221		N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
222		N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

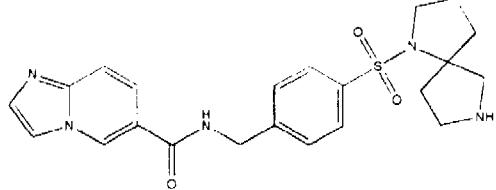
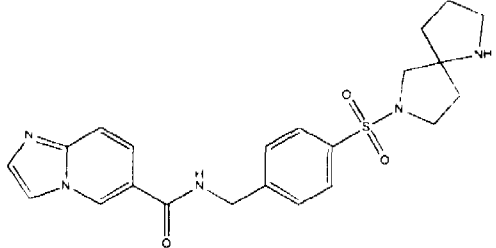
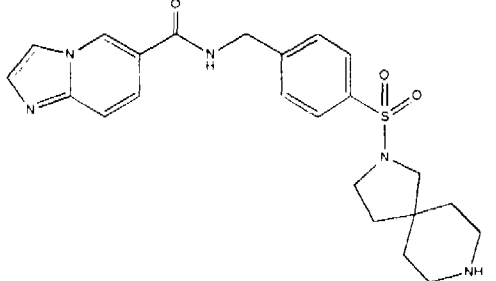
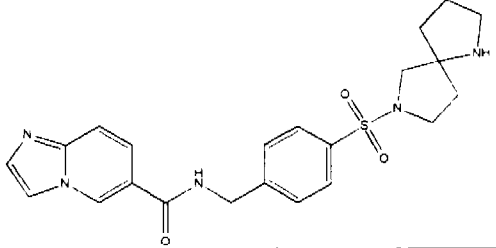
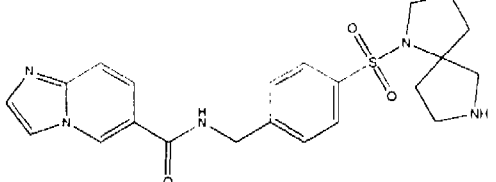
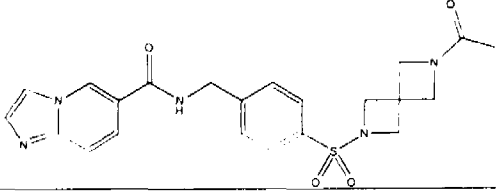
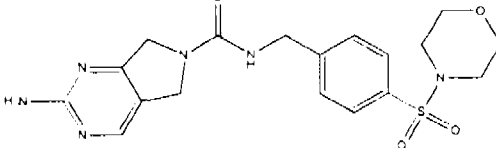
223		N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
224		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonylphenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
225		N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
226		N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
227		N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
228		N-[[4-[(1-acetyl-4-piperidyl) sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
229		N-[[4-[(1-acetyl-4-piperidyl) sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide

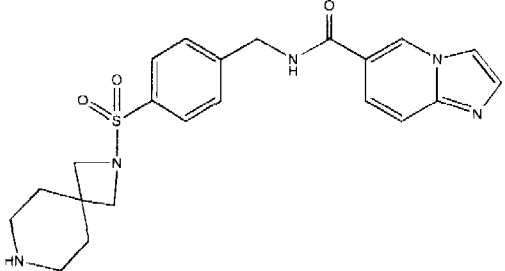
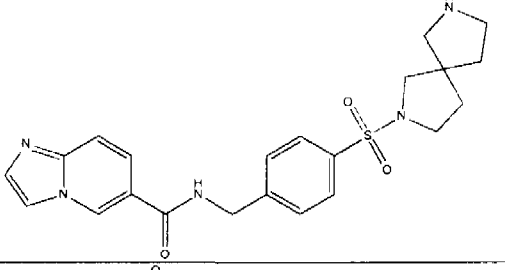
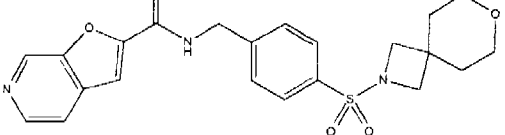
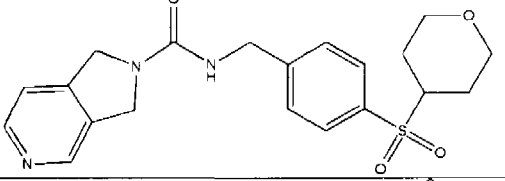
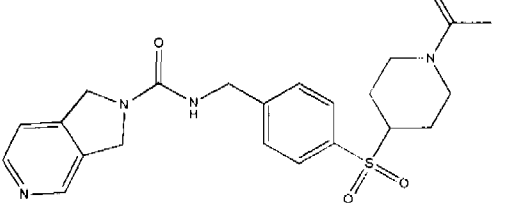
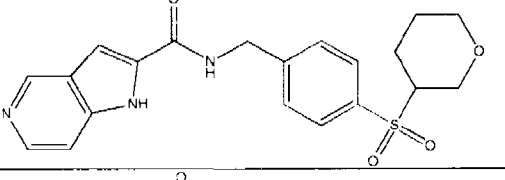
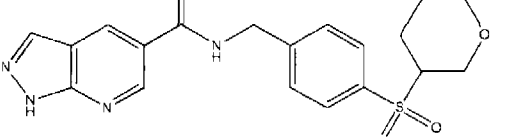
230		N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
231		N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
232		N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
233		N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
234		N-[[4-(4-piperidylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
235		tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,8-diazaspiro[4.5]decane-8-carboxylate
236		tert-butyl 7-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-1,7-diazaspiro[4.4]nonane-1-carboxylate

237		tert-butyl 1-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-1,7-diazaspiro[4.4]nonane-7-carboxylate
238		tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,8-diazaspiro[3.5]nonane-8-carboxylate
239		N-[[4-(3,3-difluoroazetidin-1-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
240		N-[[4-(azetidin-1-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
241		tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,7-diazaspiro[4.4]nonane-7-carboxylate

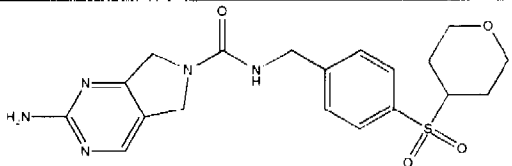
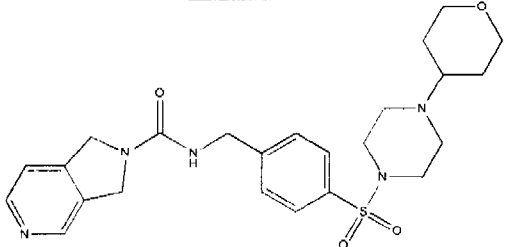
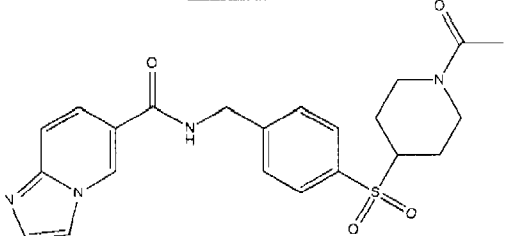
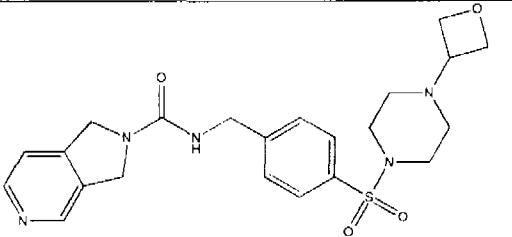
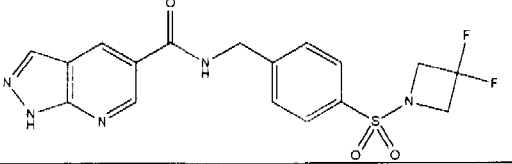
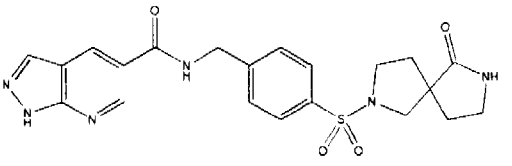
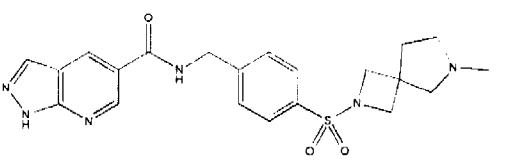
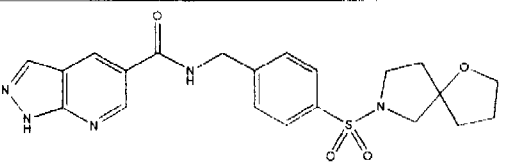
242		tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]phenyl]sulfonyl-2,9-diazaspiro[4.5]decane-9-carboxylate
243		tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]phenyl]sulfonyl-2,6-diazaspiro[4.5]decane-6-carboxylate
244		N-[[4-[3-(dimethylcarbamoyl)azetidin-1-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
245		N-[[4-[3-(3-hydroxyazetidin-1-yl)sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
246		N-[[4-[3-(4-methylpiperazine-1-carbonyl)azetidin-1-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
247		N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

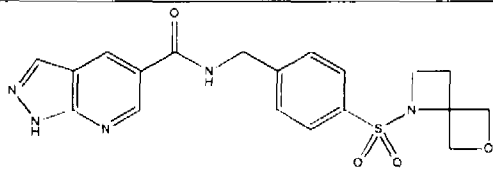
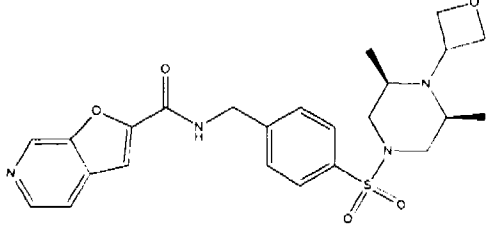
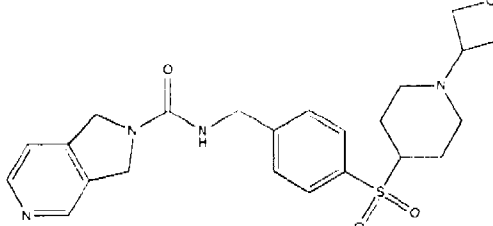
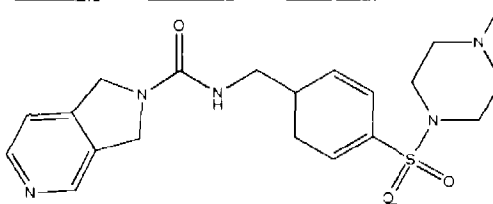
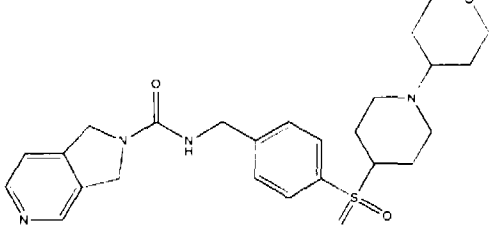
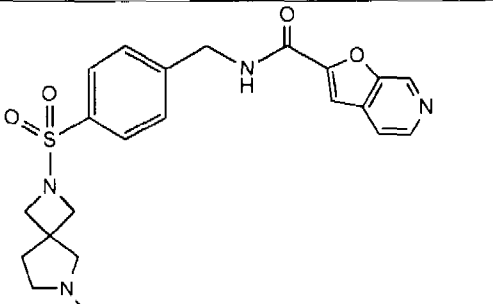
248		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
249		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
250		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
251		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide
252		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide
253		N-[[4-(2,8-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

254		N-[[4-(1,7-diazaspiro[4.4]nonan-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
255		N-[[4-(1,7-diazaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
256		N-[[4-(2,8-diazaspiro[4.5]decan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
257		N-[[4-(1,7-diazaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
258		N-[[4-(1,7-diazaspiro[4.4]nonan-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
259		N-[[4-((6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)sulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
260		2-amino-N-[(4-morpholinosulfonyl)phenyl]methyl-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide

261		N-[[4-(2,7-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
262		N-[[4-(2,7-diazaspiro[4.4]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
263		N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
264		N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
265		N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
266		N-[(4-tetrahydropyran-3-ylsulfonylphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
267		N-[(4-tetrahydropyran-3-ylsulfonylphenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

268		N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
269		N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
270		N-[[4-[(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
271		N-[[4-[(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
272		N-[[4-[(8-methyl-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
273		N-[[4-[(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
274		N-[[4-(5-oxa-2-azaspiro[3.4]octan-2-ylsulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide
275		N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]furo[2,3-c]pyridine-2-carboxamide
276		N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide

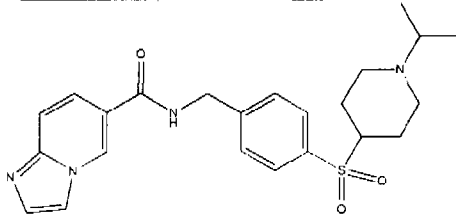
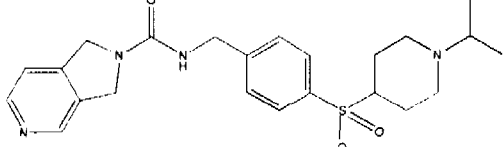
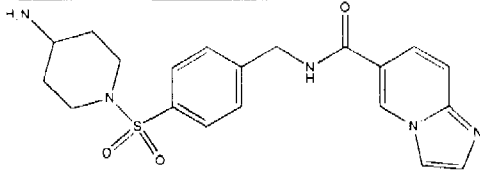
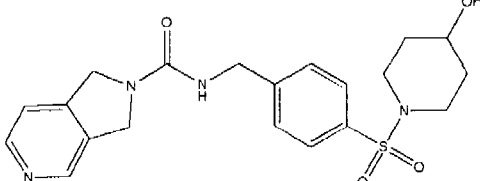
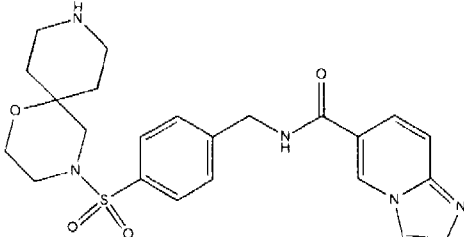
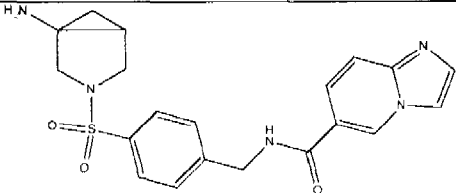
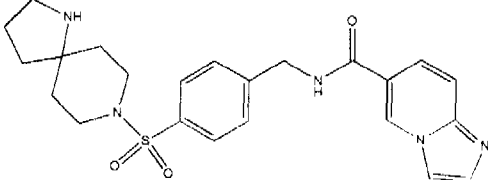
277		2-amino-N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide
278		N-[[4-(4-tetrahydropyran-4-yl)piperazin-1-yl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
279		N-[[4-[(1-acetyl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
280		N-[[4-[4-(oxetan-3-yl)piperazin-1-yl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
281		N-[[4-(3,3-difluoroazetidin-1-yl)sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
282		N-[[4-[(1-oxo-2,7-diazaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
283		N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
284		N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

285		N-[[4-(6-oxa-1-azaspiro[3.3]heptan-1-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
286		N-[[4-[(3S,5R)-3,5-dimethyl-4-(oxetan-3-yl)piperazin-1-yl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
287		N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
288		N-[[4-(4-methylpiperazin-1-yl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
289		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
290		N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide

291		N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
292		N-[[4-[(4-pyrrolidin-1-yl-1-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
294		N-[(4-morpholinosulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
296		N-[[4-[(4,4-difluoro-1,3,3a,5,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
297		N-[[4-[(5,5-difluoro-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide

298		N-[[4-[4-(2-methoxyethyl)piperazin-1-yl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
299		N-[[4-[4-(hydroxymethyl)-1-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
300		N-[[4-(3,3-difluoropyrrolidin-1-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
301		N-[[4-(3,3-difluoroazetidin-1-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
302		N-[[4-(2,3,3a,4,6,6a-hexahydrofuro[2,3-c]pyrrol-5-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
303		N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
304		N-[[4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
305		N-[[4-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
306		N-[[4-[[(3R)-3-hydroxy-1-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide

307		N-[[4-[[[(3S)-3-hydroxy-1-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
308		N-[[4-(1-piperidylsulfonyl)phenyl]methyl]imidazo[1,5-a]pyridine-7-carboxamide
309		N-[[4-[(1-methyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
310		N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
311		N-[[4-[(1-propanoyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
312		N-[[4-[(1-propanoyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
313		N-[[4-[[1-(2-methylpropanoyl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
314		N-[[4-[(1-butanoyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide

315		N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
316		N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
317		N-[[4-[(4-amino-1-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
318		N-[[4-[(4-hydroxy-1-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
319		N-[[4-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
320		N-[[4-[(5-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
321		N-[[4-(1,8-diazaspiro[4.5]decan-8-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

322		N-[[4-(1-oxa-4,8-diazaspiro[5.5]undecan-4-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
323		N-[[4-[(2-amino-7-azaspiro[3.5]nonan-7-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
324		N-[[4-(3,9-diazaspiro[5.5]undecan-3-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
325		N-[[4-(2,9-diazaspiro[5.5]undecan-9-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
326		N-[[4-(1,8-diazaspiro[5.5]undecan-8-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
327		N-[[4-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
328		N-[[4-[[4-(aminomethyl)-3-azabicyclo[2.1.1]hexan-3-yl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

329		N-[[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
330		N-[[4-[3-(3-piperidyl)indolin-1-yl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
331		N-[[4-(1,8-diazaspiro[4.5]decan-1-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
332		N-[[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-b]pyrrol-5-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
333		N-[[4-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
334		N-[[4-(1,9-diazaspiro[4.6]undecan-9-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
335		N-[[4-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide

336		N-[[4-(1,8-diazaspiro[5.5]undecan-8-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
337		N-[[4-(3,6-diazabicyclo[3.2.0]heptan-3-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
338		N-[[4-(2,9-diazaspiro[5.5]undecan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
339		N-[[4-(3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[2,3-c]pyrrol-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
340		N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
341		N-[[4-[(1-isobutyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
342		N-[[4-[(1-propyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
344		N-[[4-[(1-benzoyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

345		N-[[4-[[1-(benzenesulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
346		N-[[4-[1-(benzenesulfonyl)pyrrolidin-3-yl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
347		N-[[4-[(1-acetyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
348		N-[[4-(1-acetylpyrrolidin-3-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
349		N-[[4-[(1-methylsulfonyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
350		N-[[4-[(1-benzoyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
351		N-[[4-(1-benzoylpyrrolidin-3-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
352		N-[[4-[[1-(benzenesulfonyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
353		N-[[4-[(1-methylsulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
354		N-[[4-(1-methylsulfonylpyrrolidin-3-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

355		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
356		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
357		N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
358		N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
359		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
360		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
361		N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
362		N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
363		N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide

364		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
365		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
366		N-[[4-[(1-isopropyl-4-piperidyl) sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
367		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
368		N-[[4-[(R)-(1-isopropyl-4-piperidyl) sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
369		N-[[4-[(1-isopropyl-4-piperidyl) sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
370		N-[[4-[(1-ethyl-4-piperidyl) sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
371		N-[[4-[(1-methyl-4-piperidyl) sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
372		N-[[4-[(1-methyl-4-piperidyl) sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide

373		N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
374		N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
375		N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
376		N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
377		N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
378		N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide
379		N-[[4-[(1-methyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
380		N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
381		N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide

382		N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
383		N-[[4-[(S)-(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide
384		N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
385		N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide
386		N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide

or a stereoisomer thereof, or a pharmaceutically acceptable salt of such a compound or stereoisomer.

Pharmaceutical Description

- 5 The dosage forms of the present invention may contain a mixture of one or more compounds of this invention, and may include additional materials known to those skilled in the art as pharmaceutical excipients. "Excipient" includes any excipient commonly used in pharmaceuticals and should be selected on the basis of compatibility and the release profile properties of the desired dosage form.
- 10 Exemplary excipients include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. Exemplary excipients include, e.g., acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium
- 15 phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., Hoover,

John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pa. 1975.

Exemplary excipients include: stabilizing additives such as gum acacia, gelatin, methyl cellulose, polyethylene glycol, carboxylic acids and salts thereof, and polylysine; acidifying agents (acetic acid, glacial acetic acid, citric acid, fumaric acid, 5 hydrochloric acid, diluted hydrochloric acid, malic acid, nitric acid, phosphoric acid, diluted phosphoric acid, sulfuric acid, tartaric acid); aerosol propellants (butane, dichlorodifluoro-methane, dichlorotetrafluoroethane, isobutane, propane, trichloromonofluoromethane); air displacements (carbon dioxide, nitrogen); alcohol denaturants (denatonium benzoate, methyl isobutyl ketone, sucrose octacetate); 10 alkalizing agents (strong ammonia solution, ammonium carbonate, diethanolamine, diisopropanolamine, potassium hydroxide, sodium bicarbonate, sodium borate, sodium carbonate, sodium hydroxide, triethylamine); anticaking agents (see "glidant" below); antifoaming agents (dimethicone, simethicone); antimicrobial preservatives (benzalkonium chloride, benzalkonium chloride solution, benzethonium chloride, 15 benzoic acid, benzyl alcohol, butylparaben, cetylpyridinium chloride, chlorobutanol, chlorocresol, cresol, dehydroacetic acid, ethylparaben, methylparaben, methylparaben sodium, phenol, phenylethyl alcohol, phenylmercuric acetate, phenylmercuric nitrate, potassium benzoate, potassium sorbate, propylparaben, propylparaben sodium, 20 sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimerosal, thymol); antioxidants (ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherols excipient); buffering agents (acetic acid, ammonium 25 carbonate, ammonium phosphate, boric acid, citric acid, lactic acid, phosphoric acid, potassium citrate, potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate, sodium lactate solution, dibasic sodium phosphate, monobasic sodium phosphate); capsule lubricants; chelating agents (edetate disodium, ethylenediaminetetraacetic acid and salts, edetic acid); coating agents (sodium 30 carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl

methylcellulose, hydroxypropyl methylcellulose phthalate, methacrylic acid
 copolymer, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac,
 sucrose, titanium dioxide, carnauba wax, microcrystalline wax, zein); colorants
 (caramel, red, yellow, black or blends, ferric oxide); complexing agents
 5 (ethylenediaminetetraacetic acid and salts (EDTA), edetic acid, gentisic acid
 ethanolamide, oxyquinoline sulfate); desiccants (calcium chloride, calcium sulfate,
 silicon dioxide); emulsifying and/or solubilizing agents (acacia, cholesterol,
 diethanolamine (adjunct), glyceryl monostearate, lanolin alcohols, lecithin, mono-
 and di-glycerides, monoethanolamine (adjunct), oleic acid (adjunct), oleyl alcohol
 10 (stabilizer), poloxamer, polyoxyethylene 50 stearate, polyoxyl 35 castor oil, polyoxyl
 40 hydrogenated castor oil, polyoxyl 10 oleyl ether, polyoxyl 20 cetostearyl ether,
 polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80,
 propylene glycol diacetate, propylene glycol monostearate, sodium lauryl sulfate,
 sodium stearate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate,
 15 sorbitan monostearate, stearic acid, triethanolamine, emulsifying wax); filtering aids
 (powdered cellulose, purified siliceous earth); flavors and perfumes (anethole,
 benzaldehyde, ethyl vanillin, menthol, methyl salicylate, monosodium glutamate,
 orange flower oil, peppermint, peppermint oil, peppermint spirit, rose oil, stronger
 rose water, thymol, tolu balsam tincture, vanilla, vanilla tincture, vanillin); glidants
 20 and/or anticaking agents (calcium silicate, magnesium silicate, colloidal silicon
 dioxide, talc); humectants (glycerin, hexylene glycol, propylene glycol, sorbitol);
 plasticizers (castor oil, diacetylated monoglycerides, diethyl phthalate, glycerin,
 mono- and di-acetylated monoglycerides, polyethylene glycol, propylene glycol,
 triacetin, triethyl citrate); polymers (e.g., cellulose acetate, alkyl celluloses,
 25 hydroxyalkylcelluloses, acrylic polymers and copolymers); solvents (acetone, alcohol,
 diluted alcohol, amylene hydrate, benzyl benzoate, butyl alcohol, carbon tetrachloride,
 chloroform, corn oil, cottonseed oil, ethyl acetate, glycerin, hexylene glycol,
 isopropyl alcohol, methyl alcohol, methylene chloride, methyl isobutyl ketone,
 mineral oil, peanut oil, polyethylene glycol, propylene carbonate, propylene glycol,
 30 sesame oil, water for injection, sterile water for injection, sterile water for irrigation,
 purified water); sorbents (powdered cellulose, charcoal, purified siliceous earth);

carbon dioxide sorbents (barium hydroxide lime, soda lime); stiffening agents (hydrogenated castor oil, cetostearyl alcohol, cetyl alcohol, cetyl esters wax, hard fat, paraffin, polyethylene excipient, stearyl alcohol, emulsifying wax, white wax, yellow wax); suspending and/or viscosity-increasing agents (acacia, agar, alginic acid,

5 aluminum monostearate, bentonite, purified bentonite, magma bentonite, carbomer 934p, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carboxymethylcellulose sodium 12, carrageenan, microcrystalline and carboxymethylcellulose sodium cellulose, dextrin, gelatin, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium

10 aluminum silicate, methylcellulose, pectin, polyethylene oxide, polyvinyl alcohol, povidone, propylene glycol alginate, silicon dioxide, colloidal silicon dioxide, sodium alginate, tragacanth, xanthan gum); sweetening agents (aspartame, dextrates, dextrose, excipient dextrose, fructose, mannitol, saccharin, calcium saccharin, sodium saccharin, sorbitol, solution sorbitol, sucrose, compressible sugar, confectioner's

15 sugar, syrup); tablet binders (acacia, alginic acid, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, polyethylene oxide, povidone, pregelatinized starch, syrup); tablet and/or capsule diluents (calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate,

20 microcrystalline cellulose, powdered cellulose, dextrates, dextrin, dextrose excipient, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, compressible sugar, confectioner's sugar); tablet disintegrants (alginic acid, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch); tablet and/or

25 capsule lubricants (calcium stearate, glyceryl behenate, magnesium stearate, light mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, purified stearic acid, talc, hydrogenated vegetable oil, zinc stearate); tonicity agent (dextrose, glycerin, mannitol, potassium chloride, sodium chloride); vehicle: flavored and/or sweetened (aromatic elixir, compound benzaldehyde elixir, iso-alcoholic elixir, peppermint

30 water, sorbitol solution, syrup, tolu balsam syrup); vehicle: oleaginous (almond oil, corn oil, cottonseed oil, ethyl oleate, isopropyl myristate, isopropyl palmitate, mineral

oil, light mineral oil, myristyl alcohol, octyldodecanol, olive oil, peanut oil, persic oil, seame oil, soybean oil, squalane); vehicle: solid carrier (sugar spheres); vehicle: sterile (bacteriostatic water for injection, bacteriostatic sodium chloride injection); viscosity-increasing (see “suspending agent” below); water repelling agent

5 (cyclomethicone, dimethicone, simethicone); and wetting and/or solubilizing agent (benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, docusate sodium, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamer, polyoxyl 35 castor oil, polyoxyl 40, hydrogenated castor oil, polyoxyl 50 stearate, polyoxyl 10 oleyl ether, polyoxyl 20, cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40,

10 polysorbate 60, polysorbate 80, sodium lauryl sulfate, sorbitan monolaureate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol). This list is not meant to be exclusive, but instead merely representative of the classes of excipients and the particular excipients which may be used in dosage forms of the present invention.

15 In certain aspects, the invention relates to methods of treating diseases or conditions mediated by elevated levels of NAMPT, or which are generally mediated by NAMPT activity. Such disease or condition is one or more selected from the group consisting of cancer, ovarian cancer, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, bladder cancer, pancreatic

20 cancer, leukemia, lymphoma, Hodgkin’s disease, viral infections, Human Immunodeficiency Virus, hepatitis virus, herpes virus, herpes simplex, inflammatory disorders, irritable bowel syndrome, inflammatory bowel disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, dermatitis, atopic dermatitis, psoriasis, systemic lupus erythematosus, multiple sclerosis,

25 psoriatic arthritis, ankylosing spondylitis, graft-versus-host disease, Alzheimer’s disease, cerebrovascular accident, atherosclerosis, diabetes, glomerulonephritis, metabolic syndrome, non-small cell lung cancer, small cell lung cancer, multiple myeloma, leukemias, lymphomas, squamous cell cancers, kidney cancer, uretral and bladder cancers, cancers of head and neck, and cancers of the brain and central

30 nervous system (CNS).

The compounds of the invention can be useful in the therapy of proliferative diseases such as, but not limited to cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular
5 disease.

More specifically, the compounds of the invention can be useful in the treatment of a variety of cancers, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, non-small cell lung cancer, head and neck, esophagus, gall
10 bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma, and Burkett's lymphoma;
15 hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and other tumors, including melanoma, seminoma,
20 teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma.

The compounds of the invention may induce or inhibit apoptosis.

The compounds of the invention may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer
25 by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

A further aspect of the invention is a method of inhibiting a NAMPT pathway in a subject, said method comprising administering to said subject a pharmaceutically acceptable amount of a compound of the invention to a subject in need thereof.

Another embodiment of the invention comprises a pharmaceutical formulation of the invention, wherein the pharmaceutical formulation, upon administration to a human, results in a decrease in tumor burden.

Still another embodiment of the invention is a pharmaceutical formulation comprising at least one compound of Formula I and a pharmaceutically acceptable excipient, and further comprising one or more adjunctive active agent.

The pharmaceutical formulations of the invention may further comprise a therapeutic effective amount of an adjunctive active agent.

The compounds of the present invention are also useful in combination therapies with at least one adjunctive active agent. Such methods include regimes in which the compound of the invention and the at least one adjunctive active agent are administered simultaneously or sequentially. Also useful are pharmaceutical compositions in which at least one compound of the present invention and at least one adjunctive active agent are combined in a single formulation.

The expression "adjunctive active agent" generally refers to agents which targets the same or a different disease, symptom, or medical condition as the primary therapeutic agent. Adjunctive active agents may treat, alleviate, relieve, or ameliorate side effects caused by administration of the primary therapeutic agents. Examples of adjunctive active agents include, but are not limited to, antineoplastic agents, filgrastim, and erythropoietin. Such agents include those which modify blood cell growth and maturation. Non-limiting examples of adjunctive active agent are filgrastim, pegfilgrastim and erythropoietin. Other such adjunctive active agents include those which inhibit nausea associated with administration of chemotherapeutic agents, such as a 5-HT₃ receptor inhibitor (e.g., dolansetron, granisetron, or ondansetron), with or without dexamethasone. The invention also describes one or more uses of the compounds of the present invention with an adjunctive active agent such as TNF, GCSF, or other chemotherapeutic agents. Additional adjunctive active agents include those that mediate cytotoxicity of NAMPT inhibitors, such as nicotinic acid rescue agents, or other compounds that play a role in the NAMPT pathway, such as niacin (nicotinic acid), nicotinamide, or

related compounds, or modified release formulations of such compounds, for example, NIASPAN[®].

The terms “chemotherapeutic agent” and “antineoplastic agent” generally refer to agents, which treat, prevent, cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect malignancies and their metastasis. Examples of such agents include, but are not limited to, prednisone, fluorouracil (e.g., 5-fluorouracil (5-FU)), anastrozole, bicalutamide, carboplatin, cisplatin, chlorambucil, cisplatin, carboplatin, docetaxel, doxorubicin, flutamide, interferon-alpha, letrozole, leuprolide, megestrol, mitomycin, oxaliplatin, paclitaxel, plicamycin (MithracinTM), tamoxifen, thiotepa, topotecan, valrubicin, vinblastine, vincristine, and any combination of any of the foregoing.

The invention is also directed to a method of treating or preventing a disorder associated with excessive rate of growth of cells in a subject (e.g., a mammal) comprising administering to the subject an effective amount of the pharmaceutical formulation of the invention. Non-limiting examples of disorder include cancer or metastasis from malignant tumors.

Another aspect of the invention is a method of inhibiting tumor cell growth and rate of division in a subject (e.g., a mammal) with cancer, or other disorder associated with abnormally dividing cells comprising administering to the subject an effective amount of the pharmaceutical formulation of this invention.

Another embodiment of the invention is a method of treating bone pain due to excessive growth of a tumor or metastasis to bone in a subject (e.g., a mammal) in need thereof comprising administering to the subject an effective amount of the pharmaceutical formulation of this invention.

A further embodiment of the invention is a method of preparing a pharmaceutical formulation comprising mixing at least one compound of the present invention, and, optionally, one or more pharmaceutically acceptable excipients.

The invention is also directed to methods of synthesizing compounds of the present invention.

Still another aspect of this invention is to provide a method for treating, preventing, inhibiting or eliminating a disease or condition in a patient by inhibiting

NAMPT in said patient by administering a therapeutically effective amount of at least one compound of this disclosure, wherein said disease or condition is selected from the group consisting of cancer, ovarian cancer, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, bladder cancer, pancreatic cancer, leukemia, lymphoma, Hodgkin's disease, viral infections, Human Immunodeficiency Virus, hepatitis virus, herpes virus, herpes simplex, inflammatory disorders, irritable bowel syndrome, inflammatory bowel disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, osteoarthritis, osteoporosis, dermatitis, atopic dermatitis, psoriasis, systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, graft-versus-host disease, Alzheimer's disease, cerebrovascular accident, atherosclerosis, diabetes, glomerulonephritis, metabolic syndrome, non-small cell lung cancer, small cell lung cancer, multiple myeloma, leukemias, lymphomas, squamous cell cancers, kidney cancer, uretral and bladder cancers, cancers of head and neck, cancers of the brain and central nervous system.

In a certain embodiment, the compounds of formula I can be used in the treatment of solid and liquid tumors, non-small cell lung cancer, leukemia, lymphoma, ovarian cancer, glioma, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, rhino-gastric tumors, colorectal cancer, CNS cancer, bladder cancer, pancreatic cancer and Hodgkin's disease.

In a certain embodiment, the compounds of Formula I can be used in the treatment of solid and liquid tumors, non-small cell lung cancer, leukemia, lymphoma, ovarian cancer, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, rhino-gastric tumors, colorectal cancer, bladder cancer, pancreatic cancer and Hodgkin's disease.

Another embodiment is a pharmaceutical formulation comprising a pharmaceutically acceptable compound of the present invention, which provides, upon administration to a subject (e.g., a human), a decrease in tumor burden and/or metastases. The pharmaceutical formulation can be administered by oral means or other suitable means.

Yet another embodiment is a method of treating ovarian cancer in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating non-small cell lung cancer (NSCLC) in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating colon cancer in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating breast cancer in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating leukemia in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating colon cancer before or after surgical resection and/or radiation therapy, in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of treating cancer before or after surgical resection and/or radiation therapy, in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention, including adjunctive therapy to treat nausea, with or without dexamethasone.

Yet another embodiment is a method of treating cancer before or after surgical resection and or radiation therapy, in a subject (e.g., a human) in need thereof by administering to the subject an effective amount of the compound or the pharmaceutical formulation of the present invention, including adjunctive therapy with one or more additional therapeutic agents, or their pharmaceutically acceptable salts. Non-limiting examples of such additional therapeutic agents include cytotoxic

agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil or 5-FU); anti-metabolites (such as methotrexate); alkylating agents (such as temozolomide, cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR^{1M} (4-{2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,-6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoehtyl]-1-piperidine- carboxamide, or SCH 66336), tipifarnib (Zamestra[®] or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, N.J.), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, N.J.); signal transduction inhibitors (such as, Iressa[®] (from Astra Zeneca Pharmaceuticals, England), Tarceva[®] (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC[®] (C-abl kinase inhibitor from Novartis Pharmaceuticals, East Hanover, N.J.); interferons such as, for example, intron[®] (from Merck & Company), Peg-Intron[®] (from Merck & Company); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN[®] from Sanofi-Synthelabo Pharmaceuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone,

Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade[®], Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Ifosfomide, Rituximab, C225, and Campath, 5-fluorouracil and leucovorin, with or without a 5-HT₃ receptor inhibitor (e.g., dolansetron, granisetron, ondansetron) with or without dexamethasone.

10 Additionally, according to the present invention, the compounds of the invention described herein may be administered and/or formulated in combination with an adjunctive active agent. In certain embodiments, the adjunctive active agent is niacin, nicotinamide, nicotinic acid, nicotinamide mononucleotide (NMN), or variations thereof, including modified release formulations of niacin, such as NIASPAN[®]. Niacin, nicotinamide, nicotinic acid, nicotinamide mononucleotide (NMN), or variations thereof have also been described in the literature as “rescue agents” or “rescuing agents” and these terms have been used herein. The role of nicotinamide and/or nicotinic acid as a rescuing or rescue agent has for example been described by Beauparlant et al. in *Anti-Cancer Drugs* 2009, 20:346–354 and by Rongvaux et al. in *The Journal of Immunology*, 2008, 181: 4685–4695. These two references describe the role of a rescuing or rescue agent with regards to ameliorating possible toxic effects of NAMPT inhibitors.

25 If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein (or as known to those skilled in the art) and the other pharmaceutically active agents or treatments within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897). The compounds of the invention may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. In any combination treatment, the invention is not limited in the sequence of administration; compounds of the disclosed Formulas may

be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

Any of the aforementioned methods may be augmented by administration of fluids (such as water), loop diuretics, one or more adjunctive active agents, such as a chemotherapeutic or antineoplastic agent, such as leucovorin and fluorouracil, or an adjunctive chemotherapeutic agent (such as filgrastim and erythropoietin), or any combination of the foregoing.

Yet another embodiment is a method for administering a compound of the instant invention to a subject (e.g., a human) in need thereof by administering to the subject the pharmaceutical formulation of the present invention.

Yet another embodiment is a method of preparing a pharmaceutical formulation of the present invention by mixing at least one pharmaceutically acceptable compound of the present invention, and, optionally, one or more pharmaceutically acceptable additives or excipients.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, capsules and cachets can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pa.

The compositions and formulations of the invention can be administered as sterile compositions and sterile formulations. Sterile pharmaceutical formulations are compounded or manufactured according to pharmaceutical-grade sterilization

standards (e.g., United States Pharmacopeia Chapters 797, 1072, and 1211; California Business & Professions Code 4127.7; 16 California Code of Regulations 1751, 21 Code of Federal Regulations 21, or ex-U.S. counterparts to such regulations) known to those of skill in the art.

5 Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

10 Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

 Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral
15 administration. Such liquid forms include solutions, suspensions and emulsions.

 The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

20 The compounds of this invention may also be delivered subcutaneously.

 The compound can be administered orally or intravenously.

 The pharmaceutical preparation can be in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired
25 purpose.

 The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 1000 mg, for example from about 1 mg to about 500 mg, in particular from about 1 mg to about 250 mg, or from about 1 mg to about 25 mg, according to the particular application.

30 The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the

proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Schemes and Examples

Exemplary, non-limiting, chemical entities and methods useful in preparing compounds of the invention will now be described by reference to illustrative synthetic schemes for their general preparation below and the specific examples that follow. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds according to the invention. Although specific starting materials and reagents are depicted and discussed herein, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Each of the reactions depicted in the reaction schemes is preferably run at a temperature from about 0 °C to the reflux temperature of the solvent used. Unless

otherwise specified, the variables shown in the schemes below are as defined above in reference to Formula I.

Compounds according to the invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein, and those for other heterocycles described in: Comprehensive Heterocyclic Chemistry II, Editors Katritzky and Rees, Elsevier, 1997, e.g. Volume 3; Liebigs Annalen der Chemie, (9):1910-16, (1985); Helvetica Chimica Acta, 41:1052-60, (1958); Arzneimittel-Forschung, 40(12):1328-31, (1990), each of which are expressly incorporated by reference. Starting materials are generally available from commercial sources such as Sigma-Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (*e.g.*, prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database).

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing compounds according to the invention and necessary reagents and intermediates are known in the art and include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyloxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art.

Additional particularly useful reactions in preparing compounds of the present invention include alkylation, reductive amination, oxidation, reduction, and hydrolysis reactions. Such transformations are well within the ordinary skill in the art.

Compounds according to the invention may be prepared singly or as compound libraries comprising, for example, at least two, or 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of Formula I may be prepared by a combinatorial "split and mix" approach or by multiple parallel syntheses using either
5 solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus, according to a further aspect of the invention there is provided a compound library comprising at least two compounds of Formula I, or pharmaceutically acceptable salts thereof.

In the methods of preparing compounds according to the invention, it may be
10 advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography.

15 Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

20 Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in
25 the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like. Selection of appropriate methods of separation depends on the nature of the materials involved, such as, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography,
30 stability of materials in acidic and basic media in multiphase extraction, and the like.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302).
5 Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation
10 of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

Under method (1), diastereomeric salts can be formed by reaction of
15 enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition
20 of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322).
25 Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base,
30 or Mosher ester, α -methoxy- α -(trifluoromethyl)phenyl acetate of the racemic mixture and analyzing the ^1H NMR spectrum for the presence of the two atropisomeric

enantiomers or diastereomers (Jacob III. J. Org. Chem. (1982) 47:4165). Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

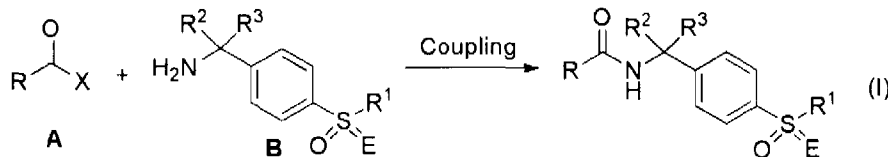
Abbreviations and acronyms used in the following Schemes and elsewhere herein are defined as follows:

DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
ELSD	Evaporative light scattering detector
equiv	Molar equivalent
ESI	Electrospray ionization (ES+ or ES-)
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethyl Acetate
EtOH	Ethanol
Et ₂ O	Diethyl ether
g	Gram
h	Hour(s)
¹ H NMR	Proton nuclear magnetic resonance
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
H ₂	Hydrogen gas
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
i-PrOH	Isopropyl alcohol
L	Liter
LC/MS	Liquid chromatography – mass spectrometry
MeOH	Methanol

Me	Methyl
min	Minute(s)
MHz	Megahertz
mL	Milliliter
NMP	N-methylpyrrolidinone
Ph	Phenyl
psi	Pounds per square inch
rt	Room temperature
Raney-Ni	Raney Nickel
R _f	Retention factor
SFC	Supercritical fluid chromatography
TEA	Triethylamine
TFA	Trifluoroacetic acid
Tf ₂ O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

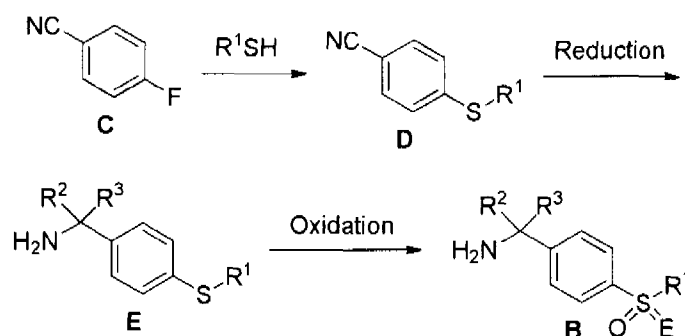
Exemplary general reaction schemes that are useful in preparing compounds of the invention are described below.

General Scheme A



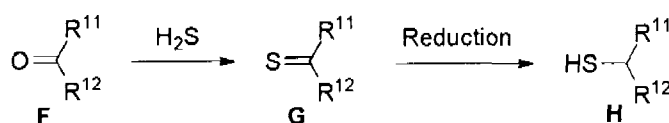
- Compounds of Formula I may be prepared as shown above in Scheme A. Compounds of Formula A, in which X is, for example, OH, chloro, or bromo, are reacted with amines B to produce compounds of Formula I. Where X is OH, coupling reactions may occur in the presence of a coupling reagent such as EDCI, HATU, or HOBt, and a base (e.g., K₂CO₃, Cs₂CO₃, trialkylamine, sodium or potassium alkoxide) in an inert solvent such as dichloromethane, N,N-dialkylformamide (such as DMF), N,N-dialkylacetamide, dialkylethers, cyclic ethers, DMSO, or NMP, or a mixture thereof, at temperatures ranging from -78 °C to 200 °C. Such coupling reactions between amines and acids are well-known in the art.
- Alternatively, compounds A where X is bromo or chloro may be reacted with amines B in the presence of a suitable base, such as triethylamine, K₂CO₃, or Cs₂CO₃, to form compounds of Formula I.

General Scheme B



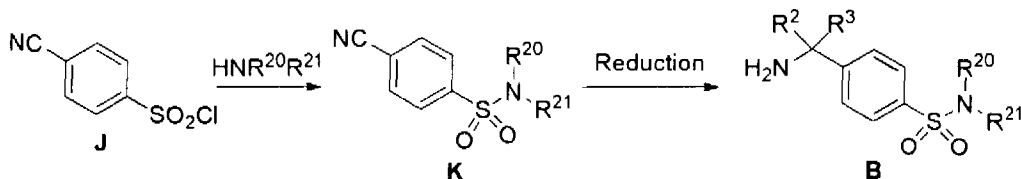
Amines B, in which R^2 and R^3 are both H, may be prepared according to General Scheme B. Fluorobenzonitrile is reacted with suitably substituted thiols R^1 -SH in the presence of a base such as K_2CO_3 or Cs_2CO_3 in a solvent such as DMSO, DMF, or NMP, preferably at elevated temperature, to form thioethers D. The nitrile group of compounds D is then reduced under hydrogenation conditions using a hydrogen source such as hydrogen gas or the like, in the presence of a suitable metal catalyst such as Raney nickel, in a solvent such as methanol or ethanol, to form amines E. The thiol group of compounds E is then oxidized to the sulfone or sulfoxide oxidation state using a suitable oxidant such as *m*-chloroperbenzoic acid in a solvent such as chloroform, or hydrogen peroxide with sulfuric acid and isopropanol. One of skill in the art will recognize that the oxidation and reduction steps may be performed in the reverse order.

General Scheme C



Certain thiols useful in preparing compounds of Formula I may be prepared according to General Scheme C. Ketones or aldehydes F, where R^{11} and R^{12} are chosen as needed to produce compounds of Formula I, are reacted with hydrogen sulfide to form the analogous thiones G, which are then reduced with a suitable reducing agent such as sodium borohydride, to produce thiols H. Thiols H may then be used in methods such as those shown in General Scheme B.

General Scheme D

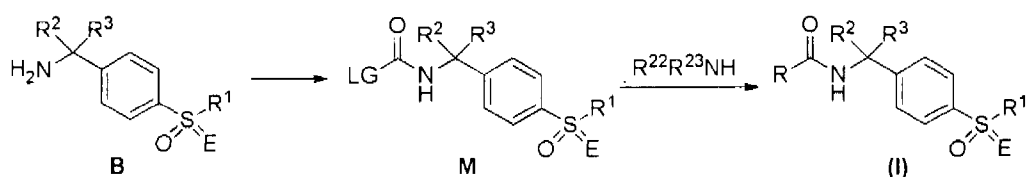


Additional embodiments of amines B that are useful in synthesizing compounds of the invention may be prepared according to General Scheme D.

- 5 Sulfonyl chloride J is reacted with a suitably substituted amine $\text{HNR}^{20}\text{R}^{21}$ in the presence of a base such as a trialkylamine base, K_2CO_3 , or Cs_2CO_3 , in a solvent such as dichloromethane, to provide sulfonamides K. Compounds K are then reduced with, for example, zinc or Raney nickel, to form amines B, which may then be used as described in General Scheme A.

10

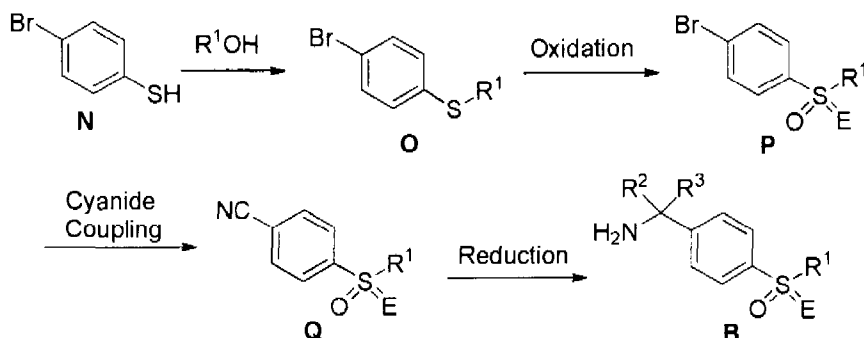
General Scheme E



Certain compounds of Formula I, wherein the R group is connected to the carbonyl carbon via a nitrogen atom within the R group (forming a urea) may be prepared according to General Scheme E. Amines B are activated using methods

- 15 known to one of skill in the art, wherein LG is a suitable leaving group such as an alkoxy or halo group, and the activated compounds M are then reacted, either in situ or in a separate reaction step, with a suitably substituted amine $\text{R}^{22}\text{R}^{23}\text{NH}$ in the presence of a base such as a trialkylamine, to form compounds of Formula I.

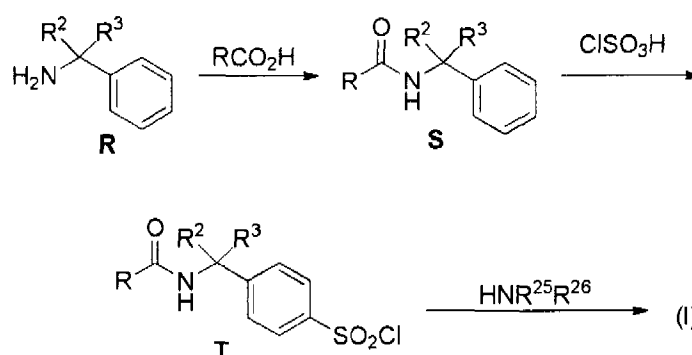
General Scheme F



20

Amines B may also be prepared as shown in General Scheme F. Thiols N are reacted with alcohols R^1OH under Mitsunobu coupling conditions to form thioethers O. Oxidation of the sulfur as described above leads to sulfoxides and sulfones P. The cyano group is introduced by coupling of compounds P with a cyanide source such as $Zn(CN)_2$ in the presence of a palladium catalyst, and a solvent such as DMF or DMSO to generate nitriles Q. The nitrile group is reduced to provide primary amines B as described above.

General Scheme G



In an alternative embodiment, compounds of Formula I are prepared as shown in General Scheme G. Coupling of benzylamines **R** with acids RCO_2H under standard amide coupling conditions provides amides **S**. Sulfonylation with chlorosulfonic acid generates benzene sulfonyl chlorides **T**. Such compounds are then reacted with suitably substituted amines $HNR^{25}R^{26}$, in the presence of a suitable base such as a trialkylamine base, K_2CO_3 , or Cs_2CO_3 , in a solvent such as dichloromethane, to provide compounds of Formula I.

Those having skill in the art will recognize that the starting materials, reagents, and conditions described in the above general schemes may be varied and additional steps employed to produce compounds encompassed by the present inventions.

Methods of Chemical Analysis

Unless otherwise indicated, ^1H NMR spectra were recorded at ambient temperature using one of the following machines: Varian Unity Inova (400 MHz) spectrometer with a triple resonance 5 mm probe, Bruker Avance DRX400 (400 MHz) spectrometer with a triple resonance 5 mm probe, a Bruker Avance DPX 300 (300

MHz) equipped with a standard 5 mm dual frequency probe for detection of ^1H and ^{13}C , a Bruker AVIII (400 MHz) using a BBI Broad Band Inverse 5 mm probe, or a Bruker AVIII (500 MHz) using a QNP (Quad Nucleus detect) 5 mm probe. Chemical shifts are expressed in ppm relative to an internal standard; tetramethylsilane (ppm = 0.00). The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

High Pressure Liquid Chromatography - Mass Spectrometry (LC/MS) experiments to determine retention times (RT) and associated mass ions (*e.g.*, $[\text{M}+\text{H}]^+$, $[\text{M}+\text{Na}]^+$, $[\text{M}-\text{H}]^-$) were performed using one of the following methods:

10

Method A

Instrument: SHIMADZU LC/MS-2010EV

LC Parameters: Column: Shim-pack XR-ODS, 2.2 μm , 3.0*50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% to 100% B in 2.0 min, 100% B for 1.1 min, 100% to 5% B in 0.2 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 $^\circ\text{C}$; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 μL .

15

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 $^\circ\text{C}$; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.7 kv.

20

Method B

Instrument: SHIMADZU LC/MS-2010EV

LC Parameters: Column: Waters XBridge C18, 3.0x50 mm, 3.5 μm ; Mobile Phase A: Water/5 mM Ammonium Acetate; Mobile Phase B: Methanol; Gradient: 10% to 100% B in 1.8 min, 100% B for 1.3 min, 100% to 10% B in 0.1 min, then stop; Flow Rate: 0.9 mL/min; Column Temperature: 40 $^\circ\text{C}$; Detector: PDA and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 μL .

25

MS Parameters: Interface: ESI (Positive & Negative); Interface Voltage: 4.0 kv; Heat Block: 250 $^\circ\text{C}$; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.5 kv.

30

Method C

Instrument: SHIMADZU LC/MS-2010EV

LC Parameters: Column: Shim-pack XR-ODS, 2.2 μ m, 3.0*50 mm; Mobile Phase A:

- 5 Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 5% to 100% B in 2.0 min, 100% B for 1.1 min, 100% to 5% B in 0.2 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 μ L.

- MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 10 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.5 kv.

Method D

Instrument: SHIMADZU LC/MS-2010EV

- 15 LC Parameters: Column: Waters Xselect C18, 3.0x50 mm, 3.5 μ m; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: Acetonitrile /0.05% formic acid; Gradient: 5% to 100% B in 2.0 min, 100% B for 1.2 min, 100% to 5% B in 0.1 min, then stop; Flow Rate: 0.9 mL/min; Column Temperature: 35 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 μ L.
- 20 MS Parameters: Interface: ESI (Positive & Negative); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.5 kv.

Method E

- 25 Instrument: SHIMADZU LC/MS-2010EV

LC Parameters: Column: Shim-pack XR-ODS, 3.0x50 mm, 2.2 μ m; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% to 100% B in 2.0 min, 100% B for 1 min, 100% to 5% B in 0.3 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample; Preparation: 1 30 mg/mL in Methanol; Injection Volume: 1 μ L.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.3 kv.

5 Method F

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Shim-pack XR-ODS, 2.2 µm, 3.0*50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% B to 100% B for 2.0 min, 100% B for 1.2 min, 100% B to 5% in 0.1 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: UV and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 70-900 (m/z); Detector voltage: 1.1 kv.

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Method G

Instrument: SHIMADZU LC/MS-2020EV

LC Parameters: Column: Shim-pack XR-ODS, 50*3.0 mm, 2.2 µm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% to 100% B in 2.1 min, 100% B for 0.8 min, 100% to 5% B in 0.1 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Acetonitrile; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.05 kv.

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Method H

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Shim-pack XR-ODS, 2.2 µm, 3.0*50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 5% to 100% B in 2.0 min, 100% B for 1.2 min, 100% to 5% B in 0.1 min, then stop; Flow Rate:

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1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage:

5 1.1 kv.

Method I

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Shim-pack XR-ODS, 50*3.0 nm, 2.2 µm; Mobile Phase A:

10 Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 5% B to 100% B for 2.0 min, 100% B for 1.2 min, 100% B to 5% B in 0.1 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block:

15 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 70-900 (m/z); Detector voltage: 1.05 kv.

Method J

Instrument: SHIMADZU LC/MS-2020

20 LC Parameters: Column: Shim-pack XR-ODS, 3.0x50 mm, 2.2 µm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% to 100% B in 2.0 min, 100% B for 1.2 min, 100% to 5% B in 0.2 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: 254 nm and ELSD; Sample Preparation: 1 mg/mL in Acetonitrile; Injection Volume: 1 µL.

25 MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 200 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 1.05 kv.

Method K

30 Instrument: HPLC-Agilent 1100

LC Parameters: Column: ZORBAX SB-C18, 1.8 mm, 20 x 2.1 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 3% to 97% B in 7.0 min, 97% B for 1.5 min, then stop; Flow Rate: 0.4 mL/min; Column Temperature: 40 °C; Detector: 220 nm and 254 nm.

5 MS Parameters: Agilent MSD; Interface: ESI (Positive).

Method L

Instrument: Waters Acquity UHPLC

10 LC Parameters: Column: UPLC BEH C18, 1.7 mm, 2.1 x 30 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: Acetonitrile/0.1% formic acid; Gradient: 5% to 95% B in 1.5 min, 95% B in 0.3 min, then stop; Flow Rate: 0.7 mL/min; Column Temperature: 40 °C; Detector: 220 nm and 254 nm.

MS Parameters: Waters SQD mass spectrometer; Interface: ESI (Positive).

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Method N

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Shim-pack XR-ODS, 2.2 um, 3.0*50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile; Gradient: 5% B to 100% B for 2.0 min, 100% B for 1.2 min, 100% B to 5% in 0.1 min, then stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: UV and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

20 MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block: 250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 70-900 (m/z); Detector voltage: 1.1 kv.

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Method O

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Shim-pack XR-ODS, 2.2 um, 3.0*50 mm; Mobile Phase A: Water/0.1% formic acid; Mobile Phase B: Acetonitrile/0.05% formic acid; Gradient: 5% B to 100% B for 2.0 min, 100% B for 1.2 min, 100% B to 5% in 0.2 min, then

stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: UV and ELSD;

Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block:

250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 70-900 (m/z); Detector voltage:

5 0.95 kv.

Method P

Instrument: SHIMADZU LC/MS-2020

LC Parameters: Column: Gemini-NX 3u C18 110A; Mobile Phase A: Water/0.04%

10 ammonia; Mobile Phase B: Acetonitrile; Gradient: 5% B to 100% B for 2.0 min,

100% B for 1.1 min, 100% B to 5% in 0.1 min, then stop; Flow Rate: 1.0 mL/min;

Column Temperature: 35 °C; Detector: UV and ELSD; Sample Preparation: 1 mg/mL in Methanol; Injection Volume: 1 µL.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.5 kv; Heat Block:

15 200 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage:

0.75 kv.

Method Q

Instrument: SHIMADZU LC/MS-2020EV

20 LC Parameters: Column: Shim-pack XR-ODS, 2.2 µm, 3.0*50 mm; Mobile Phase A:

Water/0.1% formic acid; Mobile Phase B: Acetonitrile/0.05% formic acid; Gradient:

5% B to 100% B for 2.0 min, 100% B for 1.1 min, 100% B to 5% in 0.1 min, then

stop; Flow Rate: 1.0 mL/min; Column Temperature: 40 °C; Detector: PDA and ELSD;

Sample Preparation: 1 mg/mL in acetonitrile; Injection Volume: 1 µL.

25 MS Parameters: Interface: ESI (Positive); Interface Voltage: tuning file; Heat Block:

250 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage:

0.9 kv.

Method R

30 Instrument: SHIMADZU LC/MS-2020EV

LC Parameters: Column: Shim-pack XR-ODS, 1.7 μ m, 2.0*50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 5% B to 100% B for 2.2 min, 100% B for 0.9 min, 100% B to 5% in 0.1 min, then stop; Flow Rate: 0.7 mL/min; Column Temperature: 40 $^{\circ}$ C; Detector: Diode Array

5 Detector (DAD) and ELSD; Injection Volume: 1 μ L.

MS Parameters: Interface: ESI (Positive); Interface Voltage: 4.0 kV; Heat Block: 400 °C; Nebulizing Gas: 1.50 L/min; Scan Range: 90-900 (m/z); Detector voltage: 0.9 kV.

10 Method S

Instrument: HPLC-Agilent 1200

LC Parameters: Column: ZORBAX SB-C18, 1.8 mm, 30 x 2.1 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 3% to 95% B in 7.0 min, 95% B for 1.5 min, equilibrate for 1.5 min, then stop; Flow Rate: 0.4 mL/min; Column Temperature: 35 °C; Detector: 220 nm and 254 nm; Sample preparation: 1 mg/mL in MeOH; Injection volume: 1 uL; Report: Area Normalized Purity.

MS Parameters: Agilent quadrupole 6140; Interface: ESI (Positive); Scan range: 110-800 amu; Detector: single quadrupole.

20 Method T

Instrument: Waters Acquity UPLC

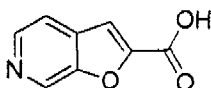
LC Parameters: Column: UPLC BEH C18, 1.7 mm, 2.1 x 50 mm; Mobile Phase A: Water/0.05% TFA; Mobile Phase B: Acetonitrile/0.05% TFA; Gradient: 2% to 98% B in 17.5 min, 98% B in 1.5 min, equilibrate for 1.5 min, then stop; Flow Rate: 0.6 mL/min; Column Temperature: 40 °C; Detector: 220 nm and 254 nm.

MS Parameters: Waters LCT Premier XE; Interface: ESI (Positive); Scan range: 80-1300 amu; Detector: time of flight.

The following examples illustrate the preparation of representative compounds of the invention. Unless otherwise specified, all reagents and solvents were of standard commercial grade and were used without further purification.

5 I. Preparation of Intermediates

Intermediate 1: Furo[2,3-c]pyridine-2-carboxylic acid



Step 1. Ethyl 3-hydroxyisonicotinate. A solution of 3-hydroxyisonicotinic acid (495 g, 3.56 mol) in EtOH (7 L) and concentrated H₂SO₄ (250 mL) was heated
10 under reflux for 72 h and then cooled to rt and concentrated under reduced pressure to remove the solvent. The residue was dissolved in water (3 L) and the pH was adjusted to 4 by addition of saturated aqueous NaHCO₃ solution. The resulting precipitate was removed by filtration and the filtrate was extracted with DCM (2 L×3). The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄,
15 and then concentrated under reduced pressure to give ethyl 3-hydroxyisonicotinate (414 g, 70%) as yellow oil.

Step 2. Ethyl 3-(2-ethoxy-2-oxoethoxy)isonicotinate. To a solution of triphenylphosphine (780 g, 2.97 mol) in THF (6 L) at -10 °C was added dropwise diisopropyl azodicarboxylate (600 mL, 2.97 mol). The reaction mixture was stirred at
20 -10 °C for 30 min and then ethyl 3-hydroxyisonicotinate (414 g, 2.48 mol) in THF (1 L) solution was added dropwise. The resulting mixture was stirred at rt for 16 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (4 L) and 1 N HCl (2 L). The aqueous layer was separated and the organic phase was extracted by 1 N HCl (1 L×2). The combined aqueous layers were slowly
25 adjusted to pH 8 by addition of solid NaHCO₃ and then extracted with ethyl acetate (2 L×2). The combined organic layers were dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure to give the title compound (380 g, 61%) as a brown oil.

Step 3. Ethyl 3-hydroxyfuro[2,3-c]pyridine-2-carboxylate. To a suspension
30 of NaH (72 g, 1.8 mol, 60% suspension in mineral oil) in anhydrous THF (2 L) at

0 °C was added dropwise a solution of ethyl 3-(2-ethoxy-2-oxoethoxy)isonicotinate (380 g, 1.5 mol) in THF (1 L) under argon. The reaction mixture was stirred at rt for 16 h and then carefully quenched with ice water (1 L). The resulting mixture was concentrated to a volume of 1.2 L and then diluted with saturated aqueous NaHCO₃ solution (2.5 L), and stirred for an additional 30 min. The precipitated solid was collected by filtration and washed with ethyl acetate (1 L). The filtrate was washed with ethyl acetate (1 L×2) and the aqueous layer was combined with the solid and carefully acidified to a pH of 5 with acetic acid. The resulting solid was collected by filtration and dried under vacuum to give the title compound (210 g, 68%) as a yellow solid.

Step 4. Ethyl 3-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridine-2-carboxylate. To a solution of ethyl 3-hydroxyfuro[2,3-c]pyridine-2-carboxylate (210 g, 1.01 mol) and pyridine (107 mL, 1.3 mol) in anhydrous DCM (3 L) at 0 °C was added dropwise triflic anhydride (203 g, 1.2 mol). The reaction mixture was stirred at rt for 16 h and then quenched with ice water (1 L). The aqueous layer was extracted with DCM (1 L×2) and the combined organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 10% ethyl acetate/petroleum ether to give the title compound (298 g, 87%) as a white solid.

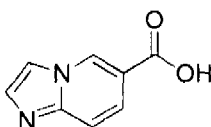
Step 5. Ethyl furo[2,3-c]pyridine-2-carboxylate. To a solution of ethyl 3-(((trifluoromethyl)sulfonyl)oxy)furo[2,3-c]pyridine-2-carboxylate (298 g, 0.88 mol) in ethanol (3 L) was added 10% Pd/C (30 g) and triethylamine (281 mL, 2.02 mol). The reaction mixture was stirred under an atmosphere of hydrogen for 16 h and then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography eluting with 20% ethyl acetate/petroleum ether to give the title compound (158 g, 94%) as a pale yellow solid.

Step 6. To a solution of ethyl furo[2,3-c]pyridine-2-carboxylate (158 g, 0.83 mol) in water:THF:MeOH (1:1:1, 2.4 L) was added KOH (139 g, 2.49 mol). The reaction mixture was stirred at rt for 16 h and then concentrated to a volume of 750 mL. To this residue was added acetic acid until pH ~ 4. The resulting solids were

collected by filtration, washed with water (300 mL×2) and dried in a vacuum oven overnight to give the title compound (101 g, 75%) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.47 (d, *J* = 5.6 Hz, 1H), 7.80 (d, *J* = 5.2 Hz, 1H), 7.61 (s, 1H). MS (ESI+) *m/z*: 164 [M+H]⁺.

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Intermediate 2: Imidazo[1,2-a]pyridine-6-carboxylic acid

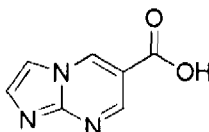


Step 1. Imidazo[1,2-a]pyridine-6-carboxylic acid hydrochloride salt. A mixture of 2-chloroacetaldehyde (277 g, 40%) and 6-aminonicotinic acid (150 g) in EtOH (330 mL) was heated to reflux and stirred for 8 h. After cooling, a solid precipitated and was isolated by vacuum filtration, then washed with ethanol and dried under vacuum to give the title compound as a light yellow solid (1.78 g, 82%).

Step 2. Imidazo[1,2-a]pyridine-6-carboxylic acid hydrochloride salt (170 g) was diluted with water (600 mL) and heated until a clear solution resulted, then an aqueous solution of NaOH (2 M) was added slowly to adjust the pH = 5-6. The reaction mixture was cooled to 0 °C using an ice-H₂O bath. The resulting precipitate was collected by vacuum filtration, then washed with ethanol and dried under vacuum to give the title product (107.2 g, 77%) as a light yellow powder. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.76–12.82 (br, 1H), 9.28 (s, 1H), 8.10 (s, 1H), 7.68 (s, 1H), 7.64–7.56 (m, 2H). MS (ESI+) *m/z*: 163 [M+H]⁺.

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Intermediate 3: Imidazo[1,2-a]pyrimidine-6-carboxylic acid



Step 1. Sodium (Z)-2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate. Methyl 3,3-dimethoxypropanoate (100 g, 675 mmol) and methyl formate (81 g, 1350 mmol) were dissolved in anhydrous THF (450 mL). Sodium hydride (60% dispersion, 32.4 g, 810 mmol, 1.2 eq.) was then added slowly in portions at 0 °C. The reaction

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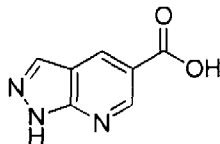
mixture was stirred at rt for 1 h, then was heated at 50 °C for 3 h. During this period, H₂ evolution was observed. After cooling to rt, the solvent was then removed under reduced pressure to give the crude product which was directly used in the next step without further purification.

5 Step 2. Methyl 2-aminopyrimidine-5-carboxylate. The crude enolate from step 1 was dissolved in DMF (200 mL), and guanidine hydrochloride (64 g, 670 mmol) was added. The mixture was heated at 100 °C under N₂ for 3 h. After cooling to rt, water was added and the mixture was cooled with an ice-water bath. The resulting precipitate was collected by vacuum filtration and dried under vacuum to
10 give the desired product (63 g, 61% yield for 2 steps).

Step 3. Methyl imidazo[1,2-a]pyrimidine-6-carboxylate. To a mixture of 2-bromo-1,1-diethoxyethane (100.6 g, 0.51 mol) and methyl 2-aminopyrimidine-5-carboxylate (63 g, 0.41 mol) in ethanol (300 mL) was added concentrated HBr (40%) (55 g). The reaction mixture was heated to reflux for 3 h under N₂. After cooling to
15 rt, the mixture was further cooled with an ice-water bath. The resulting precipitate was collected by vacuum filtration and dried under vacuum overnight to give the desired product (92 g, 87%).

Step 4. Into a round bottom flask containing methyl imidazo[1,2-a]pyrimidine-6-carboxylate (92 g, 356.5 mmol), was added water (200 mL). NaOH (6 N in H₂O, 2.5 eq.) was then added dropwise with stirring at rt. After stirring at rt for 1 h, the mixture was cooled with an ice-water bath and concentrated HCl was added (pH = 5-6). The resulting mixture was concentrated under reduced pressure to approximately 150 mL (3/4 volume) and cooled with an ice-water bath. The resulting precipitate was collected by vacuum filtration, washed with cold water (50 mL) and
25 dried to give the title compound as an off-white solid (46 g, 79%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.29 (d, *J* = 2.0 Hz, 1H), 8.89 (d, *J* = 2.0 Hz, 1H), 7.94 (s, 1H), 7.70 (s, 1H). MS (*m/z*, ES⁻): 164.1 [M+H]⁻, 186.1 [M + Na]⁻.

Intermediate 4: 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid



Step 1. 1-(4-Methoxybenzyl)-1H-pyrazol-5-amine. To a solution of acrylonitrile (30 mL, 455 mmol) in THF (250 mL), $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (23.19 mL, 478 mmol) was added drop-wise at 0 °C. After addition was complete, the mixture was stirred at rt for 2 h, then 4-methoxybenzaldehyde (55.4 mL, 455 mmol) was added drop-wise. The mixture was stirred at rt overnight, then at reflux for 2 h. After cooling to rt the mixture was quenched by addition of 300 mL of ice water. The mixture was extracted with ethyl acetate (3 x), then the combined organic layers were extracted with 1 N HCl. The aqueous layer was neutralized with aqueous 10 N NaOH, then extracted with ethyl acetate. The organic layer was washed with H_2O and brine, then dried over Na_2SO_4 . Filtration, concentration, and recrystallization with Et_2O gave the target compound as a white solid (50 g, 60%).

Step 2. Ethyl 4-hydroxy-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. 1-(4-Methoxybenzyl)-1H-pyrazol-5-amine (3.94 g, 19.39 mmol), followed by diethyl 2-(ethoxymethylene)malonate (4 mL, 20 mmol) was added to a 200 mL round bottom flask fitted with a distillation head to remove ethanol. The mixture was heated to 130 °C for 45 min, then 10 mL of diphenyl ether was added and the temperature was raised to 240 °C for 2 h. The reaction mixture was then cooled to rt and Et_2O (100 mL) was added. The resulting precipitate was collected by vacuum filtration and dried under vacuum to afford the target compound as a white solid (4 g, 62%).

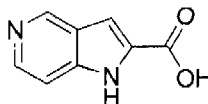
Step 3. Ethyl 4-chloro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. POCl_3 (10 mL) was added to ethyl 4-hydroxy-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (7.5 g, 19.39 mmol). The mixture was stirred at 60 °C for 3 h. The mixture was poured into ice water and the resulting precipitate was collected by vacuum filtration and dried under vacuum to afford the target compound a light yellow solid (6.4 g, 80%).

Step 4. Ethyl 1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. To a solution of ethyl 4-chloro-1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-

carboxylate (5.9 g, 17 mmol) in THF (50 mL), triethylamine (1.7 g, 17 mmol), followed by Pd(OH)₂/C (300 mg) was added. The mixture was stirred at rt for 3 h under H₂. The mixture was filtered and concentrated. The residue was dissolved in ethyl acetate and washed with saturated aqueous NaHCO₃ solution and brine, then
5 dried over Na₂SO₄. Filtration and concentration gave target compound as a light gray solid (5.3 g, 100%).

Step 5. Ethyl 1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridine-5-carboxylate (4.4 g, 14 mmol) was dissolved in TFA (158 mL) and heated to 80 °C. The mixture was stirred at 80 °C for 4 h, then was concentrated to dryness. The residue was
10 poured into ice water, then aqueous NaOH solution (2 M) was added until the pH was approximately 14. The solid formed was removed by filtration, and the aqueous layer was washed with ethyl acetate. To the aqueous layer was added concentrated HCl was added until the pH was approximately 7. The resulting precipitate was collected by vacuum filtration and dried under vacuum to afford the title compound as a white
15 solid (2.1 g, 80%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.38-13.62 (br, 1H), 9.07 (d, *J* = 1.6 Hz, 1H), 8.81 (d, *J* = 1.6 Hz, 1H), 8.32 (s, 1H). MS (*m/z*, ESI⁺): 164 [M+H]⁺.

Intermediate 5: 1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid



Step 1. 3-Iodopyridin-4-amine. To a 2 L 3-necked flask was added a solution
20 of 38 mL of concentrated sulfuric acid in 200 mL water. The solution was cooled with an ice-water bath, then 4-aminopyridine (200 g, 2.12 mol) and acetic acid (700 mL) were added in batches. The mixture was then heated to reflux. Iodine (189 g, 0.745 mol) and periodic acid dihydrate (97 g, 0.424 mol) were both equally divided
25 into four parts. One batch of iodine was added and then one batch of periodic acid dihydrate was added 15 min later. After 30 min, a new batch of iodine and periodic acid dihydrate were added in the same way. When all four batches of iodine and periodic acid dihydrate were added, the mixture was kept refluxing for an additional 3 h. After cooling to rt the reaction mixture was slowly poured into water while
30 stirring, then a 40% solution of NaOH in water was added until pH > 9. Na₂SO₃ was

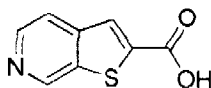
added to destroy the unreacted iodine. After cooling to rt, a filtration was performed. The collected solid was further purified by recrystallization in chloroform to give the desired product (184 g, 39%).

Step 2. To a 2 L 3-necked flask was added DMF (700 mL), triethylene
5 diamine (168 g, 1.5 mol), and 4-amino-3-iodopyridine (24, 110 g, 0.5 mol). The mixture was cooled with an ice-water bath and pyruvic acid (132 g, 1.5 mol) was slowly added, followed by palladium acetate (4.49 g, 0.02 mol). Under nitrogen atmosphere, the mixture was heated to 115 °C. The reaction generated effervescence. The reaction mixture was kept at 115-120 °C for 11 h. The mixture was concentrated
10 under reduced pressure. The residue was poured into water (500 mL), and concentrated HCl was added to adjust pH to <1. The mixture was cooled by adding ice and a filtration was performed. The cake thus obtained was a brownish black solid.

The above cake was added into 500 mL of water. Concentrated HCl was
15 added (to ensure complete protonation) followed by 5 g of active carbon. The mixture was heated to reflux for 20 min and then filtration was performed while hot. The solid was discarded and the hot filtrate was placed in a refrigerator to allow the HCl salt of the desired product to precipitate. Upon cooling, filtration was performed which afforded a dark brown solid with a wet weight of 48 g as the HCl salt of the
20 desired product.

The solid was then added to 250 mL of water and the mixture was heated until a clear solution resulted. Solid NaOH was slowly added to adjust pH to 5-6, then active carbon and an additional 500 mL of water was added. The mixture was heated to reflux for 30 min, then filtration was performed while hot. The resulting cake was
25 added to 750 mL of water, heated to reflux, and filtered again. The cake thus obtained was discarded. The two batches of filtrate were combined and cooled in a refrigerator. The resulting precipitate was collected by vacuum filtration, then washed with ethanol to give the title compound as a slightly yellow solid (25 g, 31%).
MS (*m/z*, ES⁺): 161.1 [M-1], 323.1 [2M-1]. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 12.20
30 (br s, 1H), 8.97 (s, 1H), 8.27 (d, *J* = 5.6 Hz, 1H), 7.41 (d, *J* = 6.0 Hz, 1H), 7.23 (s, 1H).

Intermediate 6: Thieno[2,3-c]pyridine-2-carboxylic acid



Step 1. 3,5-Dibromoisonicotinaldehyde. Lithium diisopropylamide (507
5 mmol, 1.2 eq.) was added to 200 mL of dry THF at -78 °C under N₂. A solution of
3,5-dibromopyridine (100 g, 424 mmol) in 537 mL of dry THF was then added drop-
wise over 30 min. The reaction mixture was stirred at -78 °C for 1 h. Ethyl formate
(34.4 g, 465 mmol) was added drop-wise and stirred at -78 °C for 30 min, then the
reaction mixture was poured into ice-cold saturated aqueous NaHCO₃ solution. The
10 mixture was extracted with 3 x 500 mL of EtOAc. The organic layer was
concentrated to provide a brown solid, which was filtered through a pad of silica gel
(eluted with dichloromethane) to give the title compound as a yellow powder (70 g,
63%).

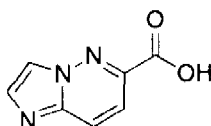
Step 2. Methyl 4-bromothieno[2,3-c]pyridine-2-carboxylate. 3,5-
15 Dibromoisonicotinaldehyde (80 g, 303 mmol), followed by cesium carbonate (98 g,
302 mmol) was added to a 2 L round bottom flask containing THF (1.3 L) under N₂.
Methyl mercaptoacetate (32 g, 302 mmol) was added and the mixture was heated at
60 °C overnight. After cooling to rt, ethyl acetate was added and the organic layer
was washed with water, aqueous saturated NaHCO₃ solution, and brine, then dried
20 over Na₂SO₄ and filtered to give a white solid. The crude product was purified by
recrystallization from ethyl acetate to give the desired product (60 g, 73%).

Step 3. Methyl thieno[2,3-c]pyridine-2-carboxylate. Methyl 4-
bromothieno[2,3-c]pyridine-2-carboxylate (115 g, 423 mmol), TEA (42.7 g, 423
mmol), THF (1.5 L), and MeOH (500 mL) were mixed and degassed. Under nitrogen,
25 palladium on carbon (10%, 14.7 g, 13.9 mmol) was added. The mixture was
hydrogenated with a Parr apparatus at 45 psi H₂ for 3 days. The catalyst was filtered
off and the filtrate was concentrated to give the desired compound as a white solid
(65 g, 80%).

Step 4. A three necked 2 L round bottom flask equipped with an overhead
30 stirrer and thermocouple was charged with methyl thieno[2,3-c]pyridine-2-

carboxylate (130 g, 674 mmol) and water (650 mL). Aqueous sodium hydroxide solution (10 N) was added with stirring at 20 °C. Over the next 20 min, the temperature rose to 25 °C and the solid dissolved. After 1 h, concentrated HCl (1.5 eq.) was slowly added to the reaction mixture with rapid stirring, generating a thick slurry. After stirring for 1 h, the slurry was filtered and the solid was dried under vacuum to give the title compound as a white solid (105.5 g, 88%). MS (*m/z*, ES⁺): 178.0 [M-1]. ¹H-NMR (DMSO-*d*₆, 400 MHz) δ 12.24 (br s, 1H), 8.97 (s, 1H), 8.27 (d, *J* = 6.0 Hz, 1H), 7.40 (d, *J* = 5.6 Hz, 1H), 7.23 (s, 1H).

10 Intermediate 7: Imidazo[1,2-b]pyridazine-6-carboxylic acid



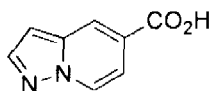
Step 1. 6-Chloro-imidazo[1,2-b]pyridazine. A solution of 6-chloro-1,2-diazinan-3-amine (10 g, 73.75 mmol, 1.00 equiv), 2-bromo-1,1-dimethoxyethane (50 g, 295.83 mmol, 4.01 equiv), and HBr (40%, 45 mL) in ethanol (100 mL) was stirred overnight at 90 °C. The majority of the ethanol was removed under reduced pressure then the pH value of the solution was adjusted to 10 with 5% aqueous potassium carbonate solution. The resulting mixture was extracted with 6x500 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1/2~1/1) to give 6.5 g (57%) of the title compound as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 7.95 (s, 1H), 7.91 (s, 1H), 7.80 (s, 1H), 7.05 (d, *J* = 9.3 Hz, 1H).

Step 2. Imidazo[1,2-b]pyridazine-6-carboxylic acid methyl ester. A mixture of 6-chloro-imidazo[1,2-b]pyridazine (200 mg, 1.30 mmol, 1.00 equiv), bis(triphenylphosphine)palladium(II) dichloride (200 mg, 0.28 mmol, 0.22 equiv), and triethylamine (0.5 mL) in methanol (4 mL) was stirred under carbon monoxide (10 atm) in a 50-mL pressure reactor overnight at 110 °C. The solid material was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1/1) to

give 100 mg (43%) of the title compound as a yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 8.16 (s, 1H), 8.08 (d, $J = 9.6$ Hz, 1H), 7.94 (s, 1H), 7.77 (d, $J = 9.6$ Hz, 1H), 4.09 (s, 3H).

Step 3. A mixture of imidazo[1,2-b]pyridazine-6-carboxylic acid methyl ester (900 mg, 5.08 mmol, 1.00 equiv) and 5% aqueous sodium hydroxide solution (15 mL, 3.75 equiv) in THF (3 mL) was stirred overnight at rt. The pH value of the solution was adjusted to 2 with 1 M HCl. The resulting mixture was concentrated under vacuum to give 3 g of crude title product as a yellow solid. The crude product was used without further purification. LC/MS (Method A, ESI): RT= 0.43 min, m/z = 164.0 $[\text{M}+\text{H}]^+$.

Intermediate 8: Pyrazolo[1,5-a]pyridine-5-carboxylic acid



Step 1. 1-Amino-4-methoxypyridinium iodide. A solution of aminooxysulfonic acid (11.4 g, 100.80 mmol, 0.50 equiv) and 4-methoxypyridine (22 g, 201.60 mmol, 1.00 equiv) in water (200 mL) was stirred under nitrogen for 0.5 h at 90 °C. Potassium carbonate (14 g, 101.30 mmol, 0.50 equiv) was added at rt. The resulting mixture was concentrated under vacuum then ethanol (150 mL) was added to dissolve the residue. The insoluble material was removed by filtration. The filtrate was cooled to -20 °C and then hydroiodic acid (16 g, 40%) was added. The resulting solution was stirred for 1 h at -20 °C. The precipitated product was collected by filtration and washed with cold ethanol to give 9.3 g (46%) of the title compound as a white solid. TLC: 1:5 MeOH/DCM, $R_f = 0.02$.

Step 2. 5-Methoxy-pyrazolo[1,5-a]pyridine-3-carboxylic acid methyl ester. A mixture of 1-amino-4-methoxypyridinium iodide (6 g, 23.80 mmol, 1.00 equiv), potassium carbonate (5 g, 36.18 mmol, 1.50 equiv), and methyl propiolate (2 g, 23.79 mmol, 1.00 equiv) in DMF (50 mL) was stirred under nitrogen for 4 h at rt. After the reaction completed, the mixture was concentrated under vacuum. The residue was dissolved in 150 mL of dichloromethane and then washed with 1x20 mL of saturated aqueous sodium bicarbonate solution. The organic layer was concentrated under

vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/hexane (1:3) to give 1.5 g (31%) of title product as a solid. LC/MS (Method D, ESI): RT= 1.30 min, m/z = 207.0 $[M+H]^+$.

Step 3. Pyrazolo[1,5-a]pyridin-5-ol. A mixture of methyl 5-methoxypyrazolo[1,5-a]pyridine-3-carboxylate (100 mg, 0.48 mmol, 1.00 equiv) in 40% HBr (5 mL) was stirred for 16 h at 100 °C. The reaction mixture was cooled to rt and the pH value of the solution was adjusted to 8 with 5 M potassium hydroxide solution. The resulting solution was extracted with 2x50 mL of ether. The organic layers were combined and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:3 to 1:1) to yield 20 mg (31%) of the title compound as a white solid. LC/MS (Method D, ESI): RT= 0.41 min, m/z = 135.0 $[M+H]^+$.

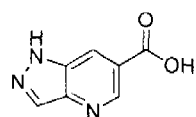
Step 4. Trifluoro-methanesulfonic acid pyrazolo[1,5-a]pyridin-5-yl ester. A mixture of pyrazolo[1,5-a]pyridin-5-ol (300 mg, 2.24 mmol, 1.00 equiv) and trifluoromethanesulfonic anhydride (0.5 mL) in pyridine (5 mL) was stirred for 10 h at rt. The resulting mixture was concentrated under vacuum and the residue was dissolved in 100 mL of dichloromethane. The mixture was washed with 1x10 mL of sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:3) to yield 200 mg (34%) of the title compound as a solid. LC/MS (Method B, ESI): RT= 2.13 min, m/z = 267.0 $[M+H]^+$.

Step 5. Pyrazolo[1,5-a]pyridine-5-carboxylic acid methyl ester. A mixture of trifluoro-methanesulfonic acid pyrazolo[1,5-a]pyridin-5-yl ester (200 mg, 0.75 mmol, 1.00 equiv), triethylamine (227 mg, 2.24 mmol, 3.00 equiv), DMSO (98 mg, 1.25 mmol, 1.67 equiv), and bis(triphenylphosphine)palladium(II) dichloride (53 mg, 0.08 mmol, 0.10 equiv) in methanol (20 mL) was stirred under carbon monoxide (10 atm) for 16 h at 100 °C in a 50-mL pressure reactor. After the reaction completed, the reaction mixture was cooled to rt and the mixture was concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum

ether (1:3) to afford 130 mg of the title compound as a solid. LC/MS (Method H, ESI): RT= 1.36 min, $m/z = 177.0$ $[M+H]^+$.

Step 6. A mixture of pyrazolo[1,5-a]pyridine-5-carboxylic acid methyl ester (130 mg, 0.74 mmol, 1.00 equiv) and potassium hydroxide (1 g, 17.82 mmol, 24.15 equiv) in methanol (2 mL), THF (2 mL), and water (5 mL) was stirred for 12 h at rt. The reaction mixture was washed with 2x50 mL of ethyl acetate. The aqueous layer was collected and the pH value of the solution was adjusted to 6 with 1 N HCl. The solution was extracted with 5x50 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to give 100 mg (84%) the title compound as a yellow solid. LC/MS (Method G, ESI): RT= 1.32 min, $m/z = 163.0$ $[M+H]^+$.

Intermediate 9: 1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid



Step 1. 5-Bromo-2-methyl-pyridin-3-ylamine. To a stirred mixture of iron filings (5 g, 89.29 mmol, 3.88 equiv) and ammonium chloride (1 g, 18.70 mmol, 0.81 equiv) in ethanol (66 mL) and water (33 mL) was added a solution of 5-bromo-2-methyl-3-nitropyridine (5 g, 23.04 mmol, 1.00 equiv) in ethanol (50 mL) dropwise at 90 °C. The reaction mixture was stirred for 10 min at 90 °C and then cooled to rt. The solid material was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:2) to yield 1.6 g (37%) of the title compound as a yellow solid. LC/MS (Method I, ESI): RT= 0.81 min, $m/z = 187.0$; 189.0 $[M+H]^+$.

Step 2. N-(5-Bromo-2-methyl-pyridin-3-yl)-acetamide. A solution of 5-bromo-2-methyl-pyridin-3-ylamine (3 g, 16.04 mmol, 1.00 equiv) in acetic anhydride (20 mL) and acetic acid (10 mL) was stirred overnight at rt. The resulting mixture was concentrated under vacuum to give 2.6 g (71%) of the title compound as a light yellow solid. LC/MS (Method I, ESI): RT= 1.05 min, $m/z = 229.0$; 231.0 $[M+H]^+$.

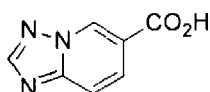
Step 3. 1-(6-Bromo-pyrazolo[4,3-b]pyridin-1-yl)-ethanone. A mixture of N-(5-bromo-2-methyl-pyridin-3-yl)-acetamide (3.5 g, 15.28 mmol, 1.00 equiv),

isopentyl nitrite (4 g, 34.73 mmol, 2.27 equiv), potassium acetate (20 g), and acetic anhydride (30 mL) in toluene (150 mL) was stirred under nitrogen overnight at 90 °C. The reaction mixture was cooled to rt and the solid material was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:5) to give in 2 g (55%) of the title compound as a light yellow solid. LC/MS (Method I, ESI): RT= 1.44 min, m/z = 240.0; 242.0 $[M+H]^+$.

Step 4. 1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid methyl ester. A mixture of 1-(6-bromo-pyrazolo[4,3-b]pyridin-1-yl)-ethanone (2 g, 8.33 mmol, 1.00 equiv), bis(triphenylphosphine)palladium(II) dichloride (1 g, 1.42 mmol, 0.17 equiv), and triethylamine (2.5 mL) in methanol (70 mL) was stirred overnight under carbon monoxide (10 atmospheres) at 100 °C in a 100 mL pressure reactor. The reaction mixture was cooled to rt and the solid material was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:5) to afford 0.8 g (54%) of the title compound as a light yellow solid. TLC: 1:1 ethyl acetate/petroleum ether, R_f = 0.2.

Step 5. A solution 1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid methyl ester (200 mg, 1.13 mmol, 1.00 equiv) and sodium hydroxide (200 mg, 5.00 mmol, 4.43 equiv) in water (10 mL) was stirred overnight at rt. After the reaction was complete, the pH value of the solution was adjusted to 3 with concentrated HCl. The resulting mixture was concentrated under vacuum to give 1 g of crude title product as a light yellow solid. LC/MS (Method I, ESI): RT= 0.91 min, m/z = 164.0; 242.0 $[M+H]^+$.

Intermediate 10: [1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid



Step 1. N'-(5-Bromo-pyridin-2-yl)-N,N-dimethyl-formamidine. A solution of 5-bromopyridin-2-amine (4 g, 23.12 mmol, 1.00 equiv) and N,N-dimethylformamide dimethyl acetal (9.6 mL, 3.00 equiv) in DMF (30 mL) was stirred under nitrogen for 12 h at 130 °C. The reaction mixture was cooled to rt and then concentrated under

vacuum to give 4 g (76%) of the title compound as an oil. TLC: 1:5 MeOH/DCM, R_f = 0.6.

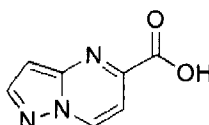
Step 2. 6-Bromo-[1,2,4]triazolo[1,5-a]pyridine. To a solution of N'-(5-bromo-pyridin-2-yl)-N,N-dimethyl-formamidine (4 g, 17.54 mmol, 1.00 equiv) in
5 methanol (40 mL) maintained under nitrogen at 0 °C was added pyridine (4 mL, 2.00 equiv) and (aminooxy)sulfonic acid (3.6 g, 31.83 mmol, 1.30 equiv). The resulting solution was stirred for 12 h at rt. After the reaction completed, the mixture was concentrated under vacuum. The residue was diluted with 150 mL of ethyl acetate then washed with 1x50 mL of saturated aqueous sodium carbonate solution and 2x50
10 mL of water. The organic layer was dried over anhydrous sodium sulfate then concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/hexane (1:1) to give 2.5 g (72%) title compound as a solid. LC/MS (Method D, ESI): RT= 1.15 min, m/z = 198.0 $[M+H]^+$.

Step 3. [1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid methyl ester. A
15 mixture of 6-bromo-[1,2,4]triazolo[1,5-a]pyridine (2.4 g, 12.12 mmol, 1.00 equiv), bis(triphenylphosphine)palladium(II) dichloride (800 mg, 1.14 mmol, 0.10 equiv) and triethylamine (4 g, 39.53 mmol, 3.00 equiv) in DMSO (1.6 g, 20.48 mmol, 1.67 equiv) and methanol (50 mL) was stirred under carbon monoxide (10 atm) for 20 h at 100 °C. The reaction mixture was cooled to rt and quenched with brine (50 mL). The resulting
20 solution was extracted with ethyl acetate (3x40 mL). The combined organic layers were dried over anhydrous sodium sulfate then concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/hexane (1:1) to give 0.98 g (46%) of the title compound as a crude solid. LC/MS (Method C, ESI): RT= 1.04 min, m/z = 178.0 $[M+H]^+$.

Step 4. A solution of [1,2,4]triazolo[1,5-a]pyridine-6-carboxylic acid methyl
25 ester (200 mg, 1.13 mmol, 1.00 equiv) in THF (2 mL) was added to a solution of potassium hydroxide (1 g, 17.82 mmol, 15.79 equiv) in water (10 mL). The resulting mixture was stirred for 10 h at rt. After the reaction completed, the pH value of the solution was adjusted to 5-6 with 1 N HCl. The mixture was extracted with 3x50 mL
30 of ethyl acetate. The combined organic layers were dried over anhydrous sodium

sulfate and concentrated under vacuum to give 112 mg (61%) of the title compound as a solid. LC/MS (Method C, ESI): RT = 0.9 min, $m/z = 164.0$ $[M+H]^+$.

Intermediate 11: Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid



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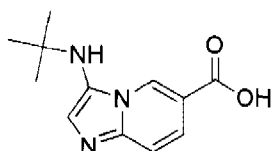
Step 1. 4H-Pyrazolo[1,5-a]pyrimidin-5-one. A solution of 1H-pyrazol-3-ylamine (7 g, 84.24 mmol, 1.00 equiv) and ethyl prop-2-ynoate (50 mL) in dioxane (10 g, 1.21 equiv) was stirred under nitrogen overnight at 110 °C. The reaction mixture was cooled to rt and the precipitated product was collected by filtration to give 4 g (36%) of the title compound as a light brown solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 8.44-8.41 (m, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 5.88 (d, *J* = 8.1 Hz, 1H), 5.79-5.76 (m, 1H).

Step 2. 5-Chloro-pyrazolo[1,5-a]pyrimidine. A solution of 4H-pyrazolo[1,5-a]pyrimidin-5-one (1 g, 7.40 mmol, 1.00 equiv) in phosphorus oxychloride (15 mL) was stirred under nitrogen for 2 h at 120 °C. The reaction mixture was cooled to rt then concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:2) to give 0.6 g (53%) of the title compound as a light yellow solid. LC/MS (Method I, ESI): RT = 1.21 min, $m/z = 154.0$ $[M+H]^+$.

Step 3. Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid methyl ester. A mixture of 5-chloro-pyrazolo[1,5-a]pyrimidine (2 g, 13.02 mmol, 1.00 equiv), triethylamine (4 mL), methanol (80 mL), and bis(triphenylphosphine)palladium(II) dichloride (1 g, 1.42 mmol, 0.11 equiv) was stirred in a 100-mL pressure reactor overnight at 100 °C under 10 atmospheres of carbon monoxide. The reaction mixture was cooled to rt then concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:5) to yield 1.2 g (52%) of the title compound as a light yellow solid. LC/MS (Method I, ESI): RT = 1.09 min, $m/z = 178.0$ $[M+H]^+$.

Step 4. To a solution of methyl pyrazolo[1,5-a]pyrimidine-5-carboxylic acid methyl ester (100 mg, 0.56 mmol, 1.00 equiv) in acetic acid (5 mL) was added concentrated HCl (37%, 5 mL). The resulting solution was stirred for 3 h at 120 °C, then concentrated under vacuum. The residue was dissolved in 3 mL of water and then adjusted to pH 5 with saturated aqueous sodium carbonate solution. The precipitated product was collected by filtration then air-dried to give 0.08 g (87%) of pyrazolo[1,5-a]pyrimidine-5-carboxylic acid as a light yellow solid. LC/MS (Method 1, ESI): RT= 0.95 min, $m/z = 164.0$ $[M+H]^+$.

10 Intermediate 12: 3-tert-Butylamino-imidazo[1,2-a]pyridine-6-carboxylic acid



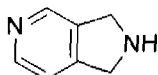
Step 1. 3-tert-Butylamino-imidazo[1,2-a]pyridine-6-carboxylic acid methyl ester. To a solution of methyl 6-aminopyridine-3-carboxylate (3.8 g, 24.98 mmol, 1.00 equiv) and 2-oxoacetic acid hydrate (3.9 g, 42.39 mmol, 1.70 equiv) in methanol (120 mL) was added perchloric acid (250 mg, 2.50 mmol, 0.10 equiv). The reaction mixture was stirred for 30 min and 2-isocyano-2-methylpropane (2.08 g, 25.02 mmol, 1.00 equiv) was then added. The reaction mixture was stirred for 12 h at rt and then concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/ethyl acetate (2:1) to give 850 mg (14%) of the title compound as a yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 8.97-8.96 (dd, $J = 0.9, 1.5$ Hz, 1H), 7.69-7.65 (dd, $J = 4.2, 9.6$ Hz, 1H), 7.53-7.50 (dd, $J = 4.2, 9.6$ Hz, 1H), 7.39 (s, 1H), 3.96 (s, 3H), 1.23 (s, 9H).

Step 2. Sodium 3-tert-Butylamino-imidazo[1,2-a]pyridine-6-carboxylate. To a solution of 3-tert-butylamino-imidazo[1,2-a]pyridine-6-carboxylic acid methyl ester (300 mg, 1.21 mmol, 1.00 equiv) in methanol (5 mL) was added a solution of sodium hydroxide (97 mg, 2.42 mmol, 2.00 equiv) in water (5 mL). The resulting solution was stirred for 1.5 h at 46 °C. The reaction mixture was cooled to rt and then quenched by the addition of 0.15 mL of HCl. The resulting mixture was concentrated under vacuum to give 345.6 mg (crude) of the title product as a yellow solid. LC/MS

(Method I, ESI): RT = 1.02 min, $m/z = 234.0$ [M+H - 22]⁺.

Step 3. Sodium 3-tert-butylamino-imidazo[1,2-a]pyridine-6-carboxylate (300 mg, 1.17 mmol, 1.00 equiv) was dissolved in acetic acid (10 mL) and then concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (20:1) to give 150 mg (54%) of the title compound as a yellow solid. LC/MS (Method F, ESI): RT = 0.94 min, $m/z = 234.0$ [M+H]⁺.

Intermediate 13: 2,3-Dihydro-1H-pyrrolo[3,4-c]pyridine.



Step 1. Ethyl N-(prop-2-yn-1-yl)carbamate. To a solution of prop-2-yn-1-amine (11.5 g, 208.79 mmol, 1.00 equiv) and sodium hydroxide (9.1 g, 227.50 mmol, 1.09 equiv) in water (40 mL) and toluene (110 mL) maintained under nitrogen was added ethyl chloroformate (23.9 g, 220.23 mmol, 1.05 equiv) dropwise in 20 min with stirring at 10 °C. The resulting solution was stirred overnight at rt then extracted with 3x100 mL of toluene. The combined organic layers were dried over anhydrous sodium sulfate then concentrated under vacuum to give 15 g (57%) of ethyl N-(prop-2-yn-1-yl)carbamate as a light yellow oil. TLC: ethyl acetate/petroleum ether (1:2), $R_f = 0.5$.

Step 2. Pyrimidine-5-carboxaldehyde. To a solution of 5-bromopyrimidine (2 g, 12.58 mmol, 1.00 equiv) in THF (20 mL) placed in a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was added n-butyllithium (1.1 mL) at -78 °C. The reaction mixture was stirred at -78 °C for another 2 h. Ethyl formate (5.2 mL) was then added and the resulting solution was stirred for 2 h at -78 °C. The resulting mixture was warmed to 0 °C and washed with 50 mL of brine. The organic layer was dried with anhydrous sodium carbonate and concentrated. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:1) to give 11 g of crude pyrimidine-5-carboxaldehyde as a yellow oil. TLC: ethyl acetate/petroleum ether (1/1), $R_f = 0.2$.

Step 3. Pyrimidin-5-ylmethanol. A mixture of pyrimidine-5-carboxaldehyde (2 g, 18.50 mmol, 1.00 equiv) and sodium borohydride (2 g) in methanol (100 mL)

was stirred at 0 - 10°C for 30 min. The reaction mixture was concentrated under vacuum and the residue was purified on a silica gel column eluted with dichloromethane/methanol (50:1) to yield 1.2 g (59%) of pyrimidin-5-ylmethanol (commercially available, CAS Reg. No. 25193-95-7) as a light yellow solid. LC/MS (Method N, ESI): RT= 0.74 min, $m/z = 111.0 [M+H]^+$.

Step 4. 5-(Chloromethyl)pyrimidine. To a solution of pyrimidin-5-ylmethanol (1.1 g, 10 mmol, 1.00 equiv) in dichloromethane (30 mL) was added thionyl chloride (2 mL) dropwise with stirring. The resulting solution was stirred at rt for 2 h then concentrated in vacuum to give 1.1 g of crude 5-(chloromethyl)pyrimidine as a yellow oil. TLC: ethyl acetate/petroleum ether (1:1), $R_f = 0.4$.

Step 5. Ethyl N-(prop-2-yn-1-yl)-N-(pyrimidin-5-ylmethyl)carbamate. A mixture of ethyl N-(prop-2-yn-1-yl)carbamate (1.27 g, 9.99 mmol, 1.00 equiv) benzyltriethylammonium chloride (500 mg, 2.60 mmol, 0.26 equiv), 5-(chloromethyl)pyrimidine (1.28 g, 9.96 mmol, 1.00 equiv) and potassium hydroxide (3 g, 53.47 mmol, 5.37 equiv) in toluene (30 mL) was stirred overnight under nitrogen at rt. The resulting mixture was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:1) to afford 0.3 g (14%) of ethyl N-(prop-2-yn-1-yl)-N-(pyrimidin-5-ylmethyl)carbamate as a light yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 9.16 (s, 1H), 8.73 (s, 2H), 4.59 (s, 2H), 4.26-4.11 (m, 4H), 2.28 (t, $J = 2.4$ Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H).

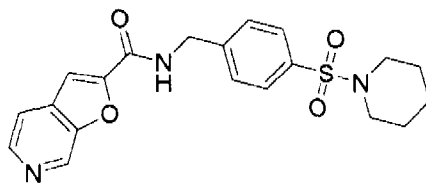
Step 6. Ethyl 1H,2H,3H-Pyrrolo[3,4-c]pyridine-2-carboxylate. A mixture of ethyl N-(prop-2-yn-1-yl)-N-(pyrimidin-5-ylmethyl)carbamate (1 g, 4.56 mmol, 1.00 equiv) in xylene (30 mL) was stirred under nitrogen at 150 °C for 2 days. The resulting mixture was concentrated under vacuum and the residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1/2) to give 0.4 g (46%) of ethyl 1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a light brown crude solid. ^1H NMR (300 MHz, CDCl_3) δ 8.93-8.53 (m, 2H), 7.24 (d, $J = 5.1$ Hz, 1H), 4.80-4.73 (m, 4H), 4.33-4.22 (m, 2H), 1.49-1.33 (m, 3H).

Step 7. 2,3-Dihydro-1H-pyrrolo[3,4-c]pyridine. A mixture of ethyl 1H,2H,3H-pyrrolo[3,4-c]pyridine-2(3H)-carboxylate (400 mg, 2.4 mmol, 1.00 equiv)

and barium hydroxide (0.8 g) in water (100 mL) was stirred overnight at 120 °C. The reaction mixture was cooled to rt and the solid material was collected by filtration. The residue was stirred in hot ethyl acetate (150 mL) and then filtered to remove solid material. The filtrate was concentrated under vacuum to give 0.18 g (72%) of 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine as a light yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 8.51 (s, 1H), 8.45-8.41 (t, *J* = 4.8 Hz, 1H), 7.20-7.13 (m, 1H), 4.25 (s, 2H), 4.22 (s, 2H).

II. Preparation of Example Compounds

Example 5: Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide



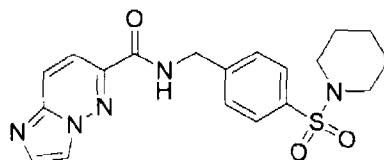
Step 1. 4-(Piperidine-1-sulfonyl)-benzonitrile. A solution of 4-cyano-benzenesulfonyl chloride (1 g, 4.86 mmol, 1.00 equiv), piperidine (500 mg, 5.75 mmol, 1.18 equiv), and triethylamine (1.5 g, 14.55 mmol, 2.99 equiv) in dichloromethane (10 mL) was stirred for 1 h at rt. The reaction was quenched by the addition of 200 mL of water and the resulting solution was extracted with 100 mL of dichloromethane. The combined organic layers were washed with 3x100 mL of water, dried over anhydrous sodium sulfate and concentrated under vacuum to give 0.8 g (66%) of the title compound as a white solid. LC/MS (Method H, ESI): RT = 1.49 min, *m/z* = 251.0 [M + H]⁺.

Step 2. 4-(Piperidine-1-sulfonyl)-benzylamine. To a solution of 4-(piperidine-1-sulfonyl)-benzonitrile (2 g, 7.83 mmol, 1.00 equiv) in methanol (40 mL) was added Raney Ni (0.2 g, 0.10 equiv) and ammonium hydroxide (4 mL, 28-30% aqueous solution). The reaction mixture was stirred under 1 atmosphere of hydrogen overnight at rt. The catalyst was removed by filtration. The filtrate was concentrated under vacuum and the residue was purified on a silica gel column eluted with

dichloromethane/methanol (1/30) to give 500 mg (25%) of the title compound as a light yellow oil. LC/MS (Method H, ESI): RT = 1.08 min, m/z = 255.0 $[M + H]^+$.

Step 3. Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide. A solution of 4-(piperidine-1-sulfonyl)-benzylamine (500 mg, 1.93 mmol, 1.00 equiv, furo[2,3-c]pyridine-2-carboxylic acid (355 mg, 2.13 mmol, 1.11 equiv), DIPEA (762 mg, 5.79 mmol, 3.00 equiv), and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (1044 mg, 2.31 mmol, 1.20 equiv) in DMF (5 mL) was stirred overnight at rt. The reaction was quenched by the addition of 20 mL of water. The precipitated product was collected by filtration and re-crystallized from ethanol to give 304.8 mg (40%) of the title compound as a light brown solid. ^1H NMR (300 MHz, DMSO- d_6) δ 9.67-9.63 (t, J = 6 Hz, 1H), 9.06 (s, 1H), 8.49-8.48 (d, J = 3 Hz, 1H), 7.84-7.83 (t, J = 3 Hz, 1H), 7.71-7.69 (d, J = 4 Hz, 3H), 7.59-7.57 (d, J = 6 Hz, 2H), 4.60 (d, J = 6.3 Hz, 2H), 2.89-2.84 (m, 4H), 1.61-1.50 (m, 4H), 1.36-1.34 (m, 2H). LC/MS (Method H, ESI): RT = 1.20 min, m/z = 400.0 $[M + H]^+$.

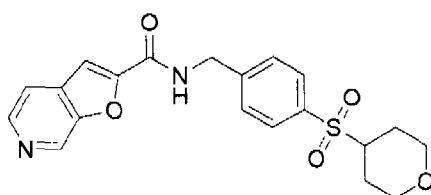
Example 16: Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide



A solution of imidazo[1,2-b]pyridazine-6-carboxylic acid (1 g, crude), 4-(piperidine-1-sulfonyl)-benzylamine (100 mg, 0.39 mmol, 1.00 equiv), HOBt (64 mg, 0.47 mmol, 1.20 equiv), EDCI (91 mg, 0.47 mmol, 1.21 equiv), and DIPEA (300 mg, 2.32 mmol, 5.90 equiv) in DMF (3 mL) was stirred for 30 min at rt. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 4x50 mL of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1/1 to 3/2) to give 39.6 mg (25%) of the title compound as a white solid. LC/MS (Method C, ESI): RT= 2.03 min, m/z = 400.2 $[M+H]^+$. ^1H NMR (300 MHz, CDCl_3) δ 8.14 (d, J =

9.3 Hz, 1H), 8.01 (s, 1H), 7.97 (s, 1H), 7.92 (d, $J = 5.4$ Hz, 1H), 7.88 (s, 1H), 7.75 (d, $J \approx 8.1$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H), 4.78 (d, $J = 6.3$ Hz, 2H), 3.01-2.97 (m, 4H), 1.68-1.60 (m, 4H), 1.46-1.42 (m, 2H).

5 Example 24: Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-4-sulfonyl)-benzylamide



Step 1. Tetrahydro-pyran-4-thione. Hydrogen sulfide gas was bubbled into a solution of tetrahydro-pyran-4-one (10 g, 99.88 mmol, 1.00 equiv) in isopropanol (100 mL) at 0-5 °C. The resulting solution was stirred at 0-5 °C for 4 h. Nitrogen gas was then bubbled into the solution to remove the excess hydrogen sulfide gas. The resulting mixture was concentrated under vacuum and the residue was used in the next step without further purification. TLC (5:1 petroleum ether/ethyl acetate): $R_f = 0.4$.

15 Step 2. Tetrahydro-pyran-4-thiol. To a solution of the crude tetrahydro-pyran-4-thione (11.6 g, 99.84 mmol, 1.00 equiv) in ethanol (100 mL) maintained under nitrogen was added sodium borohydride (5.7 g, 150.67 mmol, 1.50 equiv) in several batches. The resulting solution was stirred for 2 h at 80 °C. After cooling to rt, the reaction mixture was quenched by the addition of 100 mL of water and then concentrated under vacuum to half of its original volume. The mixture was extracted with 3x300 mL of ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to give 5 g (42%) of the title compound as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 3.93-3.83 (m, 2H), 3.81-3.74 (m, 1H), 3.38 (dt, $J = 2.4, 10.2$ Hz, 2H), 2.07 (s, 1H), 1.84 (dd, $J = 2.4, 10.5$ Hz, 2H), 1.59-1.44 (m, 2H).

Step 3. 4-(Tetrahydro-pyran-4-ylsulfonyl)-benzonitrile. A mixture of tetrahydro-pyran-4-thiol (4.2 g, 35.53 mmol, 1.20 equiv), 4-fluorobenzonitrile (3.6 g, 29.72 mmol, 1.00 equiv), and potassium carbonate (12.3 g, 89.00 mmol, 2.99 equiv)

in DF=MF (50 mL) was stirred under nitrogen for 6 h at 80 °C. The reaction mixture was cooled to rt and then quenched with 200 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was
5 purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:10 to 1:5) to give 700 mg (11%) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, *J* = 6.6 Hz, 2H), 7.35 (d, *J* = 12 Hz, 2H), 3.99-3.92 (m, 2H), 3.52-3.40 (m, 3H), 1.97-1.92 (m, 2H), 1.75-1.66 (m, 2H).

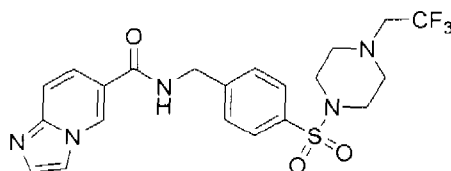
Step 4. 4-(Tetrahydro-pyran-4-sulfonyl)-benzonitrile. To a solution of 4-
10 (tetrahydro-pyran-4-ylsulfanyl)-benzonitrile (700 mg, 3.19 mmol, 1.00 equiv) in chloroform (20 mL) at 0-5 °C was added *m*-chloroperbenzoic acid (2.75 g, 15.94 mmol, 4.99 equiv) in several batches. The resulting solution was stirred for 6 h at rt and then diluted with 100 mL of chloroform. The mixture was washed with aqueous sodium bisulfite (2x200 mL), 1 N sodium hydroxide (2x200 mL), and brine (3x200
15 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:10 to 1:2) to give 400 mg (50%) of the title compound as a white solid. TLC (5:1 petroleum ether/ethyl acetate): *R*_f = 0.3.

Step 5. 4-(Tetrahydro-pyran-4-ylsulfanyl)-benzonitrile. To a solution of 4-
20 (tetrahydro-pyran-4-sulfonyl)-benzonitrile (400 mg, 1.59 mmol, 1.00 equiv) in methanol (20 mL) was added ammonium hydroxide (3 mL, 28-30% aqueous solution) followed by Raney Ni (500 mg). The resulting solution was stirred under 1 atmosphere of hydrogen for 5 h at rt. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to give 400 mg of crude title product as a
25 white solid. LC/MS (Method G, ESI): RT = 1.02 min, *m/z* = 256.0 [*M* + *H*]⁺.

Step 6. A solution of furo[2,3-*c*]pyridine-2-carboxylic acid (60.5 mg, 0.37 mmol, 1.10 equiv), 4-(tetrahydro-pyran-4-ylsulfanyl)-benzonitrile (86 mg, 0.34 mmol, 1.00 equiv), EDCI (129 mg, 0.67 mmol, 2.00 equiv), HOBt (55 mg, 0.41 mmol, 1.21 equiv), and triethylamine (102.2 mg, 1.01 mmol, 3.00 equiv) in DMF (10 mL) was
30 stirred overnight at rt. The reaction mixture was diluted with 100 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate. The combined

organic layers were washed with 3x100 mL of brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (50:1 to 30:1) to give 37.1 mg (28%) the title compound as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.64 (t, *J* = 6.3 Hz, 1H), 9.06 (s, 1H), 8.48 (d, *J* = 5.4 Hz, 1H), 7.84-7.80 (m, 3H), 7.66-7.61 (m, 3H), 4.61 (d, *J* = 6.0 Hz, 2H), 3.90-3.85 (m, 2H), 3.59-3.46 (m, 1H), 3.25-3.21 (m, 2H), 1.71-1.68 (m, 2H), 1.56-1.44 (m, 2H). LC/MS (Method F, ESI): RT = 1.12 min, *m/z* = 401.2 [M + H]⁺.

10 Example 25: Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide



Step 1. 4-(4-Cyano-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester. A solution of 4-cyanobenzene-1-sulfonyl chloride (2 g, 9.92 mmol, 1.00 equiv),
 15 tert-butyl piperazine-1-carboxylate (1.86 g, 9.99 mmol, 1.00 equiv), and DIPEA (3.87 g, 29.94 mmol, 3.00 equiv) in dichloromethane (40 mL) was stirred for 12 h at 25 °C. The resulting solution was washed with 1x50 mL of water and 1x50 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum and the residue was purified on a silica gel column eluted with
 20 dichloromethane/ethyl acetate (25%) to give 2.7 g (77%) of the title compound as a white solid. LC/MS (Method B, ESI): RT = 2.12 min, *m/z* = 252.0 [M-100+H]⁺.

Step 2. 4-(Piperazine-1-sulfonyl)-benzonitrile. To a solution 4-(4-cyano-benzenesulfonyl)-piperazine-1-carboxylic acid tert-butyl ester (2.7 g, 7.68 mmol, 1.00 equiv) in dichloromethane (50 mL) was added TFA (10 mL) dropwise with stirring at
 25 25 °C in 10 min. The resulting solution was stirred for 5 h at 25 °C and then concentrated under vacuum. The residue was dissolved in 100 mL of dichloromethane then washed sequentially with aqueous sodium bicarbonate solution (1x100 mL), water (1x100 mL), and brine (1x100 mL). The organic layer was dried

over anhydrous sodium sulfate and concentrated under vacuum to give 1.8 g (93%) of the title compound as a white solid. LC/MS (Method J, ESI): RT= 1.03 min, m/z = 252.0 $[M+H]^+$.

5 Step 3. 4-[4-(2,2,2-Trifluoro-ethyl)-piperazine-1-sulfonyl]-benzonitrile. To a solution of 4-(piperazine-1-sulfonyl)-benzonitrile (150 mg, 0.60 mmol, 1.00 equiv) and DIPEA (232 mg, 1.80 mmol, 3.00 equiv) in DMF (5 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (208 mg, 0.90 mmol, 1.50 equiv) dropwise with stirring in 10 min. The resulting solution was stirred for 12 h at 25 °C and then quenched by the addition of 30 mL of water. The resulting solution was extracted
10 with 2x20 mL of dichloromethane. The combined organic layers were washed with 2x50 mL of brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified on a silica gel column with eluted 20% ethyl acetate/petroleum ether to give 150 mg (75%) of the title compound as a white solid. LC/MS (Method I, ESI): RT= 1.05 min, m/z = 334.0 $[M+H]^+$.

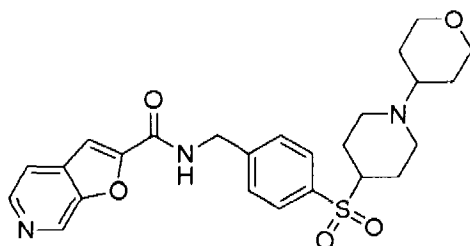
15 Step 4. 4-[4-(2,2,2-Trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamine. To a solution of 4-[4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzonitrile (150 mg, 0.45 mmol, 1.00 equiv) in methanolic ammonia solution (10 mL) was added Raney Ni (300 mg). The reaction mixture was stirred under 1 atmosphere of hydrogen for 2 h at 25 °C. The catalyst was removed by filtration and the filtrate was concentrated
20 under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (95/5) to give 80 mg (53%) of the title compound as a white solid. LC/MS (Method I, ESI): RT= 1.12 min, m/z = 338.0 $[M+H]^+$.

Step 5. A solution of imidazo[1,2-a]pyridine-6-carboxylic acid (58 mg, 0.36 mmol, 1.50 equiv), EDCI (55 mg, 0.29 mmol, 1.20 equiv), HOBt (39 mg, 0.29 mmol, 1.20 equiv), and DIPEA (93 mg, 0.72 mmol, 3.00 equiv) in DMF (10 mL) was stirred
25 at 25 °C for 10 min. 4-[4-(2,2,2-Trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamine (82 mg, 0.24 mmol, 1.00 equiv) was then added and the mixture was stirred for 12 h at 25 °C. The reaction was then quenched by the addition of 50 mL of water and the resulting solution was extracted with 2x50 mL of dichloromethane. The combined
30 organic layers were washed with 100 mL of brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified on a silica gel

column eluted with dichloromethane/methanol (100/5) to give 24.1 mg (21%) of the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.93 (s, 1H), 7.69-7.28 (m, 9H), 4.75 (s, 2H), 3.03-2.88 (m, 6H), 2.84-2.68 (m, 4H). LC/MS (Method B, ESI): RT= 1.93 min, m/z = 482.2 $[\text{M}+\text{H}]^+$.

5

Example 47: Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide



Step 1. 4-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester. To a solution of piperidin-4-ol (50.5 g, 499.27 mmol, 1.00 equiv) and triethylamine (75 g, 741.18 mmol, 1.16 equiv) in dichloromethane (800 mL) was added di-tert-butyl dicarbonate (130 g, 595.66 mmol, 1.19 equiv) at 0 °C. The mixture was warmed to rt and then stirred overnight. The resulting solution was concentrated to 300 mL in volume under vacuum then washed with 3x100 mL of water and 3x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 110 g of crude title product as light yellow oil. TLC: 1:1 ethyl acetate/petroleum ether, R_f = 0.6.

Step 2. 4-(4-Bromo-phenylsulfonyl)-piperidine-1-carboxylic acid tert-butyl ester. To a solution of 4-bromobenzene-1-thiol (46 g, 243.29 mmol, 1.22 equiv), 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (40 g, 198.75 mmol, 1.00 equiv), and triphenylphosphine (72 g) in THF (800 mL) maintained under nitrogen atmosphere was added diethyl azodicarboxylate (50 g, 287.11 mmol, 1.44 equiv) dropwise within 30 min. The reaction mixture was stirred for 16 h at rt then concentrated under vacuum. The residue was dissolved in 1000 mL of ethyl acetate then washed with 2x400 mL of water and 2x400 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:9) to give 30

g (41%) of the title compound as a colorless oil. TLC: 1:10 ethyl acetate/petroleum ether, R_f = 0.4.

Step 3. 4-(4-Bromo-benzenesulfonyl)-piperidine-1-carboxylic acid tert-butyl ester. To a solution of 4-(4-bromo-phenylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester (30 g, 80.58 mmol, 1.00 equiv) in dichloromethane (500 mL) was added m-chloroperoxybenzoic acid (50 g, 289.74 mmol, 3.02 equiv) in several portions. The resulting solution was stirred for 2 h at rt. After the reaction completed, the reaction mixture was washed sequentially with 2x200 mL of saturated potassium carbonate solution, 2x200 mL of water, and 2x200 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:6) to afford 27 g (83%) of the title compound as a white solid. LC/MS (Method C, ESI): RT = 1.55 min, m/z = 348.0, 350.0 [M-56+H]⁺.

Step 4. 4-(4-Cyano-benzenesulfonyl)-piperidine-1-carboxylic acid tert-butyl ester. A mixture of 4-(4-bromo-benzenesulfonyl)-piperidine-1-carboxylic acid tert-butyl ester (25 g, 61.83 mmol, 1.00 equiv), tetrakis(triphenylphosphine)palladium (7 g, 6.06 mmol, 0.10 equiv), and zinc cyanide (8.6 g) in DMF (400 mL) was stirred overnight at 85 °C under nitrogen atmosphere. The reaction mixture was quenched with 1 L of ice/water. The precipitate was collected by filtration and washed with water. The solid was dissolved in a minimal amount of methylene chloride and then purified on a silica gel column eluted with ethyl acetate/petroleum ether (6:4) to give 19 g (88%) of the title compound as a white solid. TLC: 1:2 ethyl acetate/petroleum ether, R_f = 0.5.

Step 5. 4-(Piperidine-4-sulfonyl)-benzonitrile hydrochloride. To a saturated solution of hydrogen chloride in 1,4-dioxane (60 mL) was added 4-(4-cyano-benzenesulfonyl)-piperidine-1-carboxylic acid tert-butyl ester (2.5 g, 7.13 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at rt. After the reaction completed, the precipitate was collected by filtration and washed with ether. The solid was dried under vacuum to yield 1.6 g (78%) of the title compound as a white solid. TLC: 1:5 methanol/dichloromethane, R_f = 0.2.

Step 6. 4-[1-(Tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzonitrile. A solution of 4-(piperidine-4-sulfonyl)-benzonitrile hydrochloride (2 g, 6.97 mmol, 1.00 equiv), oxan-4-one (700 mg, 6.99 mmol, 1.00 equiv), triethylamine (1 g, 9.88 mmol, 1.42 equiv), and titanium tetrakisopropoxide (2 g, 7.04 mmol, 1.01 equiv) in ethanol (100 mL) was stirred for 2 h at 60 °C. Sodium cyanoborohydride (2 g) and acetic acid (1.5 mL) were then added and the resulting solution was stirred overnight at 60 °C. The reaction mixture was concentrated under vacuum. The pH value of the solution was adjusted to 1 with 5% aqueous hydrochloric acid solution. The solution was stirred for 1 h at rt and the pH of the solution was then adjusted to 9-10 by adding saturated aqueous sodium carbonate solution. The resulting solution was extracted with 200 mL of ethyl acetate. The organic layer was washed with 100 mL of water then dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (20:1) to give 0.6 g (26%) of the title compound as a white solid. LC/MS (Method I, ESI): RT = 1.02 min, m/z = 335.0 [M+H]⁺.

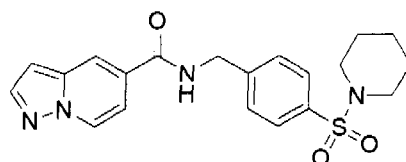
Step 7. 4-[1-(Tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamine. To a solution of 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzonitrile (600 mg, 1.79 mmol, 1.00 equiv) in methanolic ammonia solution (150 mL) was added Raney Ni (2 g). The reaction mixture was stirred under 1 atmosphere of hydrogen for 2 h at rt. The catalyst was removed by filtration and the filtrate was concentrated under vacuum to yield 0.55 g (91%) of the title compound as a gray solid. LC/MS (Method C, ESI): RT = 0.99 min, m/z = 339.0 [M+H]⁺.

Step 8. Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide. A solution of 4-furo[2,3-c]pyridine-2-carboxylic acid (70 mg, 0.43 mmol, 1.45 equiv), EDCI (70 mg, 0.37 mmol, 1.24 equiv), HOBt (52 mg, 0.38 mmol, 1.30 equiv), and triethylamine (0.5 mL) in DMF (4 mL) was stirred for 10 min at rt. 4-[1-(Tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamine (100 mg, 0.30 mmol, 1.00 equiv) was then added and the resulting solution was stirred overnight at 40 °C. The reaction mixture was diluted with 120 mL of ethyl acetate then washed with 2x100 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude

product was purified by Preparative HPLC (column: Xbridge Phenyl 19*150, detection: UV 254 nm, mobile phase A: H₂O containing NH₄HCO₃ 10 mmol/L, mobile phase B: CH₃CN; flow rate: 20 mL/min; B/A = 20%~57%/10 min). This resulted in 19 mg (13%) of the title compound as a light yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.65 (t, *J* = 6.0 Hz, 1H), 9.06 (s, 1H), 8.47 (d, *J* = 5.4 Hz, 1H), 7.84-7.79 (m, 3H), 7.67-7.60 (m, 3H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.85-3.82 (m, 2H), 3.29-3.17 (m, 3H), 2.95-2.86 (m, 2H), 2.45-2.38 (m, 1H), 2.17-1.99 (m, 2H), 1.83-1.79 (m, 2H), 1.60-1.56 (m, 2H), 1.43-1.34 (m, 4H). LC/MS (Method C, ESI): RT = 1.13 min, *m/z* = 484.3 [M+H]⁺.

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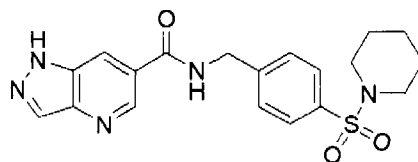
Example 48: Pyrazolo[1,5-a]pyridine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide



A solution pyrazolo[1,5-a]pyridine-5-carboxylic acid (100 mg, 0.62 mmol, 1.00 equiv), 4-(piperidine-1-sulfonyl)-benzylamine (190 mg, 0.75 mmol, 1.20 equiv), DIPEA (240 mg, 3.00 equiv), EDCI (143 mg, 0.75 mmol, 1.20 equiv), and HOBT (101 mg, 0.75 mmol, 1.20 equiv) in DMF (10 mL) was stirred for 12 h at rt. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (20:1) to give 110 mg (45%) of the title compound as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 8.59 (d, *J* = 6.9 Hz, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 6.9 Hz, 1H), 6.90 (br, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 4.77 (d, *J* = 3.6 Hz, 2H), 3.00-2.96 (m, 4H), 1.67-1.61 (m, 4H), 1.47-1.43 (m, 2H). LC/MS (Method D, ESI): RT = 1.81 min, *m/z* = 399.0 [M+H]⁺.

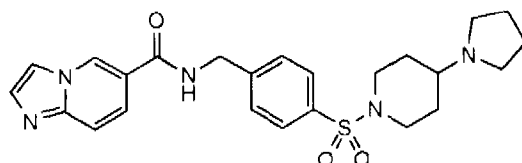
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Example 49: 1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide



A solution of 4-(piperidine-1-sulfonyl)-benzylamine (130 mg, 0.51 mmol, 1.04 equiv), 1H-pyrazolo[4,3-b]pyridine-6-carboxylic acid (80 mg, 0.49 mmol, 1.00 equiv), HOBt (140 mg, 1.04 mmol, 2.11 equiv), EDCI (200 mg, 1.04 mmol, 2.63 equiv), and DIPEA (0.5 mL) in DMF (5 mL) was stirred overnight at rt. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/hexane (5:1) to give 42.3 mg (22%) of the title compound as an off-white solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.62 (s, 1H), 9.41 (t, *J* = 6.0 Hz, 1H), 8.97 (d, *J* = 1.8 Hz, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.61 (d, *J* = 6.0 Hz, 2H), 2.82 (t, *J* = 5.4 Hz, 4H), 1.49-1.45 (m, 4H), 1.32-1.30 (m, 2H). LC/MS (Method J, ESI): RT= 1.58 min, *m/z* = 400.0 [M+H]⁺.

Example 97: Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide



Step 1. Imidazo[1,2-a]pyridine-6-carboxylic acid benzylamide. To a mixture of benzylamine (2.62 g, 23.9 mmol), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (6.42 g, 11.96 mmol), and imidazo[1,2-a]pyridine-6-carboxylic acid (2.00 g, 11.96 mmol) in methylene chloride (100 mL), was added triethylamine (10.5 mL, 59.8 mmol). The reaction mixture was stirred at rt for 24 h and then concentrated to dryness under vacuum. The crude material was washed with an aqueous solution of saturated sodium bicarbonate (2x), water (2x), and ether (2x). The crude white solid was collected by filtration to yield the title compound (2.67 g, 89%). This material was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (s, 1H), 9.11 (t, *J* = 5.8 Hz, 1H), 8.06 (s, 1H), 7.73-7.54

(m, 3H), 7.34 (d, $J = 4.7$ Hz, 4H), 7.28-7.16 (m, 1H), 4.51 (d, $J = 5.9$ Hz, 2H).

LC/MS (Method L, ESI): RT = 0.54 min, $m/z = 252.2$ [M + H]⁺.

Step 2. 4-[[[Imidazo[1,2-a]pyridine-6-carbonyl]-amino]-methyl]-benzenesulfonyl chloride. Imidazo[1,2-a]pyridine-6-carboxylic acid benzylamide

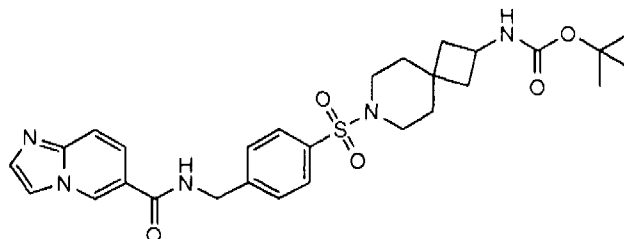
5 (2.00 g, 7.80 mmol) was added portionwise to a cooled flask containing chlorosulfonic acid (6.51 ml, 97.5 mmol). The reaction mixture was kept at ice bath temperature for another 30 min, then warmed to at rt, and stirred for 2 h. The reaction mixture was slowly poured into 25 mL of ice-water, and the newly formed milky suspension was allowed to set for 30 min. The water layer was decanted off and the
10 remaining oil was washed with ether (2x), and concentrated in vacuo to give the title compound as glass solid (1.93 g, 71%). This material was used in the next step without further purification.

Step 3. Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-pyrrolidin-1-yl)-piperidine-1-sulfonyl)-benzylamide. 4-[[[Imidazo[1,2-a]pyridine-6-carbonyl]-

15 amino]-methyl]-benzenesulfonyl chloride (0.049 g, 0.14 mmol) was added to a mixture of 4-pyrrolidin-1-yl-piperidine hydrochloride (57 mg, 0.30 mmol) and triethyl amine (0.10 mL, 0.70 mmol) in methylene chloride (1 mL). The reaction mixture was stirred at rt for 24 h and then concentrated to dryness under vacuum to give the crude title product. The compound was purified by preparative chiral SFC to remove
20 a small amount of contaminating imidazo[1,2-a]pyridine-6-carboxylic acid 3-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide (column: Lux Cellulose-3, 3 x 25 cm, 5 μ m; detection: UV 254 nm, mobile phase A: CO₂, mobile phase B: MeOH containing 0.1% NH₄OH; flow rate: 200 mL/min; gradient: isocratic, A:B = 70:30). The desired compound was then further purified by preparative HPLC (column:
25 Gemini-NX, 3 x 10 cm, 10 μ m; detection: UV 254 nm; mobile phase A: H₂O containing 0.1% NH₄OH, mobile phase B: Acetonitrile; flow rate: 60 mL/min, gradient: 0-1 min 5% B, 1-10 min. 5-50% B, 10-11 min. 50% B, 11-11.2 min. 50-95% B, 11.2-13 min. 95% B, 13-13.2 min 95-5% B, 13.2-15 min. 5% B). Isolation and concentration of the appropriate fractions afforded the title product as a white
30 solid (4.1 mg, 6%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.25 (t, $J = 8$ Hz, 1H), 9.18 (s, 1H), 8.08 (s, 1H), 7.75-7.55 (m, 6H), 4.61 (d, $J = 8$ Hz, 2H), 3.47-3.36 (m, 2H), 2.48-

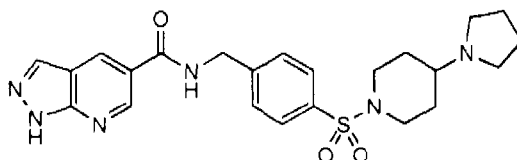
2.35 (m, 6H), 1.96-1.77 (m, 3H), 1.66-1.54 (m, 4H), 1.49-1.33 (m, 2H). LC/MS (Method K, ESI): RT = 3.70 min, m/z = 468.2 $[M + H]^+$.

Example 127: [7-(4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-7-aza-spiro[3.5]non-2-yl]-carbamic acid tert-butyl ester



4-{[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl chloride (45.0 mg, 0.13 mmol) was added to a mixture of (7-aza-spiro[3.5]non-2-yl)-carbamic acid tert-butyl ester (47.8 mg, 0.19 mmol) and triethyl amine (0.09 mL, 0.64 mmol) in methylene chloride (2 mL). The reaction mixture was stirred at rt for 24 h and then concentrated to dryness under vacuum to give the crude title product. The residue was purified by preparative HPLC (column: Gemini-NX, 3 x 10 cm, 10 μ m; detection: UV 254 nm; mobile phase A: H₂O containing 0.1% NH₄OH, mobile phase B: Acetonitrile; flow rate: 60 mL/min, gradient: 0-1 min 5% B, 1-10 min. 5-50% B, 10-11 min. 50% B, 11-11.2 min. 50-95% B, 11.2-13 min. 95% B, 13-13.2 min 95-5% B, 13.2-15 min. 5% B), then by preparative chiral SFC to remove a small amount of contaminating [7-(3-{[(imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-7-aza-spiro[3.5]non-2-yl]-carbamic acid tert-butyl ester (Column: Lux Cellulose-3, 3 x 25 cm, 5 μ m; detection: UV 254 nm, mobile phase A: CO₂, mobile phase B: MeOH containing 0.1% NH₄OH; flow rate: 200 mL/min; gradient: isocratic, A:B = 75:25). Isolation and concentration of the appropriate fractions afforded the desired product as a white solid (31 mg, 42%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.21 (t, J = 6.0 Hz, 1H), 9.17 (s, 1H), 8.07 (s, 1H), 7.73-7.65 (m, 4H), 7.63 (d, J = 9.5 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 5.9 Hz, 2H), 3.88-3.77 (m, 1H), 2.86 (t, J = 5.4 Hz, 2H), 2.78 (t, J = 5.3 Hz, 2H), 1.98-1.88 (m, 3H), 1.60-1.47 (m, 5H), 1.33 (s, 9H). LC/MS (Method K, ESI): RT = 4.11 min, m/z = 554.2 $[M + H]^+$.

Example 156: 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide



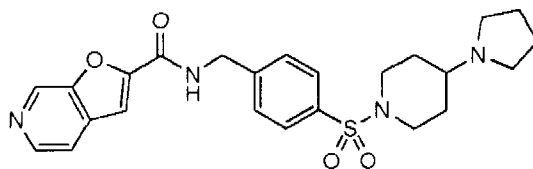
5 Step 1. 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid benzylamide. To a mixture of benzylamine (2.80 g, 26.0 mmol), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (14.0 g, 27.0 mmol), and 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (4.0 g, 25.0 mmol) in methylene chloride (340 mL), was added DIPEA (8.6mL, 49.0 mmol). The reaction mixture was stirred
10 at rt for 24 h. To the reaction mixture was added saturated aqueous sodium bicarbonate solution, and the resulting solid was collected by vacuum filtration. The crude solid was washed with water and ether to yield the title compound as a white solid (4.60 g, 74.0%). This material was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.91 (s, 1H), 9.22 (t, *J* = 6.0 Hz, 1H),
15 9.03 (d, *J* = 1.8 Hz, 1H), 8.76 (d, *J* = 1.9 Hz, 1H), 8.29 (s, 1H), 7.35 (m, 4H), 7.30-7.17 (m, 1H), 4.53 (d, *J* = 5.8 Hz, 2H). LC/MS (Method L, ESI): RT = 0.75 min, *m/z* = 253.1 [M + H]⁺.

Step 2. 4-([(1H-Pyrazolo[3,4-b]pyridine-5-carbonyl)-amino]-methyl)-benzenesulfonyl chloride. 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid
20 benzylamide (3.0 g, 11.9 mmol) was added portionwise to a cooled flask containing chlorosulfonic acid (9.92 mL, 149 mmol). The reaction mixture was kept at ice bath temperature for another 30 min, then warmed to rt and stirred for 6 h. The reaction mixture was slowly poured into 30 mL of ice-water. The resulting sticky suspension was left to stand for 30 min, then the aqueous layer was decanted. The oily residue
25 was washed with ether (2x), then dried under vacuum to give the title compound as glass solid (3.60 g, 86%). This material was used in the next step without further purification.

Step 3. 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide. 4-([(1H-Pyrazolo[3,4-b]pyridine-5-carbonyl)-

amino]-methyl}-benzenesulfonyl chloride (0.049 g, 0.14 mmol) was added to a mixture of 4-pyrrolidin-1-yl-piperidine hydrochloride (57 mg, 0.30 mmol) and triethylamine (0.10 mL, 0.70 mmol) in methylene chloride (1 mL). The reaction mixture was stirred at rt for 24 h and then concentrated to dryness under vacuum to give the crude title product. The compound was purified by preparative HPLC (column: Gemini-NX, 3 x 10 cm, 10 μ m; detection: UV 254 nm; mobile phase A: H₂O containing 0.1% NH₄OH, mobile phase B: Acetonitrile; flow rate: 60 mL/min, gradient: 0-1 min 5% B, 1-10 min. 5-50% B, 10-11 min. 50% B, 11-11.2 min. 50-95% B, 11.2-13 min. 95% B, 13-13.2 min 95-5% B, 13.2-15 min. 5% B), then by preparative chiral SFC to remove a small amount of contaminating 1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 3-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide (Column: Lux Cellulose-3, 21.2 x 150 mm, 5 μ m; detection: UV 230 nm, mobile phase A: CO₂, mobile phase B: MeOH containing 0.1% NH₄OH; flow rate: 70 mL/min; gradient: isocratic, A:B = 70:30). Isolation and concentration of the appropriate fractions afforded the title as a white solid (14.6 mg, 22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.96 (br s, 1H), 9.34 (t, *J* = 8 Hz, 1H), 9.04 (s, 1H), 8.78 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 7.71 (d, *J* = 8 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 4.63 (d, *J* = 4 Hz, 2H), 3.47-3.36 (m, 2H), 2.48-2.35 (m, 6H), 2.09-1.98 (m, 1H), 1.90-1.80 (m, 2H), 1.66-1.54 (m, 4H), 1.49-1.33 (m, 2H). LC/MS (Method K, ESI): RT = 2.96 min, *m/z* = 469.2 [M + H]⁺.

Example 157: Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide



Step 1. Furo[2,3-c]pyridine-2-carboxylic acid benzylamide. To a flask containing furo[2,3-c]pyridine-2-carboxylic acid (2.50 g, 13.8 mmol), was added thionyl chloride (20 ml), followed by a few drops of DMF. The reaction mixture was heated at 85 °C for 2 h. The mixture was then cooled to rt and concentrated under vacuum. The crude furo[2,3-c]pyridine-2-carbonyl chloride was suspended in

methylene chloride (30 mL), then treated with a solution of benzylamine (1.35 mL, 12.4 mmol) and triethylamine (4.81 mL, 27.5 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at rt for 24 h and then washed with a saturated solution of aqueous sodium bicarbonate, dried over MgSO_4 , and concentrated to dryness under vacuum to give the crude title product as yellow solid (3.60 g, 100%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.57 (t, $J = 5.9$ Hz, 1H), 9.07 (s, 1H), 8.48 (d, $J = 5.2$ Hz, 1H), 7.84 (d, $J = 5.2$ Hz, 1H), 7.67 (s, 1H), 7.35 (d, $J = 4.4$ Hz, 4H), 7.30-7.19 (m, 1H), 4.50 (d, $J = 6.1$ Hz, 2H). LC/MS (Method L, ESI): RT = 0.64 min, $m/z = 253.1$ $[\text{M} + \text{H}]^+$.

10 Step 2. 4-([(Furo[2,3-c]pyridine-2-carbonyl)-amino]-methyl)-benzenesulfonyl chloride. Furo[2,3-c]pyridine-2-carboxylic acid benzylamide (500 mg, 1.98 mmol) was added portionwise to a cooled flask containing chlorosulfonic acid (1.65 mL, 24.8 mmol). The reaction mixture was kept in an ice bath for another 30 mins, then warmed to at rt and continued stirring for 2 h. The reaction mixture
15 was slowly poured into 10 mL ice-water, and the resulting mixture was allowed to stand for 30 min. The water layer was removed, washed with ether twice, and dried in vacuo to give 4-([(furo[2,3-c]pyridine-2-carbonyl)-amino]-methyl)-benzenesulfonyl chloride as glassy solid (120 mg, 17%). The crude material was used in the next step without further purification.

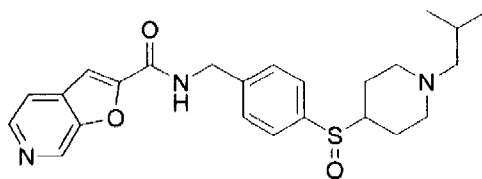
20 Step 3. Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-pyrrolidin-1-yl)-piperidine-1-sulfonyl)-benzylamide. 4-([(Furo[2,3-c]pyridine-2-carbonyl)-amino]-methyl)-benzenesulfonyl chloride (0.049 g, 0.14 mmol) was added to a mixture of 4-pyrrolidin-1-yl-piperidine hydrochloride (57 mg, 0.30 mmol) and triethylamine (0.10 mL, 0.70 mmol) in methylene chloride (1 mL). The reaction mixture was stirred at rt
25 for 24 h and then concentrated to dryness under vacuum to give the crude title product. The compound was purified by preparative HPLC (column: Gemini-NX, 3 x 10 cm, 10 μm ; detection: UV 254 nm; mobile phase A: H_2O containing 0.1% NH_4OH , mobile phase B: Acetonitrile; flow rate: 60 mL/min, gradient: 0-1 min 5% B, 1-10 min. 5-50% B, 10-11 min. 50% B, 11-11.2 min. 50-95% B, 11.2-13 min. 95% B, 13-
30 13.2 min 95-5% B, 13.2-15 min. 5% B), then by preparative chiral SFC to remove a small amount of contaminating furo[2,3-c]pyridine-2-carboxylic acid 3-(4-pyrrolidin-

1-yl-piperidine-1-sulfonyl)-benzylamide (Column: Lux Cellulose-3, 21.2 x 150 mm, 5 μ m; detection: UV 230 nm, mobile phase A: CO₂, mobile phase B: MeOH containing 0.1% NH₄OH; flow rate: 70 mL/min; gradient: isocratic, A:B = 70:30).

Isolation and concentration of the appropriate fractions afforded the title product as a white solid (17.4 mg, 27%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.67 (t, *J* = 8 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.19 (s, 1H), 7.83 (d, *J* = 4.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.59 (d, *J* = Hz, 2H), 4.61 (d, *J* = 4 Hz, 2H), 3.47-3.36 (m, 2H), 2.48-2.35 (m, 6H), 2.09-1.98 (m, 1H), 1.90-1.80 (m, 2H), 1.66-1.54 (m, 4H), 1.49-1.33 (m, 2H). LC/MS (Method K, ESI): RT = 2.73 min, *m/z* = 469.2 [M + H]⁺.

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Example 189: Furo[2,3-*c*]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide



Step 1. 4-(4-Bromo-benzenesulfinyl)-piperidine-1-carboxylic acid tert-butyl ester. A solution of 4-(4-bromo-phenylsulfanyl)-piperidine-1-carboxylic acid tert-butyl ester (6 g, 16.12 mmol, 1.00 equiv), catalytic H₂SO₄/i-PrOH (0.1 g per 2 mL; 6 g), and H₂O₂ (10 mL) in dichloromethane (100 mL) was stirred for 2 h at 50 °C. The reaction mixture was diluted with 300 mL of dichloromethane and washed with 50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10), affording 2.7 g (43%) of the title compound as a white solid. TLC: 1:1 petroleum ether/ethyl acetate, R_f = 0.15.

Step 2. 4-(4-Cyano-benzenesulfinyl)-piperidine-1-carboxylic acid tert-butyl ester. A solution of 4-(4-bromo-benzenesulfinyl)-piperidine-1-carboxylic acid tert-butyl ester (3.5 g, 9.01 mmol, 1.00 equiv), 1,1'-bis(diphenylphosphino)ferrocene (350 mg, 0.63 mmol, 0.07 equiv), tris(dibenzylideneacetone)dipalladium (350 mg, 0.38 mmol, 0.04 equiv), and zinc cyanide (1.7 g, 14.47 mmol, 1.61 equiv) in DMF (25 mL) was stirred under nitrogen for 2 h at 100 °C. The solid material was removed by

25

filtration. The filtrate was diluted with 80 mL of ethyl acetate then washed with 2x20 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:30) to give 1.5 g (50%) of the title compound as a light yellow solid. TLC: 1:1 petroleum ether/ethyl acetate, $R_f = 0.1$.

Step 3. 4-(Piperidine-4-sulfinyl)-benzonitrile. Thionyl chloride (10 mL) was added dropwise to methanol (100 mL) at 0 °C. After stirring for 5 min, 4-(4-cyano-benzenesulfinyl)-piperidine-1-carboxylic acid tert-butyl ester (2.3 g, 6.88 mmol, 1.00 equiv) was added in several portions. The reaction mixture was stirred for another 30 min at rt and then concentrated under reduced pressure. The residue was dissolved in 10 mL of water and the pH value of the solution was adjusted to 10 with saturated aqueous sodium carbonate solution. The mixture was extracted with dichloromethane (3x20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 1.7 g (crude) of title compound as a light yellow solid. LC/MS (Method G, ESI), $RT = 1.03$ min, $m/z = 235.0$ $[M+H]^+$.

Step 4. 4-(1-Isobutyl-piperidine-4-sulfinyl)-benzonitrile. A solution of 4-(piperidine-4-sulfinyl)-benzonitrile (1.7 g, 7.26 mmol, 1.00 equiv), 2-methylpropanal, (2.6 g, 36.06 mmol, 5.00 equiv) and titanium isopropoxide (2.5 g) in acetic acid (2 mL) and ethanol (20 mL) was stirred for 2 h at 60 °C. Sodium cyanoborohydride (4.6 g) was then added and the resulting solution was stirred for 1 h at 60 °C. The resulting mixture was concentrated under vacuum. The residue was dissolved in 60 mL of ethyl acetate and 10 mL of water. The pH value of the solution was adjusted to 4 with 1 M HCl. The organic layer was discarded and the aqueous layer was adjusted to pH 8 with saturated aqueous sodium carbonate solution. The aqueous layer was then extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:1) to give 0.9 g (43%) of the title compound as a light yellow solid. LC/MS (Method C, ESI), $RT = 0.34$ min, $m/z = 291.0$ $[M+H]^+$.

Step 5. 4-(1-Isobutyl-piperidine-4-sulfinyl)-benzylamine. To a solution of 4-(1-isobutyl-piperidine-4-sulfinyl)-benzonitrile (800 mg, 2.75 mmol, 1.00 equiv) in

methanol (150 mL) was added Raney Ni (1 g). The reaction mixture was stirred under 1 atmosphere of hydrogen for 30 min at rt. The nickel catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified on a silica gel column eluted with dichloromethane/methanol (10:1) to yield 478 mg (59%) of the title compound as an off-white solid. LC/MS (Method H, ESI), RT = 0.81 min, $m/z = 295.1$ $[M+H]^+$.

Step 6. Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide. A solution of furo[2,3-c]pyridine-2-carboxylic acid (65 mg, 0.40 mmol, 1.47 equiv), HOBt (50 mg, 0.37 mmol, 1.36 equiv), EDCI (80 mg, 0.42 mmol, 1.53 equiv), DIPEA (129 mg, 1.00 mmol, 3.67 equiv), and 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamine (80 mg, 0.27 mmol, 1.00 equiv) in DMF (3 mL) was stirred for 30 min at rt. The reaction mixture was diluted with 30 mL of ethyl acetate then washed with 2x10 mL of water and 1x10 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was first purified on a silica gel column eluted with dichloromethane/methanol (1:10) and the partially purified product was further purified by preparative HPLC with the following conditions (IntelFlash-1; Column, C₁₈ column; mobile phase, water:acetonitrile = 1:20 increasing to water:acetonitrile = 1:10 within 2 hr; Detector, UV 254 nm) to give 10 mg (8%) of the title compound as a white solid. LC/MS (Method I, ESI): RT= 1.06 min, $m/z = 440.0$ $[M+H]^+$. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.55 (t, $J = 6.0$ Hz, 1H), 9.01 (s, 1H), 8.43 (d, $J = 5.1$ Hz, 1H), 7.78 (dd, $J = 5.1, 0.9$ Hz, 1H), 7.62 (s, 1H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 4.52 (d, $J = 6.3$ Hz, 2H), 2.78-2.70 (m, 2H), 2.68-2.61 (m, 1H), 1.93-1.91 (m, 2H), 1.84-1.75 (m, 4H), 1.67-1.47 (m, 2H), 1.39-1.31 (m, 1H), 0.76 (d, $J = 6.3$ Hz, 6H).

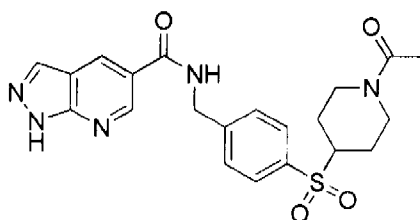
Examples 192 and 193: Enantiomers of Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide

The two enantiomers of furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutyl-piperidine-4-sulfinyl)-benzylamide (Example 189) were separated by preparative HPLC using the following conditions: Column, Chiralpak IC2*25 cm, 5 μ m Chiral-

P(IC)0011C00CJ-L0016; mobile phase, Phase A: Hex (0.2% diethylamine), Phase B: EtOH (0.2% diethylamine); A/B = 6/4, Flow Rate, 20 mL/min; Wavelength, 220/254 nm; Pressure, 80~90 bar, Temperature: 25 °C. The retention time of Example 192 and Example 193 are RT = 11.23 min and RT = 15.37 min, respectively.

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Example 228. N-[[4-(1-Acetylpiperidine-4-sulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide.



Step 1. tert-Butyl 4-hydroxypiperidine-1-carboxylate. To a solution of
 10 piperidin-4-ol (50.5 g, 499.27 mmol, 1.00 equiv) and triethylamine (75 g, 741.18 mmol, 1.16 equiv) in DCM (800 mL) at 0°C was added di-tert-butyl dicarbonate (130 g, 595.66 mmol, 1.19 equiv). The mixture was warmed to rt and stirred overnight. The reaction mixture was washed with 3x100 mL of water and 3x100 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under
 15 vacuum to give 110 g of crude tert-butyl 4-hydroxypiperidine-1-carboxylate as a light yellow oil. The crude product was used directly without further purification. TLC: DCM/MeOH = 10:1, R_f = 0.4.

Step 2. tert-Butyl 4-[(4-bromophenyl)sulfonyl]piperidine-1-carboxylate. To a solution of 4-bromobenzene-1-thiol (46 g, 243.29 mmol, 1.22 equiv), tert-butyl 4-hydroxypiperidine-1-carboxylate (40 g, 198.75 mmol, 1.00 equiv) and PPh_3 (72 g) in THF (800 mL) maintained under nitrogen at rt was added a solution of diethylazodicarboxylate (50 g, 287.11 mmol, 1.44 equiv) in THF (200 mL) dropwise within 30 min. The resulting solution was stirred at rt for 16 h and then concentrated under vacuum. The residue was redissolved in 1000 mL of ethyl acetate then washed
 20 with 2x400 mL of water and 2x400 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (1:9) to give 30 g

(41%) of tert-butyl 4-[(4-bromophenyl)sulfonyl]piperidine-1-carboxylate as a colorless oil. TLC: ethyl acetate/petroleum ether = 1:5, R_f = 0.6.

Step 3. tert-Butyl 4-[(4-bromobenzene)sulfonyl]piperidine-1-carboxylate. To a stirred solution of tert-butyl 4-[(4-bromophenyl)sulfonyl]piperidine-1-carboxylate (30 g, 80.58 mmol, 1.00 equiv) in DCM (500 mL) was added 3-chloroperoxybenzoic acid (50 g, 289.74 mmol, 3.02 equiv) in small portions. The reaction mixture was stirred at rt for 2 h. The mixture was washed sequentially with 2x200 mL of saturated potassium carbonate solution, 2x200 mL of water and 2x200 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:6) to give 27 g (83%) of tert-butyl 4-[(4-bromobenzene)sulfonyl]piperidine-1-carboxylate as a white solid. TLC: ethyl acetate/petroleum ether = 1:4, R_f = 0.3.

Step 4. tert-Butyl 4-[(4-cyanobenzene)sulfonyl]piperidine-1-carboxylate. A mixture of tert-butyl 4-[(4-bromobenzene)sulfonyl]piperidine-1-carboxylate (25 g, 61.83 mmol, 1.00 equiv), $\text{Pd}(\text{PPh}_3)_4$ (7 g, 6.06 mmol, 0.10 equiv) and $\text{Zn}(\text{CN})_2$ (8.6 g) in DMF (400 mL) was stirred under nitrogen overnight at 85°C. The reaction mixture was cooled to rt. Ice/water (1000 mL) was added to precipitate the product. The solid was collected by filtration then washed with water. The solid was dissolved in a small amount of methylene chloride then loaded onto a silica gel column. The column was eluted with ethyl acetate/petroleum ether (6:4) to give 19 g (88%) of tert-butyl 4-[(4-cyanobenzene)sulfonyl]piperidine-1-carboxylate as a white solid. TLC: ethyl acetate/petroleum ether = 1:2, R_f = 0.4.

Step 5. 4-(Piperidine-4-sulfonyl)benzonitrile hydrochloride. Hydrogen chloride gas was bubbled into a solution of tert-butyl 4-[(4-cyanobenzene)sulfonyl]piperidine-1-carboxylate (2.5 g, 7.13 mmol, 1.00 equiv) in 1,4-dioxane at 0°C (60 mL) for 20 min. The reaction mixture was stirred at rt for 2 h. The precipitate was collected by filtration, washed with ether and then dried in vacuum to give 1.6 g (78%) of 4-(piperidine-4-sulfonyl)benzonitrile hydrochloride as a white solid.

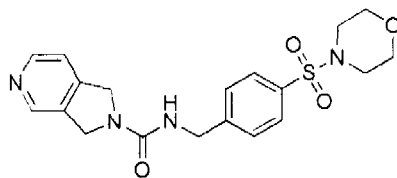
Step 6. 4-(1-Acetyl piperidine-4-sulfonyl)benzonitrile. To a stirred solution of 4-(piperidine-4-sulfonyl)benzonitrile hydrochloride (1.6 g, 5.58 mmol, 1.00 equiv)

and DIPEA (1.5 g, 11.61 mmol, 2.08 equiv) in DCM (40 mL) at 0°C was added a solution of acetyl chloride (500 mg, 6.37 mmol, 1.14 equiv) in DCM (10 mL) dropwise. The resulting solution was stirred at rt for 30 min. The reaction mixture was washed with 2x20 mL of water and 2x20 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to give 1.5 g (92%) of 4-(1-acetylpiperidine-4-sulfonyl)benzonitrile as a white solid. TLC: ethyl acetate: petroleum ether = 1:1, R_f = 0.6.

Step 7. 1-(4-[[4-(Aminomethyl)benzene]sulfonyl]piperidin-1-yl)ethan-1-one.
To a mixture of 4-(1-acetylpiperidine-4-sulfonyl)benzonitrile (1.5 g, 5.13 mmol, 1.00 equiv), and Raney Ni (0.5 g) in MeOH (150 mL) was added a 7N solution of NH_3 in MeOH (3 mL). The mixture was stirred under 1 atmosphere of H_2 at rt for 2 h. The catalyst was removed by filtration and the filtrate was concentrated under vacuum. The residue was purified on a silica gel column eluted with DCM/MeOH (90/10) to give 1 g (66%) of 1-(4-[[4-(aminomethyl)benzene]sulfonyl]piperidin-1-yl)ethan-1-one as a white solid. TLC: MeOH/ CH_2Cl_2 = 1:10, R_f = 0.1.

Step 8. A solution of 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid (120 mg, 0.74 mmol, 1.45 equiv), 1-(4-[[4-(aminomethyl)benzene]sulfonyl]piperidin-1-yl)ethan-1-one (150 mg, 0.51 mmol, 1.00 equiv), EDCI (130 mg, 0.68 mmol, 1.34 equiv), HOBt (90 mg, 0.67 mmol, 1.32 equiv) and DIPEA (0.5 mL) in DMF (5 mL) was stirred at rt overnight. The reaction mixture was diluted with 50 mL of DCM then washed with 2x50 mL of water and 2x50 mL of brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column eluted with DCM/MeOH (94/6) to give 65 mg (29%) of N-[[4-(1-acetylpiperidine-4-sulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide as a white solid. LC/MS (Method C, ESI): RT = 1.31 min, m/z = 442.0 $[\text{M}+1]^+$. ^1H NMR (300 MHz, $\text{DMSO}-d_6$, ppm): δ 9.33 (t, J = 6.0 Hz, 1H), 9.05 (d, J = 2.1 Hz, 1H), 8.78 (d, J = 2.1 Hz, 1H), 8.31 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 6.0 Hz, 2H), 4.45 (d, J = 13.2 Hz, 1H), 4.38 (d, J = 13.2 Hz, 1H), 3.56-3.47 (m, 1H), 3.03-2.96 (m, 1H), 2.51-2.44 (m, 1H), 1.96 (s, 3H), 1.87-1.80 (m, 2H), 1.52-1.38 (m, 1H), 1.34-1.28 (m, 1H).

Example 294. N-[[4-(Morpholine-4-sulfonyl)phenyl]methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxamide.



- Step 1. [4-(Morpholine-4-sulfonyl)phenyl]methanamine. A mixture of 4-(morpholine-4-sulfonyl)benzonitrile (200 mg, 0.79 mmol, 1.00 equiv) and Raney Ni (2 g) in MeOH (30 mL) was stirred at rt under 1 atmosphere of H₂ for 20 min. The catalyst was removed by filtration. The filtrate was concentrated under vacuum to give 0.15 g (74%) of [4-(morpholine-4-sulfonyl)phenyl]methanamine as a light yellow solid. LC/MS (Method F, ESI): RT = 0.91 min, *m/z* = 257.0 [M+H]⁺.
- Step 2. 4-Nitrophenyl N-[[4-(morpholine-4-sulfonyl)phenyl]methyl]carbamate. A solution of [4-(morpholine-4-sulfonyl)phenyl]methanamine (150 mg, 0.59 mmol, 1.00 equiv) and 4-nitrophenyl chloroformate (130 mg, 0.64 mmol, 1.10 equiv) in toluene (30 mL) was stirred under nitrogen at 110°C for 50 min. The reaction mixture was cooled to 0°C. The precipitate was collected by filtration and air-dried to give 0.12 g (49%) of 4-nitrophenyl N-[[4-(morpholine-4-sulfonyl)phenyl]methyl]carbamate as a light yellow solid. TLC: petroleum ether/ethyl acetate = 1:1, R_f = 0.2.
- Step 3. A solution of 4-nitrophenyl N-[[4-(morpholine-4-sulfonyl)phenyl]methyl]carbamate (0.10 g, 0.24 mmol, 1.00 equiv) and 1H,2H,3H-pyrrolo[3,4-c]pyridine (60 mg, 0.50 mmol, 2.10 equiv) in ethanol (20 mL) was stirred at 90°C for 1 h. The reaction mixture was cooled to rt and concentrated under vacuum. The residue was purified on a silica gel column eluted with ethyl acetate/petroleum ether (5:1) to yield 0.04 g (42%) of N-[[4-(morpholine-4-sulfonyl)phenyl]methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxamide as a light yellow solid. LC/MS (Method D, ESI): RT = 2.63 min, *m/z* = 403.0 [M+H]⁺. ¹H NMR (300 MHz, DMSO-*d*₆, ppm): δ 8.54 (s, 1H), 8.43 (d, *J* = 4.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 5.1 Hz, 1H), 7.14 (d, *J* = 6.0 Hz, 1H), 4.65 (m, 4H), 4.37 (d, *J* = 5.7 Hz, 2H), 3.57 (t, *J* = 4.6 Hz, 4H), 2.79 (t, *J* = 4.6 Hz, 4H).

Additional examples were prepared using methods analogous to those described above. In particular, certain exemplified compounds were prepared according to the methods described in, for example, Examples 5, 24, 25, 47, 97, 156, 228, and 294.

Analytical Characterization:

Each of the specifically exemplified compounds described herein was prepared using the methods analogous to those described above, and were analyzed by LC/MS. Data for each compound, along with the LC/MS method used to generate the data, if applicable, is provided in Tables 1a and 1b (NA = not available).

Table 1a. LC/MS Data for Example Compounds.

Ex.	Retention time (min)	<i>m z</i>	LC/MS Method
2	1.35	427.2	C
3	1.33	444.1	G
4	1.34	427.0	I
5	1.20	400.0	H
6	1.88	400.0	B
7	1.44	430.0	A
8	1.63	402.2	C
9	1.45	402.3	E
10	2.35	401.0	J
11	1.34	418.2	C
12	1.42	425.0	A
13	1.97	439.2	F
14	1.20	401.1	I
15	1.52	402.2	C
16	2.03	400.2	C
17	1.56	414.2	C
18	1.70	414.2	C
19	1.13	415.0	I
20	3.13	401.0	A
21	1.08	401.1	F
22	1.26	400.0	A
23	1.27	400.0	A
24	1.12	401.2	F
25	1.93	482.2	B
26	1.78	428.0	C

27	1.52	428.2	C
28	1.25	415.0	A
29	1.24	416.0	A
30	1.88	416.0	A
31	1.16	414.9	J
32	1.70	416.0	C
33	2.05	416.2	C
34	1.18	416.0	I
35	1.72	415.2	C
36	1.69	431.0	H
37	1.09	479.2	F
38	1.15	416.0	I
39	1.09	473.2	F
40	1.13	482.0	I
41	1.08	400.0	I
42	1.01	416.0	I
43	1.06	456.0	I
44	1.08	457.1	G
45	3.01	400.1	B
46	3.13	445.2	G
47	1.12	484.3	C
48	1.58	399.0	D
49	1.58;	400.0	J
50	1.16	415.0	I
51	1.16	416.0	I
52	1.15	415.0	I
53	1.14	415.0	I
54	1.16	415.2	J
55	3.80	514.2	K
56	1.23	484.3	C
57	2.63	468.2	J
58	2.78	400.0	I
59	1.12	404.0	I
60	1.13	428.0	I
61	1.03	429.0	I
62	1.25	442.2	C
63	1.52	482.0	H
64	1.34	482.0	H
65	1.41	481.2	C
66	2.40	481.2	C
67	1.37	482.0	H
68	1.13	483.2	C
69	1.48	483.2	C
70	3.62	461.1	K
71	3.62	461.1	K

72	3.02	427.1	K
73	3.69	461.1	K
74	3.69	461.1	K
75	1.13	386.0	H
76	1.11	387.0	H
77	1.11	386.0	H
78	5.11	484.2	C
79	1.40	386.0	H
80	1.35	387.1	J
81	1.24	386.0	E
82	1.18	416.0	I
83	1.54	510.0	I
84	2.83	413.1	K
85	2.17	442.2	C
86	2.24	442.2	C
87	1.09	387.2	F
88	1.25	387.2	F
89	1.09	387.2	F
90	1.25	387.1	F
91	0.94	399.0	I
92	1.08	456.2	C
93	2.87	442.1	K
94	2.47	444.1	K
95	3.19	424.1	K
96	3.17	429.1	K
97	3.70	468.2	K
98	3.51	458.1	K
99	3.35	421.1	K
100	2.88	456.1	K
101	3.29	456.1	K
102	4.15	554.2	K
103	4.13	554.2	K
104	2.58	453.1	K
105	2.58	471.2	K
106	2.85	415.1	K
107	2.85	415.1	K
108	2.52	428.1	K
109	2.71	525.2	K
110	2.52	497.2	K
111	3.66	453.1	K
112	3.55	435.1	K
113	1.54	441.0	A
114	1.04	455.0	C
115	1.27	455.0	A
116	1.28	456.0	A

117	1.20	457.0	C
118	1.10	456.0	C
119	1.03	457.0	I
120	1.09	472.0	C
121	4.29	568.3	K
122	4.21	568.2	K
123	4.46	568.2	K
124	4.09	570.2	K
125	4.19	554.2	K
126	4.01	570.2	K
127	4.11	554.2	K
128	3.70	512.2	K
129	3.96	526.2	K
130	3.87	542.2	K
131	4.35	568.2	K
132	3.69	512.2	K
133	3.70	542.2	K
134	3.94	542.2	K
135	3.89	526.2	K
136	3.86	526.2	K
137	3.81	526.2	K
138	2.66	457.1	K
139	2.88	415.1	K
140	2.92	457.1	K
141	3.51	447.1	K
142	2.42	456.1	K
143	2.52	440.1	K
144	2.49	440.1	K
145	3.04	429.1	K
146	3.19	441.1	K
147	3.59	447.1	K
148	1.62	400.2	F
149	1.84	457.0	B
150	2.93	416.1	K
151	2.94	416.1	K
152	2.66	454.2	K
153	3.06	428.1	K
154	1.97	399.8	C
155	2.07	400.9	C
156	2.96	469.2	K
157	2.73	469.2	K
158	3.36	428.1	K
159	3.25	397.1	K
160	3.41	397.1	K
161	2.83	415.1	K

162	2.48	456.1	K
163	2.80	454.1	K
164	3.27	429.1	K
165	2.42	440.1	K
166	3.29	397.1	K
167	3.10	457.1	K
168	1.22	401.0	H
169	1.25	399.9	C
170	1.06	485.0	I
171	1.24	441.0	A
172	3.24	414.1	K
173	2.95	459.2	K
174	3.30	430.1	K
175	3.81	422.1	K
176	4.12	462.1	K
177	4.07	462.1	K
178	3.43	428.1	K
179	1.26	440.3	C
180	1.06	440.0	I
181	1.25	440.2	C
182	1.32	439.3	C
183	4.28	568.2	K
184	3.99	584.2	K
185	4.13	554.2	K
186	4.77	616.2	K
187	1.57	439.3	C
188	1.26	440.3	C
189	1.06	440.0	I
190	1.25	440.2	C
191	1.32	439.3	C
192	1.10	439.9	C
193	1.11	440.0	C
194	3.09	441.1	K
195	2.50	440.1	K
196	0.98	486.0	I
197	0.54	441.0	L
198	3.13	401	A
199	1.08	401.1	F
200	1.26	400	A
201	1.27	400	A
202	1.12	401.2	F
203	1.08	400	I
204	1	416	I
205	1.12	484.3	C
206	1.23	484.3	C

207	1.25	442.2	C
208	1.52	482	H
209	1.34	482	H
210	1.6	481.2	O
211	2.4	481.2	C
212	1.37	482	H
213	1.13	483.2	C
214	1.48	483.2	C
215	2.52	426.1	S
216	2.48	440.1	S
217	2.90	454.1	S
218	3.14	441.1	S
219	3.27	441.1	S
220	2.97	427.1	S
221	1.13	386	H
222	1.11	387	H
223	1.11	386	H
224	5.11	484.2	C
225	1.4	386	H
226	1.35	387.1	J
227	1.24	386	E
228	1.31	442	C
229	2.24	442	C
230	1.09	387.2	F
231	1.25	387.2	F
232	1.09	387.2	F
233	1.25	387.1	F
234	0.94	399	I
235	4.16	554.2	S
236	4.16	554.2	S
237	4.08	540.2	S
238	4.01	540.2	S
239	3.28	407.1	S
240	2.99	371.1	S
241	4.01	540.2	S
242	4.11	540.2	S
243	4.17	554.2	S
244	2.93	442.1	S
245	2.71	387.1	S
246	2.62	497.1	S
247	1.54	441	A
248	1.04	455	C
249	1.27	455	A
250	1.28	456	A
251	1.1	456	C

252	1.09	472	C
253	2.44	440.2	S
254	2.62	440.2	S
255	2.45	440.2	S
256	2.57	454.2	S
257	2.39	440.2	S
258	2.63	440.2	S
259	2.85	454.1	S
260	1.15	419.2	F
261	2.50	440.1	S
262	2.61	440.1	S
263	3.23	442.1	S
264	1.66	402	A
265	1.35	442.9	C
266	1.97	399.8	C
267	2.07	400.9	C
268	1.51	402	C
269	3.53	442.1	S
270	3.63	447.1	S
271	2.60	454.1	S
272	2.60	456.1	S
273	2.59	440.1	S
274	3.28	427.1	S
275	1.22	401	H
276	1.25	399.9	C
277	1.55	418	A
278	0.98	486	I
279	1.24	441	A
280	1.57	458.2	O
281	3.73	408	S
282	3.23	455.1	S
283	2.90	441.1	S
284	3.71	442.1	S
285	3.35	414.1	S
286	1.52	485.3	P
287	1.54	457.1	B
288	1.02	514.9	C
289	1.12	485	C
290	2.59	441.2	T
291	3.73	443.2	T
292	1.08	470	C
294	2.63	403.0	D
296	4.52	462.2	S
297	4.47	462.2	S
298	3.33	459.2	S

299	3.74	430.2	S
300	4.22	422.1	S
301	4.10	408.1	S
302	3.87	428.2	S
303	4.08	442.2	S
304	3.65	414.1	S
305	4.00	428.2	S
306	1.12	417	I
307	1.11	417	I
308	1.43	399	I
309	0.86	415.1	G
310	1.71	442.1	B
311	1.25	457	A
312	1.45	456.2	C
313	1.23	470.2	C
314	1.98	470.2	C
315	1.22	441	J
316	1.34	443.1	J
317	3.11	414.2	S
318	1.07	417	C
319	3.31	470.2	S
320	3.15	412.2	S
321	3.25	454.2	S
322	3.28	470.2	S
323	3.44	454.2	S
324	3.41	468.3	S
325	3.42	468.3	S
326	3.37	468.3	S
327	3.18	442.2	S
328	3.15	426.2	S
329	3.10	426.2	S
330	3.93	516.3	S
331	3.35	454.2	S
332	3.04	426.2	S
333	2.94	442.2	S
334	3.43	468.2	S
335	3.13	442.2	S
336	3.42	468.2	S
337	2.92	412.2	S
338	3.48	468.2	S
339	3.04	426.2	S
340	1.46	440.9	C
341	1.14	455.9	C
342	1.1	441.9	C
344	1.53	504.1	C

345	2.89	540	I
346	1.7	526	I
347	1.37	442	I
348	1.28	428	I
349	1.34	478.1	N
350	1.6	504	I
351	1.39	490.2	Q
352	1.78	540.3	F
353	1.47	478	I
354	1.39	463.9	I

Table 1b. MS Data for Example Compounds.

Ex.	MS Data
355	m/z: 439.19 (100.0%), 440.20 (26.4%), 441.19 (4.8%), 441.20 (4.2%), 440.19 (1.9%), 442.19 (1.2%)
356	m/z: 465.13 (100.0%), 466.14 (24.2%), 467.13 (4.8%), 467.14 (3.6%), 466.13 (1.9%), 468.13 (1.1%)
357	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
358	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
359	m/z: 439.19 (100.0%), 440.20 (26.4%), 441.19 (4.8%), 441.20 (4.2%), 440.19 (1.9%), 442.19 (1.2%)
360	m/z: 439.19 (100.0%), 440.20 (26.4%), 441.19 (4.8%), 441.20 (4.2%), 440.19 (1.9%), 442.19 (1.2%)
361	m/z: 467.19 (100.0%), 468.19 (28.3%), 469.19 (4.9%), 469.18 (4.5%), 470.19 (1.3%), 468.18 (1.1%)
362	m/z: 424.19 (100.0%), 425.20 (25.3%), 426.19 (4.9%), 426.20 (3.7%), 425.19 (2.3%), 427.19 (1.2%)
363	m/z: 426.21 (100.0%), 427.21 (27.2%), 428.20 (4.5%), 428.22 (3.1%), 429.21 (1.2%)
364	m/z: 464.15 (100.0%), 465.15 (26.1%), 466.15 (5.5%), 466.16 (2.8%), 467.15 (1.1%)
365	m/z: 468.22 (100.0%), 469.22 (29.4%), 470.22 (5.8%), 470.23 (3.6%), 471.22

	(1.3%)
366	m/z: 425.19 (100.0%), 426.19 (26.8%), 427.18 (4.5%), 427.20 (2.8%), 428.19 (1.2%), 427.19 (1.1%)
367	m/z: 465.14 (100.0%), 466.15 (23.0%), 467.14 (4.5%), 467.15 (3.6%), 466.14 (2.6%), 468.14 (1.1%)
368	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
369	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
370	m/z: 410.18 (100.0%), 411.18 (25.0%), 412.17 (4.5%), 412.18 (3.7%), 411.17 (1.5%), 413.18 (1.2%)
371	m/z: 396.16 (100.0%), 397.17 (23.1%), 398.16 (5.1%), 398.17 (3.0%), 397.16 (2.3%), 399.16 (1.1%)
372	m/z: 398.18 (100.0%), 399.18 (23.9%), 400.17 (4.5%), 400.18 (3.4%), 399.17 (1.5%), 401.18 (1.1%)
373	m/z: 411.17 (100.0%), 412.18 (23.1%), 413.17 (5.0%), 413.18 (3.1%), 412.17 (2.6%), 414.17 (1.1%)
374	m/z: 440.22 (100.0%), 441.23 (26.4%), 442.22 (4.9%), 442.23 (4.0%), 441.22 (2.3%), 443.22 (1.2%)
375	m/z: 424.19 (100.0%), 425.20 (25.3%), 426.19 (4.9%), 426.20 (3.7%), 425.19 (2.3%), 427.19 (1.2%)
376	m/z: 466.17 (100.0%), 467.17 (24.2%), 468.16 (4.5%), 468.17 (3.8%), 467.16 (2.3%), 469.16 (1.1%)
377	m/z: 426.21 (100.0%), 427.21 (27.2%), 428.20 (4.5%), 428.22 (3.1%), 429.21 (1.2%)
378	m/z: 425.19 (100.0%), 426.19 (26.8%), 427.18 (4.5%), 427.20 (2.8%), 428.19 (1.2%), 427.19 (1.1%)
379	m/z: 397.15 (100.0%), 398.15 (23.9%), 399.14 (4.5%), 399.15 (3.5%), 400.15 (1.2%), 398.14 (1.1%)
380	m/z: 411.16 (100.0%), 412.17 (24.2%), 413.16 (5.0%), 413.17 (3.4%), 412.16 (1.9%), 414.16 (1.1%)

381	m/z: 467.20 (100.0%), 468.20 (28.7%), 469.19 (4.5%), 469.21 (3.3%), 469.20 (1.3%), 470.20 (1.3%)
382	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
383	m/z: 425.18 (100.0%), 426.18 (26.1%), 427.17 (4.5%), 427.18 (4.1%), 428.18 (1.4%), 426.17 (1.1%)
384	m/z: 466.20 (100.0%), 467.21 (27.5%), 468.20 (4.9%), 468.21 (4.5%), 467.20 (2.3%), 469.20 (1.3%)
385	m/z: 412.19 (100.0%), 413.20 (24.2%), 414.19 (4.9%), 414.20 (3.4%), 413.19 (2.3%), 415.19 (1.2%)
386	m/z: 424.19 (100.0%), 425.20 (25.3%), 426.19 (4.9%), 426.20 (3.7%), 425.19 (2.3%), 427.19 (1.2%)

It is understood that the person skilled in the art will be able to prepare the compounds of the present invention using methods known in the art along with the general method of synthesis described herein.

5

Assay 1: Biochemical Inhibition Assay

NAMPT protein purification. Recombinant His-tagged NAMPT was produced in *E.coli* cells, purified over a Ni column, and further purified over a size-exclusion column by XTAL Biostructures.

10

The NAMPT enzymatic reaction. The NAMPT enzymatic reactions were carried out in Buffer A (50mM Hepes pH 7.5, 50 mM NaCl, 5 mM MgCl₂, and 1 mM THP) in 96-well V-bottom plates. The compound titrations were performed in a separate dilution plate by serially diluting the compounds in DMSO to make a 100X stock. Buffer A (89 μ L) containing 33 nM of NAMPT protein was added to 1 μ L of 100X compound plate containing controls (e.g. DMSO or blank). The compound and enzyme mixture was incubated for 15 min at rt, then 10 μ L of 10X substrate and co-factors in Buffer A were added to the test well to make a final concentration of 1 μ M NAM, 100 μ M 5-Phospho-D-ribose 1-diphosphate (PRPP), and 2.5 mM Adenosine 5'-triphosphate (ATP). The reaction was allowed to proceed for 30 min at rt, then

15

was quenched with the addition of 11 μ L of a solution of formic acid and L-Cystathionine to make a final concentration of 1% formic acid and 10 μ M L-Cystathionine. Background and signal strength was determined by addition (or non-addition) of a serial dilution of NMN to a pre-quenched enzyme and cofactor mix.

5 Quantification of NMN. A mass spectrometry-based assay was used to measure the NAMPT reaction product, β -nicotinamide mononucleotide (NMN), and the internal control (L-Cystathionine). NMN and L-Cystathionine were detected using the services of Biocius Lifesciences with the RapidFire system. In short, the NMN and L-Cystathionine were bound to a graphitic carbon cartridge in 0.1% formic
10 acid, eluted in 30% acetonitrile buffer, and injected into a Sciex 4000 mass spectrometer. The components of the sample were ionized with electrospray ionization and the positive ions were detected. The Q1 (parent ion) and Q3 (fragment ion) masses of NMN were 334.2 and 123.2, respectively. The Q1 and Q3 for L-Cystathionine were 223.1 and 134.1, respectively. The fragments are quantified and
15 the analyzed by the following method.

Determination of IC₅₀ Values. First, the NMN signal was normalized to the L-Cystathionine signal by dividing the NMN signal by the L-Cystathionine signal for each well. The signal from the background wells were averaged and subtracted from the test plates. The compound treated cells were then assayed for percent inhibition
20 by using this formula:

$$\% \text{ Inh} = 100 - 100 * x/y$$

wherein x denotes the average signal of the compound treated wells and y denotes the average signal of the DMSO treated wells.

IC₅₀ values were then determined using the following formula:

$$25 \quad \text{IC}_{50} = 10^{(\text{LOG}_{10}(X) + (((50 - \% \text{ Inh at Cmpd Concentration 1}) / (\text{XX} - \text{YY})) * (\text{LOG}_{10}(X) - \text{LOG}_{10}(Y))))}$$

wherein X denotes the compound concentration 1, Y denotes the compound concentration 2, XX denotes the % inhibition at compound concentration 1 (X), and YY denotes the % inhibition at compound concentration 2 (Y).

The compounds of this invention have IC₅₀ values that are preferably under 1 μM, more preferably under 0.1 μM, and most preferably under 0.01 μM. Results for the compounds tested in this assay are provided in Table 2 below.

5 Assay 2: *In-Vitro* Cell Proliferation Assay

Assay Method. A2780 cells were seeded in 96-well plates at 1×10^3 cells/well in 180 μL of culture medium (10% FBS, 1% Pen/Strep Amphotecricin B, RPMI-1640) with and without the addition of either NMN or nicotinamide (NAM). After overnight incubation at 37 °C and 5% CO₂, the compound titrations were
10 performed in a separate dilution plate by serially diluting the compounds in DMSO to make a 1000X stock. The compounds were then further diluted to 10X final concentration in culture media, whereupon 20 μL of each dilution was added to the plated cells with controls (e.g. DMSO and blank) to make a final volume of 200 μL. The final DMSO concentration in each well was 0.1%. The plates were then
15 incubated for 72 hours at 37 °C in a 5% CO₂ incubator. The number of viable cells was then assessed using sulforhodamine B (SRB) assay. Cells were fixed at 4 °C for 1 hour with the addition of 50 μL 30% trichloroacetic acid (TCA) to make a final concentration of 6 % TCA. The plates were washed four times with H₂O and allowed to dry for at least 1 hour, whereupon 100 μL of a 4% SRB in 1% acetic acid solution
20 was added to each well and incubated at rt for at least 30 min. The plates were then washed three times with 1% acetic acid, dried, and treated with 100 μL of 10mM Tris-Base solution. The plates were then read in a microplate reader at an absorbance of 570 nm. Background was generated on a separate plate with media only.

Determination of IC₅₀ Values. First, the signals from the background plate
25 were averaged, then the background was subtracted from the test plates. The compound-treated cells were then assayed for % inhibition by using the following formula:

$$\% \text{ Inh} = 100 - 100 * x / y$$

 wherein x denotes the average signal of the compound-treated cells and y denotes the
30 average signal of the DMSO-treated cells.

 IC₅₀ values were then determined using the following formula:

$$IC_{50} = 10^{(\log_{10}(X) + ((50 - \% \text{ Inh at Cmpd Concentration 1}) / (XX - YY)) * (\log_{10}(X) - \log_{10}(Y)))}$$

wherein X denotes the compound concentration 1, Y denotes the compound concentration 2, XX denotes the % inhibition at compound concentration 1 (X), and YY denotes the % inhibition at compound concentration 2 (Y).

Specificity of cytotoxicity. Inhibition of NAMPT could be reversed by the addition of NAM or NMN. The specificity of the compounds were determined *via* cell viability assay in the presence of the compound and either NAM or NMN. Percent inhibitions were determined using the method given above.

The compounds of this invention have IC_{50} values that are preferably under 1 μ M, more preferably under 0.1 μ M, and most preferably under 0.01 μ M. Most preferable compounds of this invention are compounds that have IC_{50} values in the enzymatic assay and the cell proliferation assay that are both under 1 μ M, more preferably both of the values are under 0.1 μ M, and most preferably both of the values are under 0.01 μ M. Results for the compounds tested in this assay are provided in Table 2 (NT = not tested).

Table 2. Biochemical and Cell Proliferation Assay Results.

Ex.	Biochemical (IC_{50}) [μ M]	Cell Proliferation (IC_{50}) [μ M]
1	8.1000	19.1000
2	0.0281	0.0138
3	0.0126	0.0064
4	0.0720	0.0074
5	0.0094	0.0292
6	0.0035	0.1290
7	0.0109	0.0133
8	0.0315	0.0641
9	0.1050	0.2780
10	0.0251	0.0148
11	0.0208	0.0171
12	0.0262	0.1860
13	0.0126	0.0338
14	0.0770	0.0365
15	0.0068	0.6240
16	0.0220	0.1630
17	0.1010	0.0534
18	0.0484	0.0129

19	0.0181	0.0253
20	0.3080	0.4520
21	0.0087	0.1850
22	0.0345	0.0142
23	0.1040	0.0469
24	0.0322	0.0444
25	0.0242	0.0105
26	0.0046	0.1350
27	0.1420	0.1320
28	0.0235	0.0276
29	0.0075	0.5450
30	0.1780	0.2050
31	0.0550	0.0482
32	0.0077	0.8610
33	0.1690	0.1840
34	0.0257	0.0519
35	0.0383	0.0351
36	0.0113	0.0463
37	0.0441	0.0139
38	0.0265	0.0621
39	0.0835	0.0947
40	0.0171	0.0069
41	0.6690	0.7310
42	0.0660	0.1370
43	0.0216	0.0072
44	0.0058	0.0232
45	0.0172	1.0000
46	0.0435	0.0044
47	0.0080	0.0022
48	0.0461	2.0000
49	2.0000	NT
50	0.0362	0.0239
51	0.0222	0.0397
52	0.0276	0.0186
53	0.0169	0.0226
54	0.0156	0.0114
55	0.0077	0.0043
56	0.0592	0.0211
57	0.0648	0.0555
58	0.2400	2.0000
59	0.0107	0.0030
60	0.0294	0.0152
61	0.0215	0.0233
62	0.0293	0.0250
63	0.0477	0.0108

64	0.0037	0.0088
65	0.0124	0.0021
66	0.0154	0.0032
67	0.0135	0.0054
68	0.0207	0.0073
69	0.0136	0.0047
70	0.0064	0.0080
71	0.0167	0.0064
72	0.0143	0.0057
73	0.0030	0.0008
74	0.0050	0.0027
75	0.1250	0.3470
76	0.0098	0.4230
77	0.0642	0.1050
78	0.0040	0.0479
79	0.1180	0.3200
80	0.0089	0.4570
81	0.0513	0.0984
82	0.0261	0.0348
83	0.0077	0.0026
84	0.0374	0.0166
85	0.2070	0.1510
86	0.0051	0.5270
87	0.0738	0.2430
88	0.3150	0.9770
89	0.1750	0.4450
90	0.2270	1.8000
91	0.0906	0.1300
92	0.0294	0.0075
93	0.0224	0.0130
94	0.0759	0.0290
95	0.0410	0.0335
96	0.0247	0.0094
97	0.0144	0.0054
98	0.0461	0.0101
99	0.0158	0.0077
100	0.0257	0.0254
101	0.0203	0.0097
102	0.0345	0.0051
103	0.0295	0.0394
104	0.0269	0.0088
105	0.0068	0.0090
106	0.0486	0.0577
107	0.0237	0.0154
108	0.0256	0.0053

109	0.0027	0.0039
110	0.0031	0.0033
111	0.0056	0.0025
112	0.0259	0.0205
113	0.0642	0.0446
114	0.0194	0.0056
115	0.0373	0.0115
116	0.0178	0.0146
117	0.2290	0.0445
118	0.0041	0.1210
119	0.0044	0.3520
120	0.0043	0.0015
121	0.0058	0.0011
122	0.0255	0.0026
123	0.0374	0.0172
124	0.0405	0.00465
125	0.0112	0.00137
126	0.0175	0.00125
127	0.01451	0.00277
128	0.0469	0.0114
129	0.034	0.00875
130	0.0758	0.0113
131	0.0404	0.0058
132	0.0194	0.00322
133	0.33	0.0969
134	0.166	0.0495
135	0.0202	0.00552
136	0.0437	0.0391
137	0.0105	0.00423
138	0.0288	0.0249
139	0.0145	0.0103
140	0.0464	0.0141
141	0.0148	0.0095
142	0.1130	0.0286
143	0.1000	0.0204
144	0.0540	0.0096
145	0.0284	0.0125
146	0.0127	0.0031
147	0.0137	0.0125
148	NT	NT
149	0.0283	0.0230
150	0.0315	0.0458
151	0.0274	0.0450
152	0.0321	0.0305
153	0.0165	0.0489

154	0.0331	0.0185
155	0.2190	0.1760
156	0.0941	0.0351
157	0.0179	0.0149
158	0.1500	0.1820
159	0.0120	0.0133
160	0.0047	0.0153
161	0.0521	0.0472
162	0.1220	0.0598
163	0.0815	0.0581
164	0.0081	0.0124
165	0.0958	0.0220
166	0.0172	0.0096
167	0.0237	0.0088
168	0.0304	0.0503
169	0.0329	0.0199
170	0.0304	0.0119
171	0.0398	0.0422
172	0.2110	0.3540
173	0.1830	0.0862
174	0.1520	0.0844
175	0.0652	0.1270
176	0.0379	0.0227
177	0.0203	0.1050
178	0.1330	0.1720
179	0.0076	0.0311
180	0.0093	0.0037
181	0.1300	0.0230
182	0.0263	0.0056
183	0.00899	0.00076
185	0.283	0.118
186	NT	NT
187	0.0142	0.0058
188	0.0077	0.0311
189	0.0093	0.0037
190	0.1300	0.0230
191	0.0263	0.0056
192	1.7000	2.000
193	0.0047	0.0025
194	0.0103	0.00345
195	0.0142	0.0256
196	0.0124	0.00952
197	0.00283	0.0168
198	0.308	0.452
199	0.00865	0.185

200	0.0345	0.0142
201	0.104	0.0469
202	0.0322	0.0755
203	0.669	0.731
204	0.066	0.137
205	0.0146	0.00326
206	0.0592	0.0211
207	0.0293	0.025
208	0.0477	0.0108
209	0.00372	0.00884
210	0.0177	0.00347
211	0.0154	0.00323
212	0.0135	0.00535
213	0.0207	0.00728
214	0.0136	0.00473
215	0.0815	0.166
216	0.0304	0.0137
217	0.016	0.0101
218	0.0103	0.00345
219	0.00845	0.00217
220	0.025	0.0168
221	0.125	0.347
222	0.00977	0.423
223	0.0642	0.105
224	0.00398	0.0479
225	0.118	0.32
226	0.00888	0.457
227	0.0513	0.0984
228	0.207	0.151
229	0.00512	0.527
230	0.0738	0.243
231	0.315	0.977
232	0.175	0.445
233	0.227	1.59
234	0.0906	0.13
235	0.0164	0.0363
236	0.0133	0.00179
237	0.109	0.0388
238	0.0118	0.00183
239	0.0333	0.0356
240	0.041	0.14
241	0.0144	0.00414
242	0.00634	0.00299
243	0.0149	0.0433
244	0.0141	0.0144

245	0.0523	0.274
246	0.00703	0.0273
247	0.0642	0.0446
248	0.0194	0.00558
249	0.0373	0.0115
250	0.0178	0.0139
251	0.00413	0.121
252	0.00427	0.00148
253	0.0274	0.0313
254	NT	NT
255	0.057	0.0362
256	0.0537	0.0669
257	0.0468	0.0265
258	NT	NT
259	0.0378	0.07
260	NT	NT
261	0.0142	0.0256
262	0.0649	0.106
263	0.0182	0.0234
264	0.0212	0.0351
265	0.0326	0.106
266	0.0331	0.0185
267	0.219	0.176
268	0.0173	0.0315
269	0.113	0.0451
270	0.00877	0.00607
271	0.0275	0.0121
272	0.0336	0.01
273	0.0254	0.0104
274	0.019	0.00593
275	0.0304	0.0503
276	0.0329	0.0199
277	2	2
278	0.0124	0.00952
279	0.0398	0.0422
280	0.0507	0.0456
281	0.0956	0.378
282	0.101	0.233
283	0.199	0.129
284	0.0709	0.0429
285	0.206	2
286	0.0145	0.000488
287	0.0172	0.00743
288	0.058	0.0708
289	0.0124	0.00703

290	0.00283	0.0168
291	0.0236	0.00989
292	0.00736	0.00564
294	0.0667	0.0676
296	0.00984	0.0101
297	0.0166	0.0512
298	0.0906	0.0246
299	0.0244	0.0111
300	0.0214	0.0215
301	0.0467	0.0836
302	0.0418	0.0271
303	0.0227	0.0154
304	0.0652	0.0419
305	0.0414	0.0178
306	0.0282	0.0697
307	0.0815	0.151
308	1.42	2
309	0.0478	0.0988
310	0.0431	0.049
311	0.0397	0.0535
312	0.113	0.0489
313	0.035	0.0538
314	0.0203	0.0519
315	0.089	0.0303
316	0.0565	0.0262
317	0.0821	0.0877
318	0.0447	0.098
319	0.106	0.102
320	0.0687	0.0619
321	0.0651	0.054
322	0.0434	0.039
323	0.0177	0.0133
324	0.0192	0.0248
325	0.0256	0.0275
326	0.107	0.0601
327	1.3	2
328	1.68	2
329	0.0793	0.0933
330	0.0222	0.0428
331	0.355	0.774
332	0.174	0.171
333	0.32	0.286
334	0.0267	0.026
335	0.965	2
336	0.379	0.399

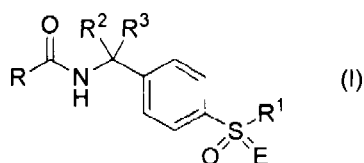
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338	NT	NT
339	NT	NT
340	0.0885	0.0266
341	0.0366	0.0249
342	0.0203	0.023
344	0.302	0.451
345	0.118	0.307
346	0.102	0.198
347	0.381	0.64
348	2	2
349	0.0735	0.0522
350	0.3	0.258
351	0.0711	0.107
352	0.018	0.0203
353	3.97	2
354	0.413	0.726
355	0.00933	0.00374
356	0.0135	0.00325
357	0.0472	0.0187
358	0.0193	0.00458
359	1.6	2.0
360	0.00723	0.00186
361	0.0185	0.0061
362	0.035	0.0221
363	0.0537	0.0456
364	0.00293	0.00351
365	0.00202	0.020
366	0.029	0.0776
367	0.0881	0.015
368	2.0	2.0
369	0.0258	0.00799
370	0.0434	0.0134
371	0.038	0.0124
372	0.0576	0.0612
373	0.113	0.0154
374	0.0152	0.00283
375	0.0275	0.0245
376	0.00582	0.00854
377	0.0249	0.0241
378	0.594	0.143
379	0.114	0.0414
380	0.0683	0.499
381	0.29	0.201
382	2.0	2.0

383	0.0357	0.00646
384	0.0362	0.0391
385	0.0302	0.0567
386	0.060	0.0706

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such
5 alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

1. A compound of Formula (I):



wherein:

E is O or is absent;

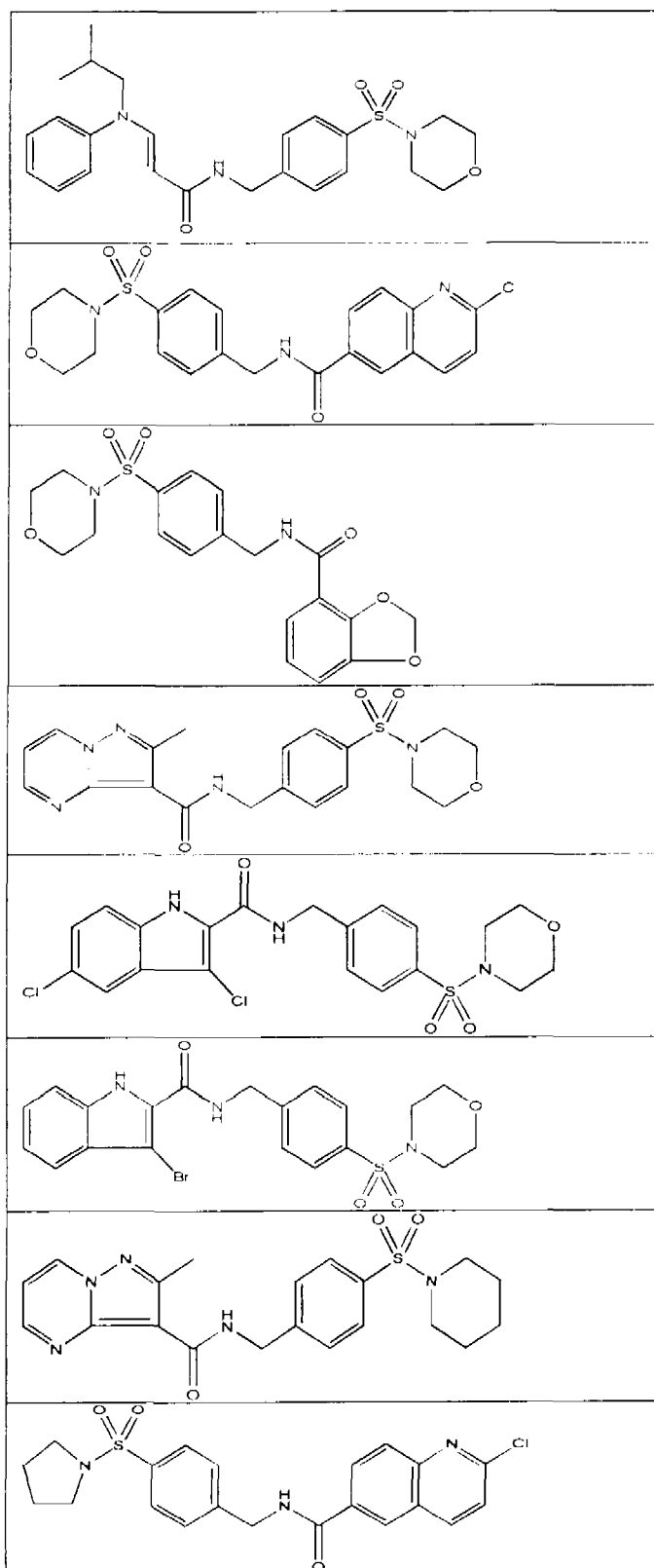
R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

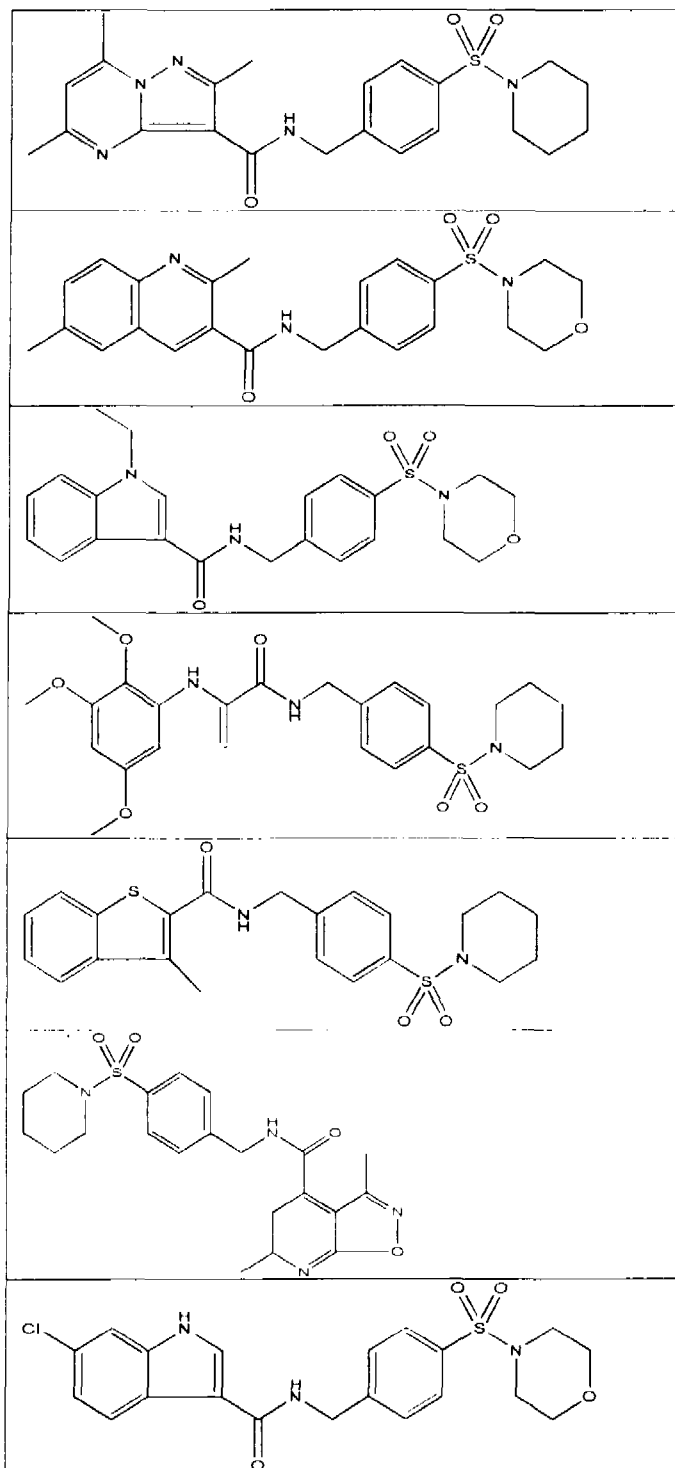
(b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

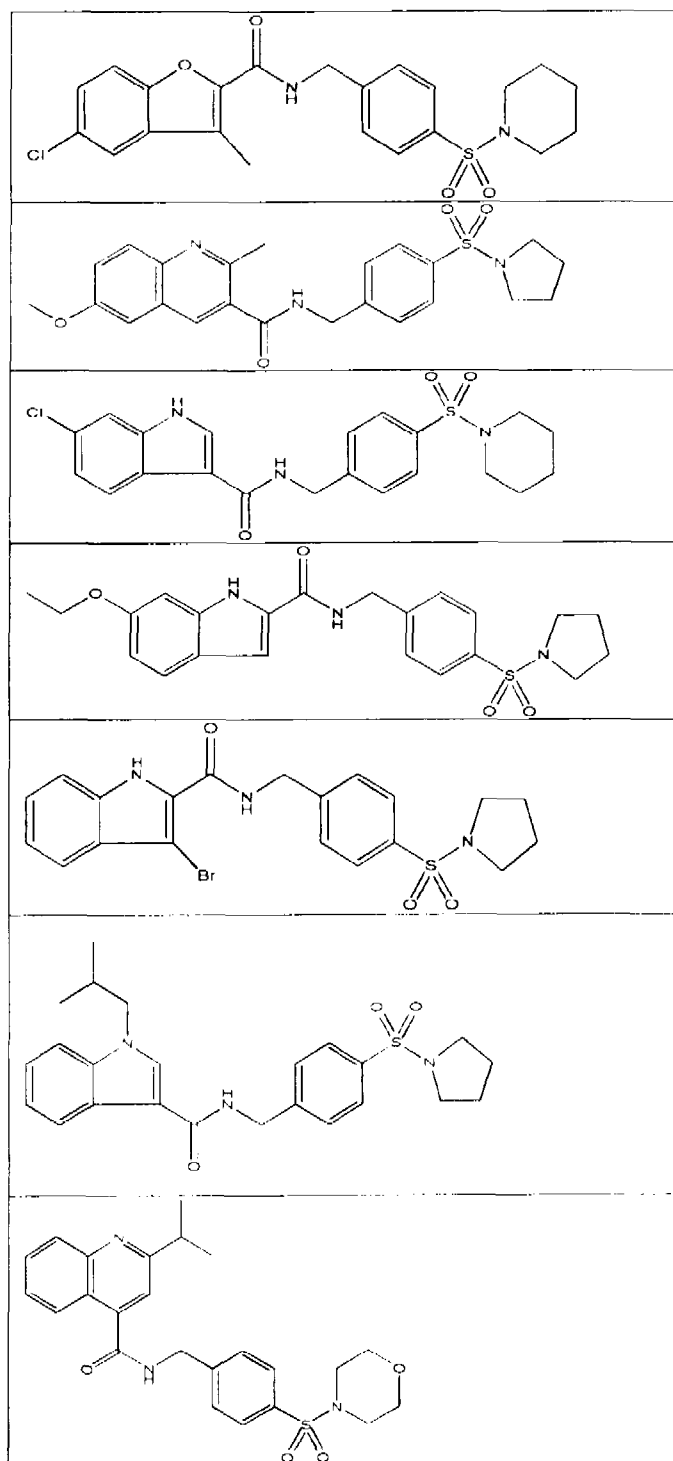
R¹ is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R^x;

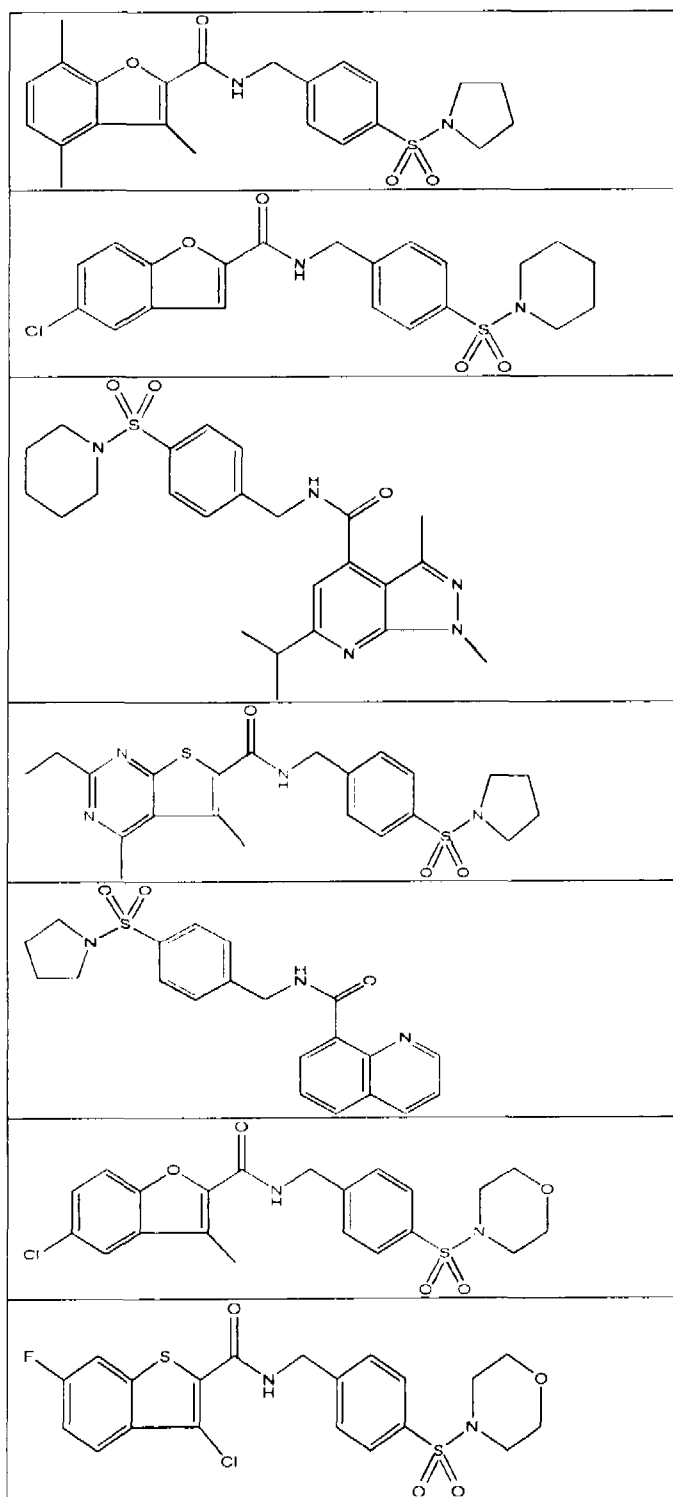
wherein each R^x substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, cyano, -NR^aR^b, -alkylenyl-, NR^aR^b, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl-, aryloxy-, arylalkoxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, -C(O)alkyl, -CO₂alkyl, -CO₂H, -C(O)cycloalkyl, -C(O)aryl,

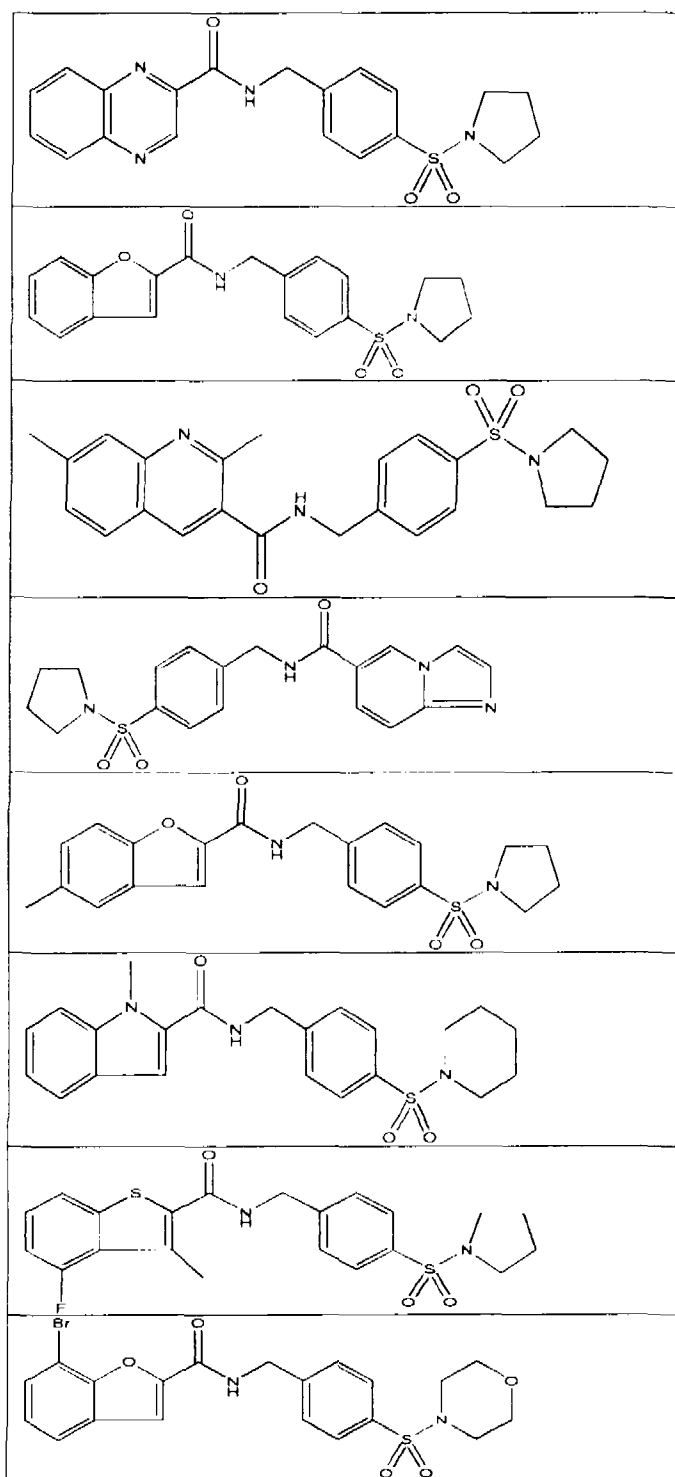
- C(O)heterocycloalkyl, -S(O)-alkyl, -SO₂-alkyl, -SO₂-aryl, -SO₂-
 (haloalkyl), -CONH₂, C(O)NH(alkyl), -C(O)NH(haloalkyl),
 -C(O)N(alkyl)₂, -C(O)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl-,
 -N(R^c)-C(O)-alkyl, -N(R^c)-C(O)-aryl, -N(R^c)-CO₂-alkyl, -SO₂NH₂,
 5 -SO₂NH(alkyl), -SO₂N(alkyl)₂, -SO₂NH(cycloalkyl), and
 -N(H)(SO₂alkyl), or two adjacent R^s substituents taken together form a
 phenyl ring,
 wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and
 phenyl substituents within R^s is independently unsubstituted or
 10 substituted with one or more substituents selected from the group
 consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,
 -NHCO₂alkyl, -C(O)alkyl, and -CO₂alkyl;
 wherein R^a and R^b are each independently H, alkyl, alkoxy,
 alkoxyalkyl, cyanoalkyl, or haloalkyl; and
 15 R^c is H or alkyl; or
 (2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein
 said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system,
 and said heterocycloalkyl is unsubstituted or substituted with one or more
 substituents independently selected from the group consisting of: alkyl,
 20 halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo,
 -NR^dR^e, -alkylenyl-NR^dR^e, -C(O)alkyl, -CO₂alkyl, and -SO₂alkyl;
 wherein R^d is H or alkyl; and
 R^e is H, alkyl, haloalkyl, -C(O)alkyl, -CO₂alkyl, or -SO₂alkyl; and
 R² and R³ are each independently H or deuterium;
 25 or a pharmaceutically acceptable salt thereof,
 with the proviso that the compound of Formula I is not one of the following
 compounds:

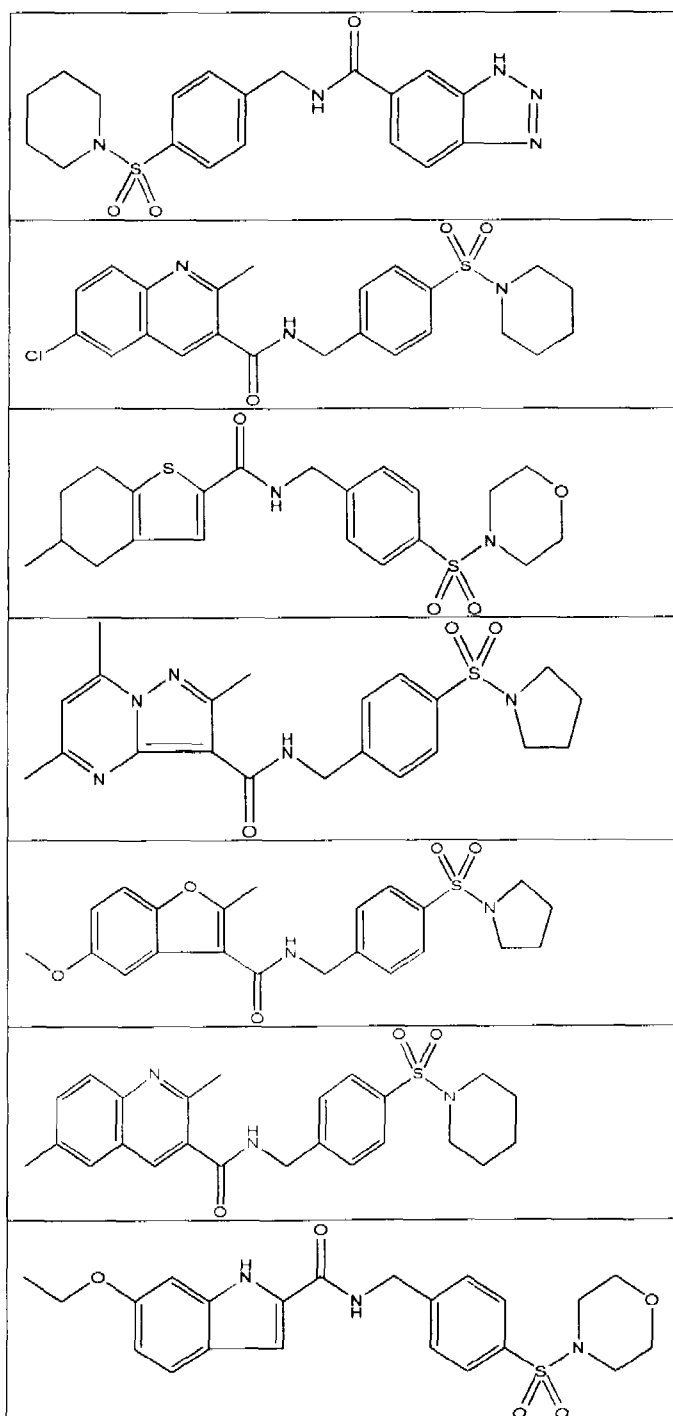


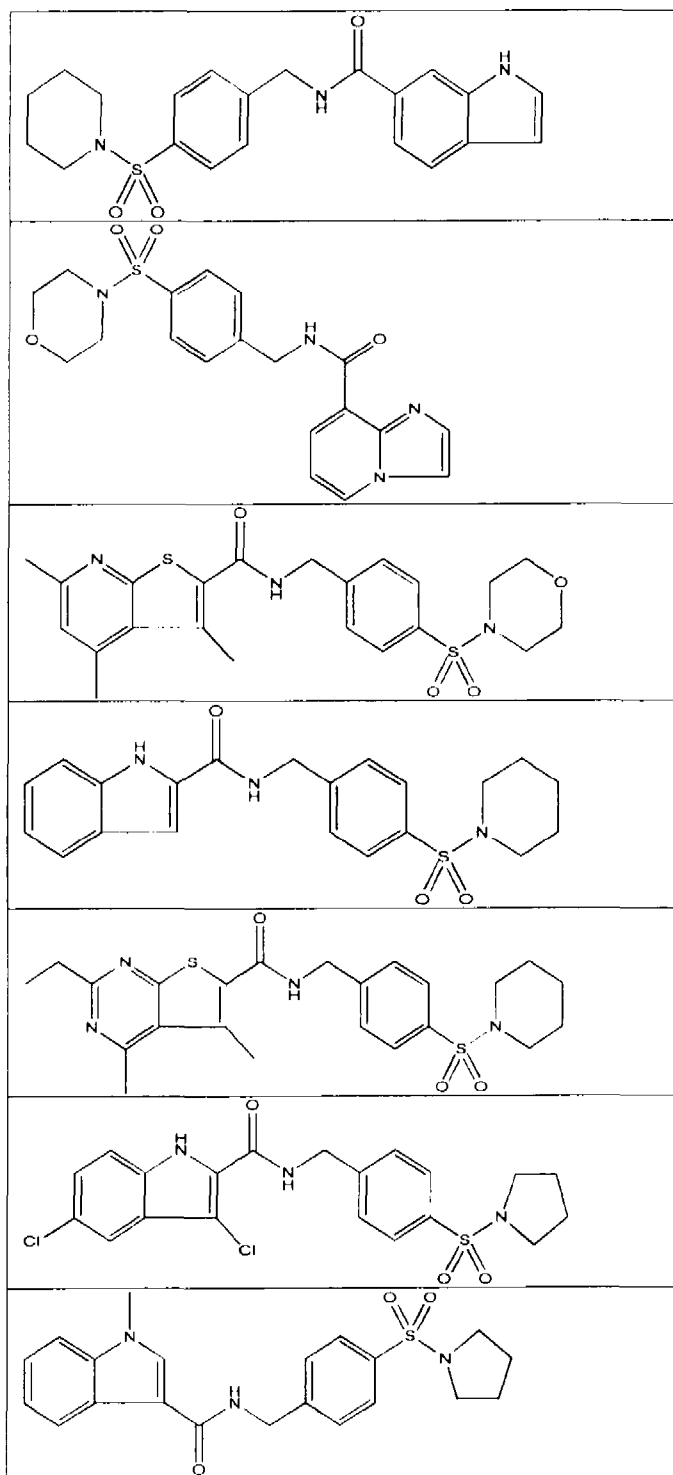


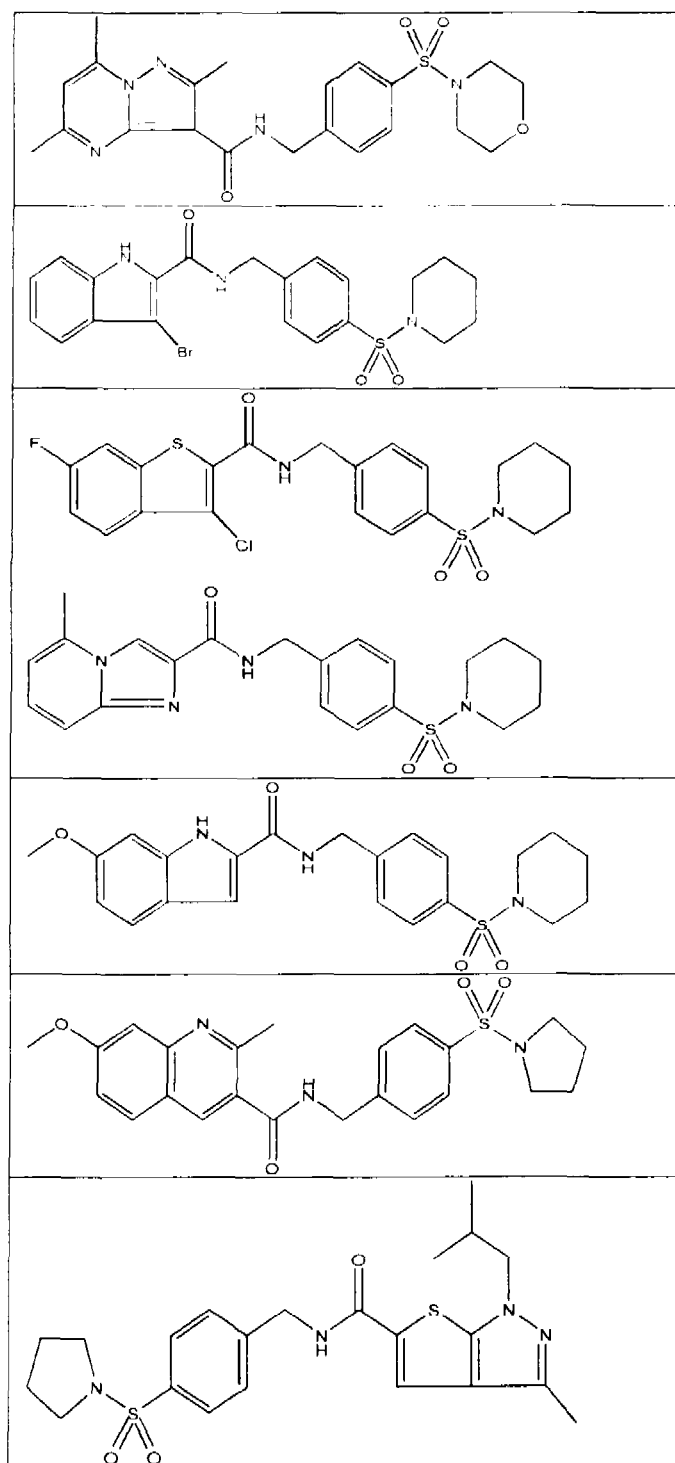


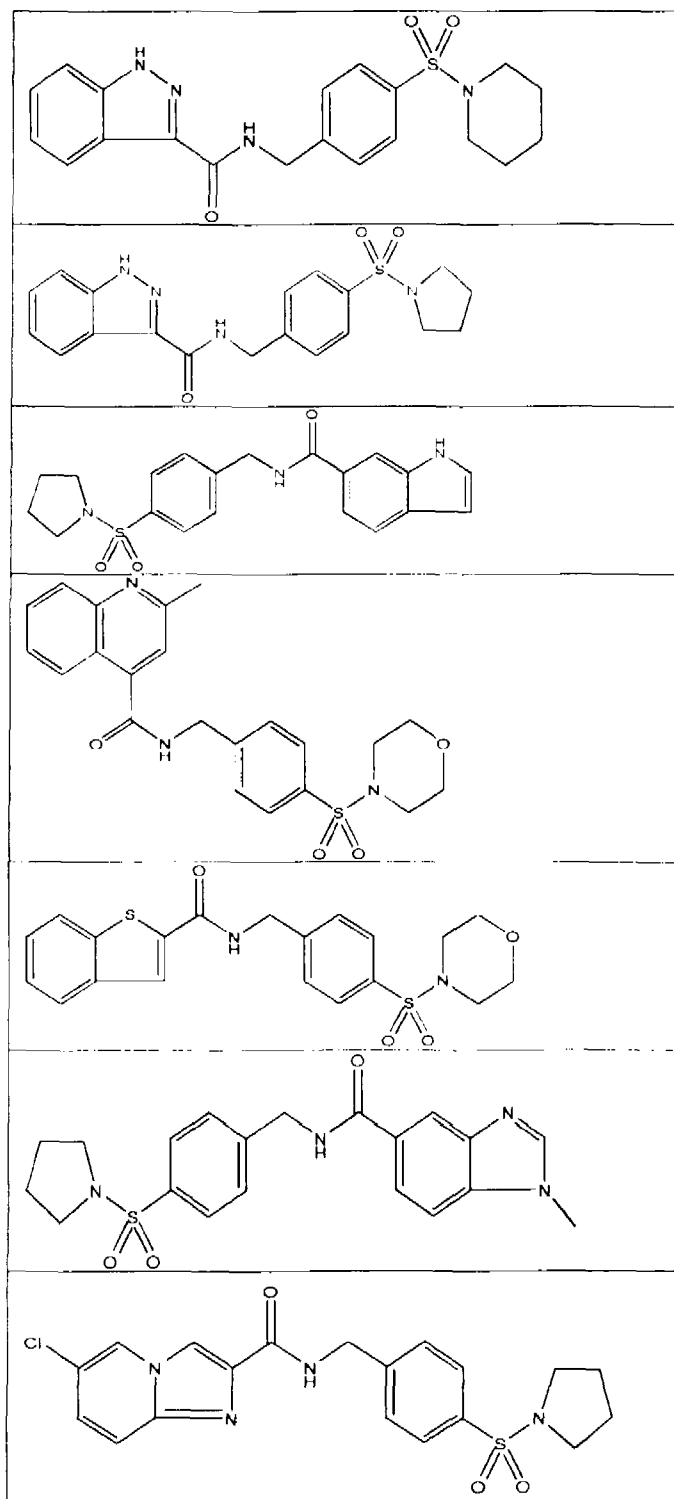


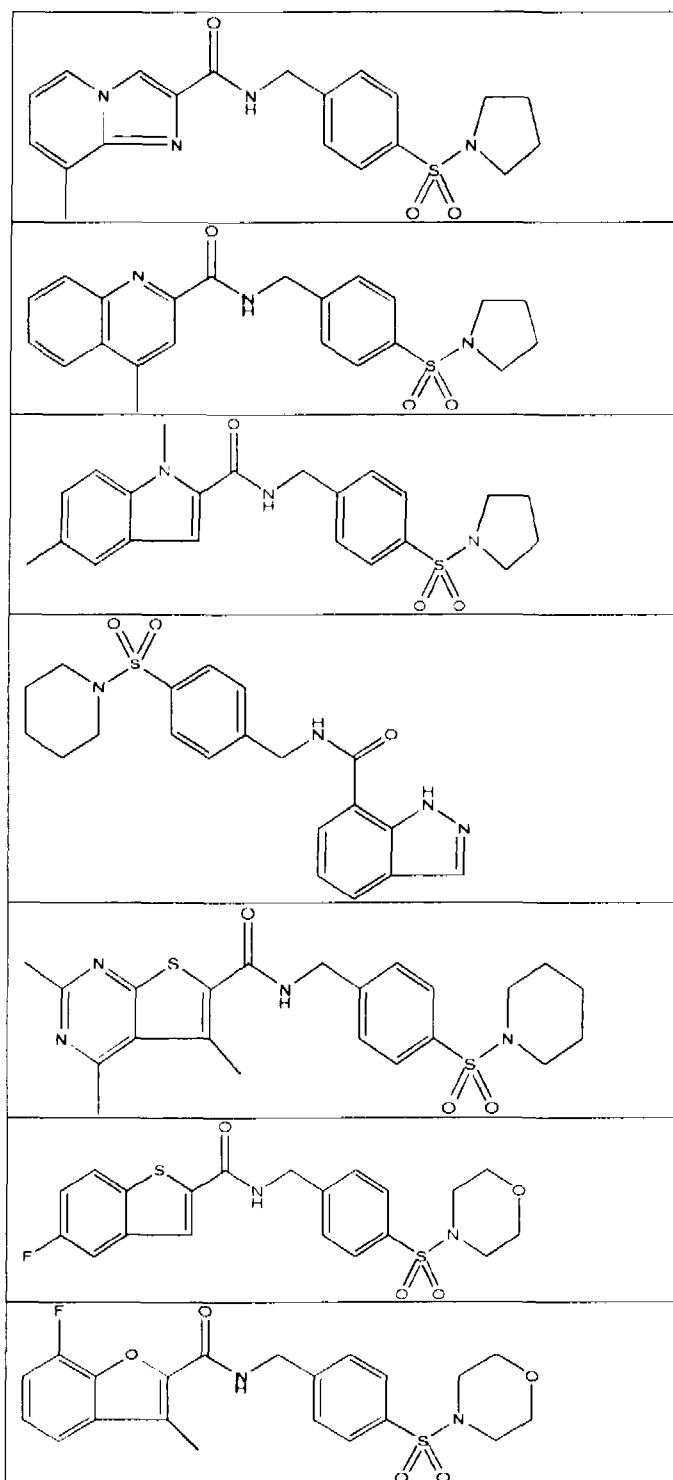


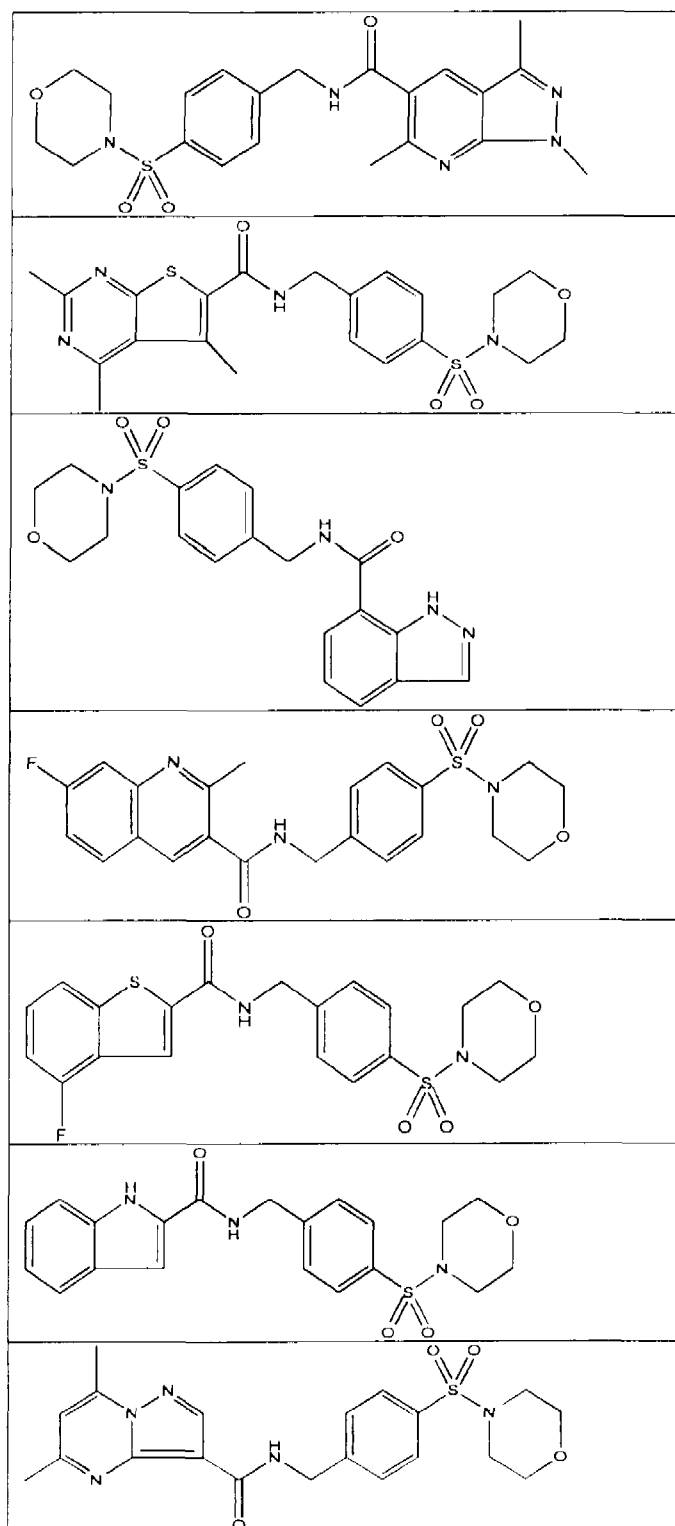


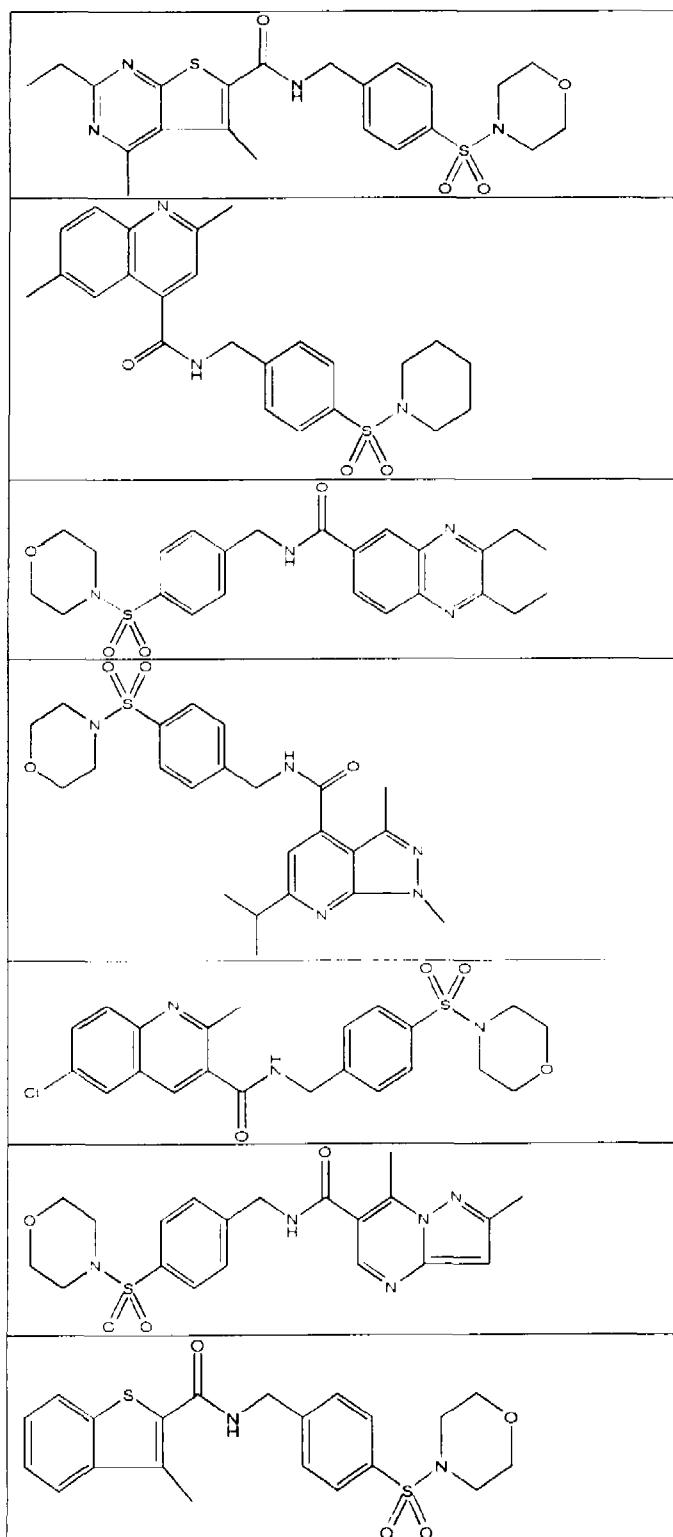


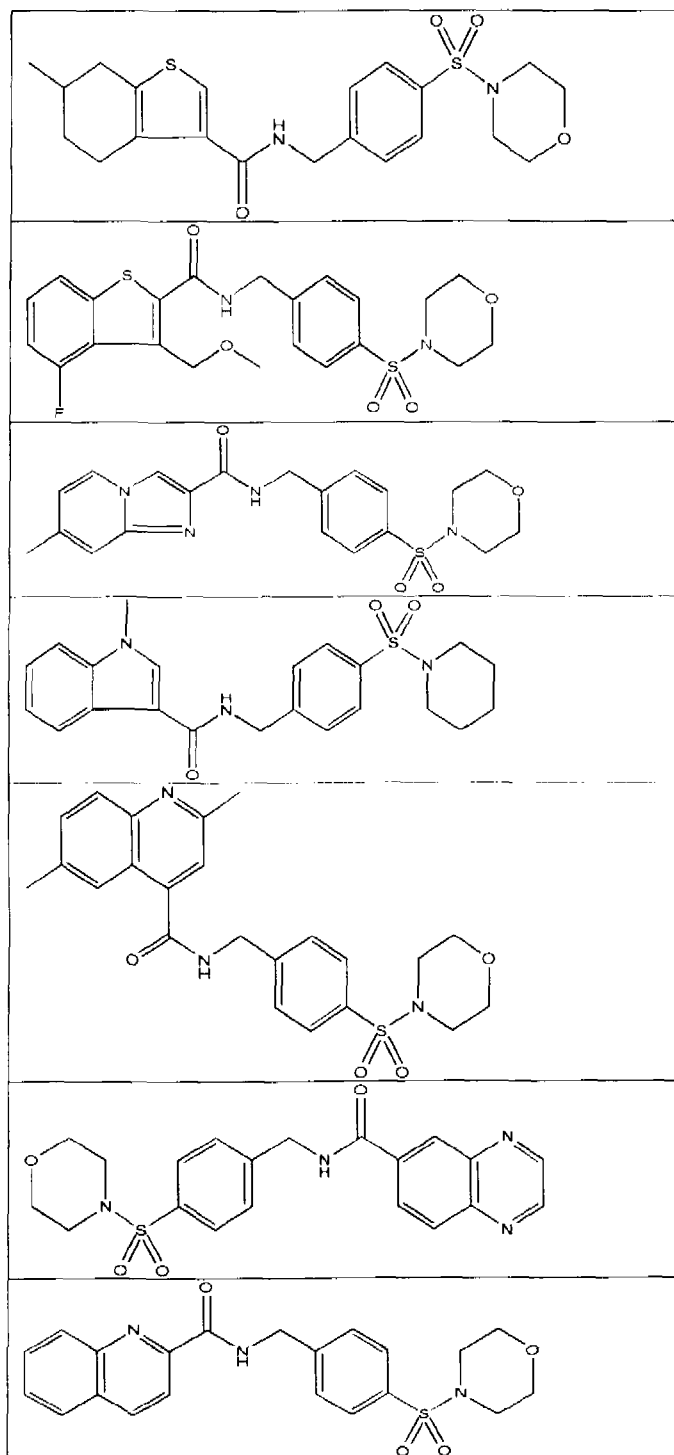


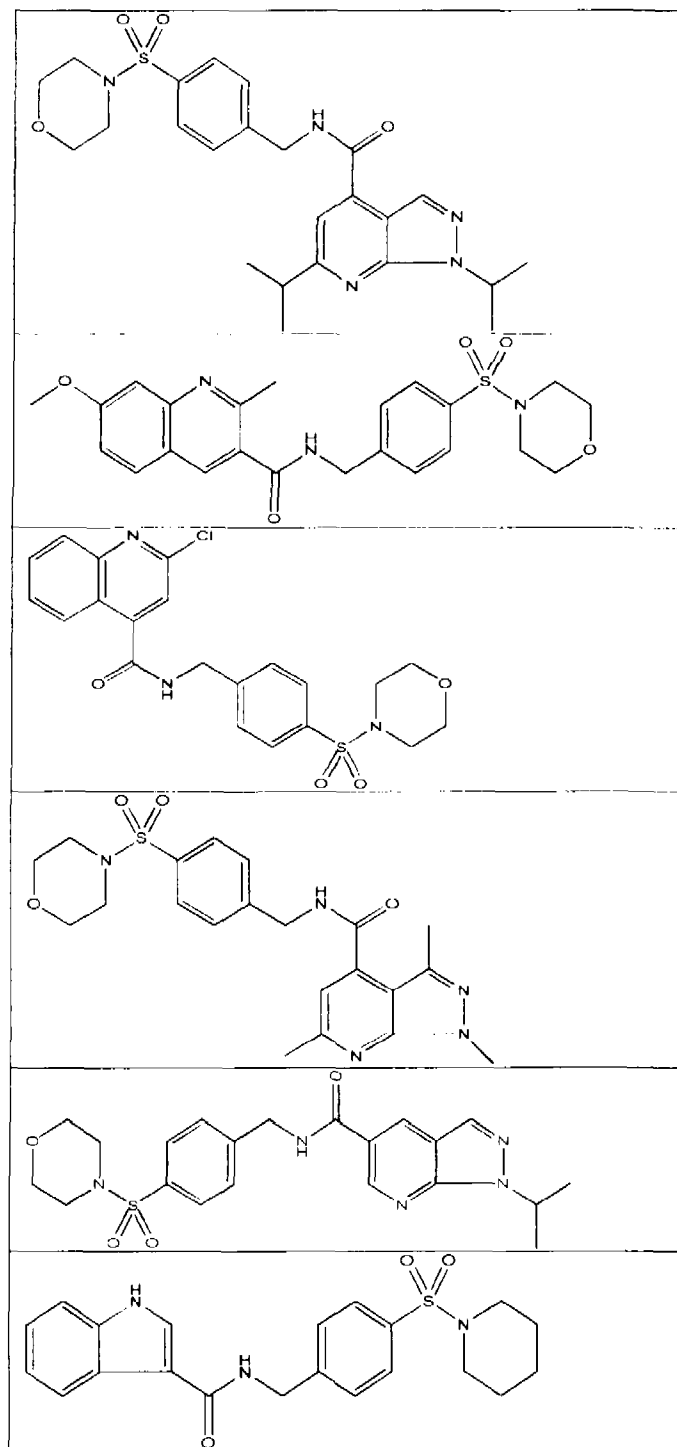


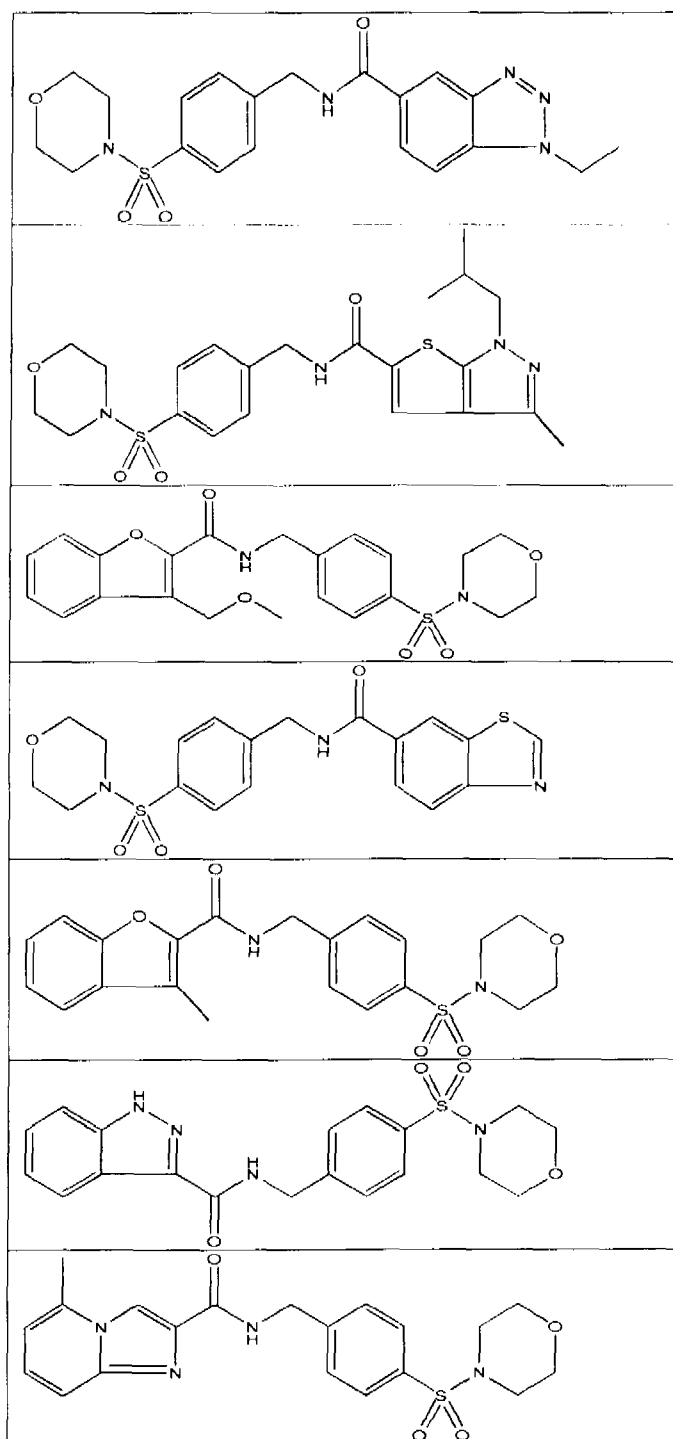


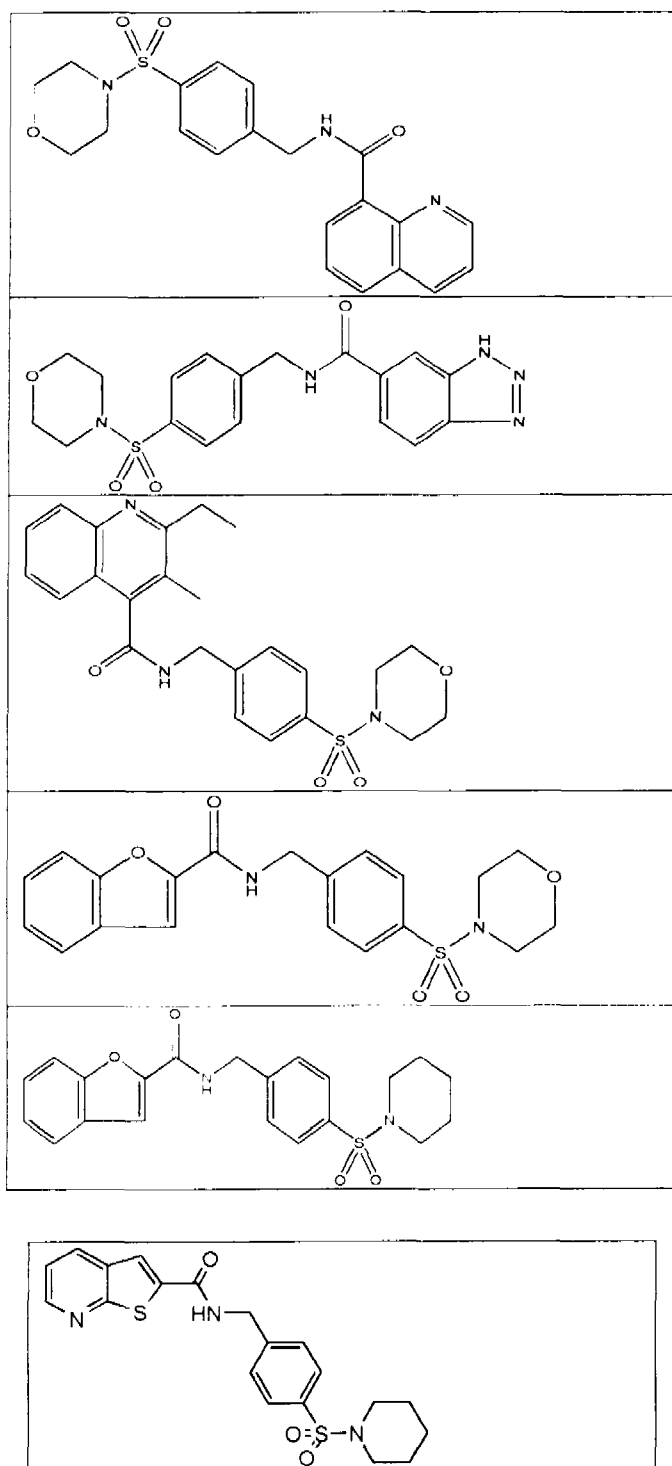


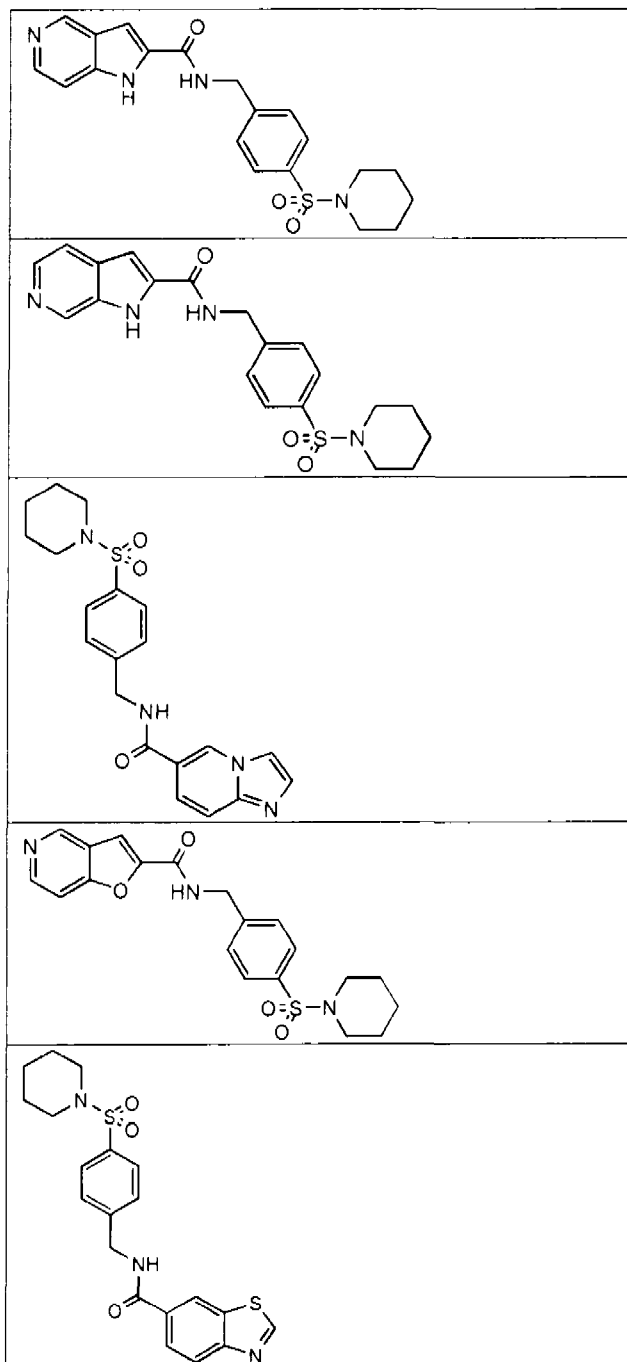


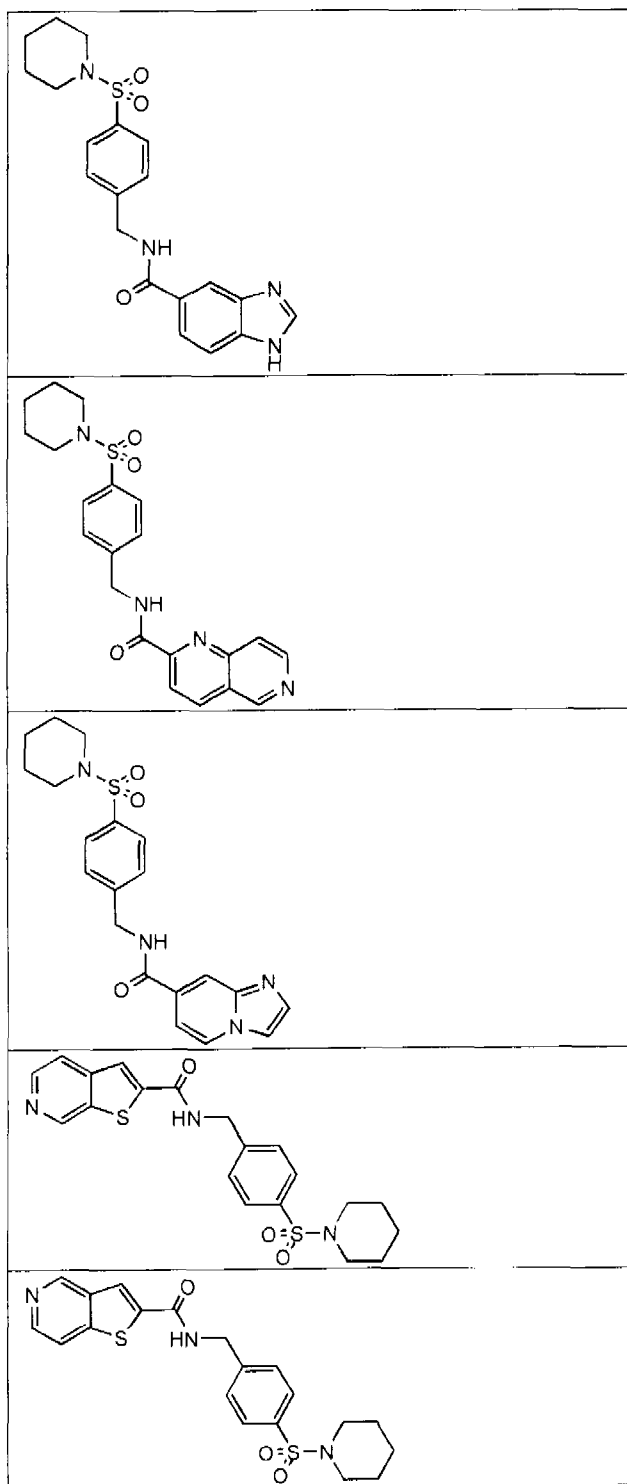


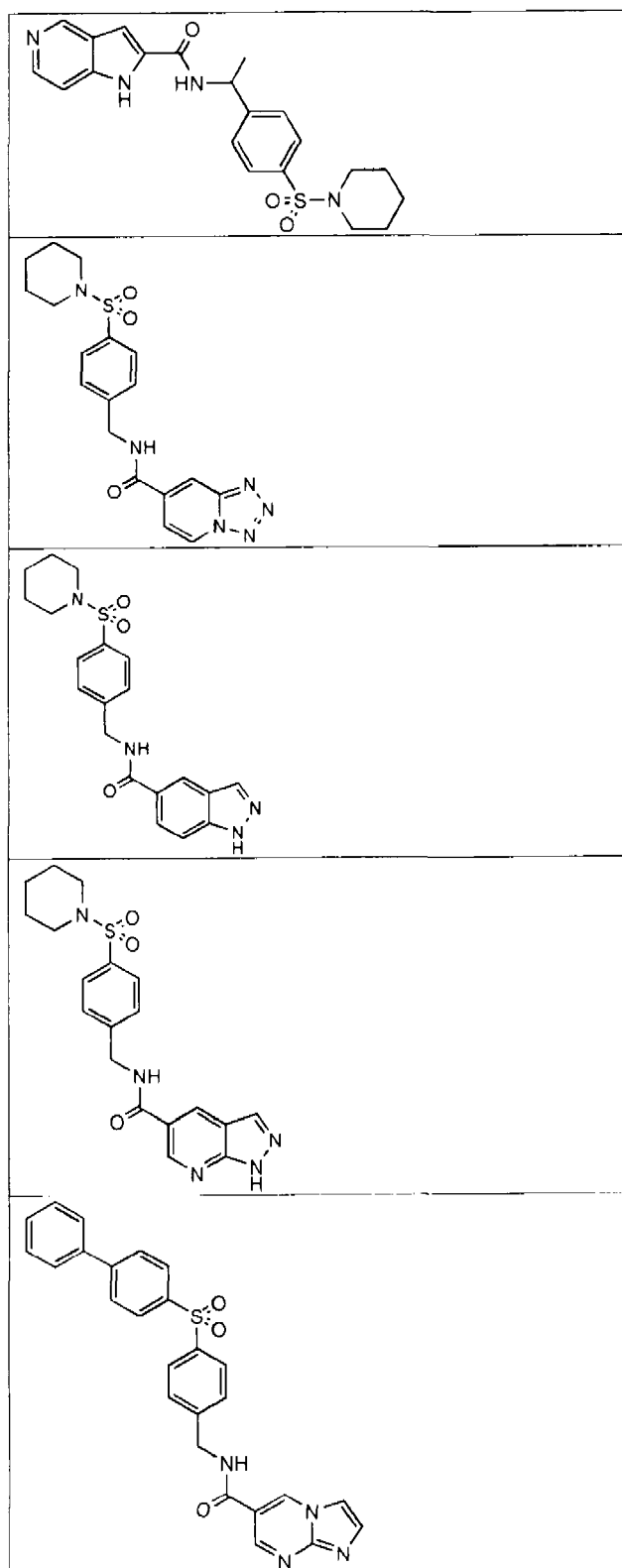


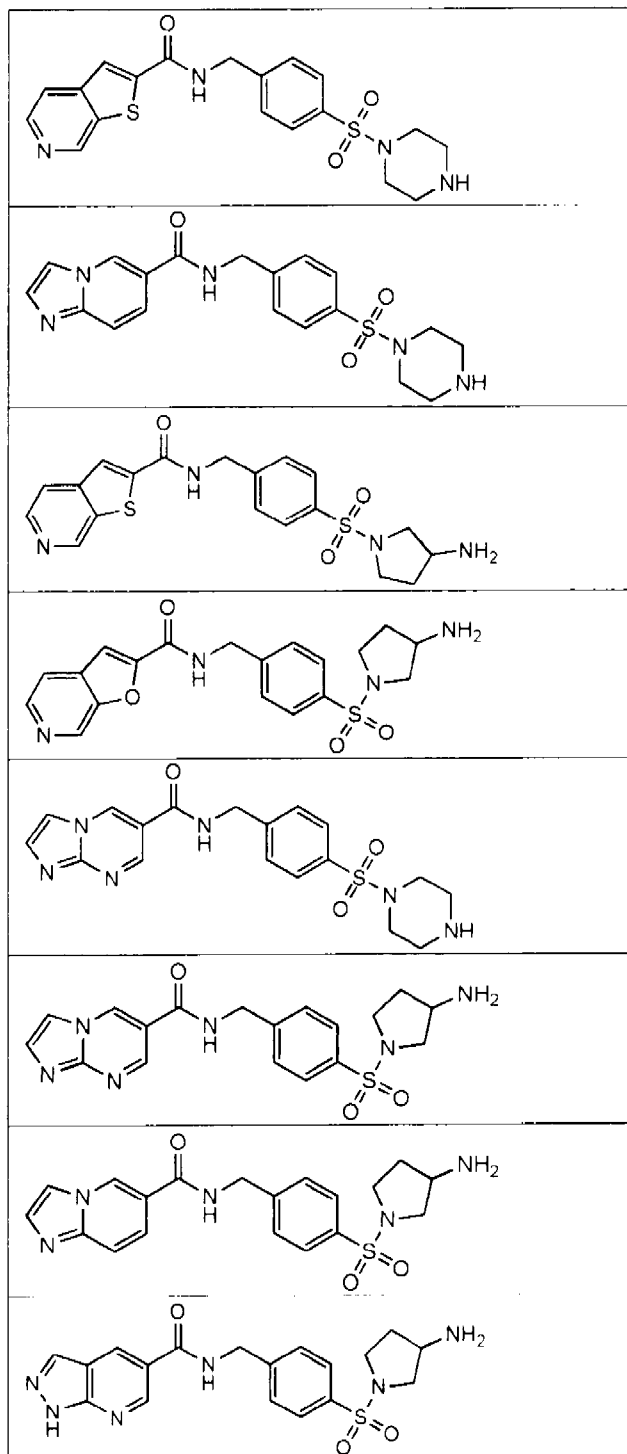


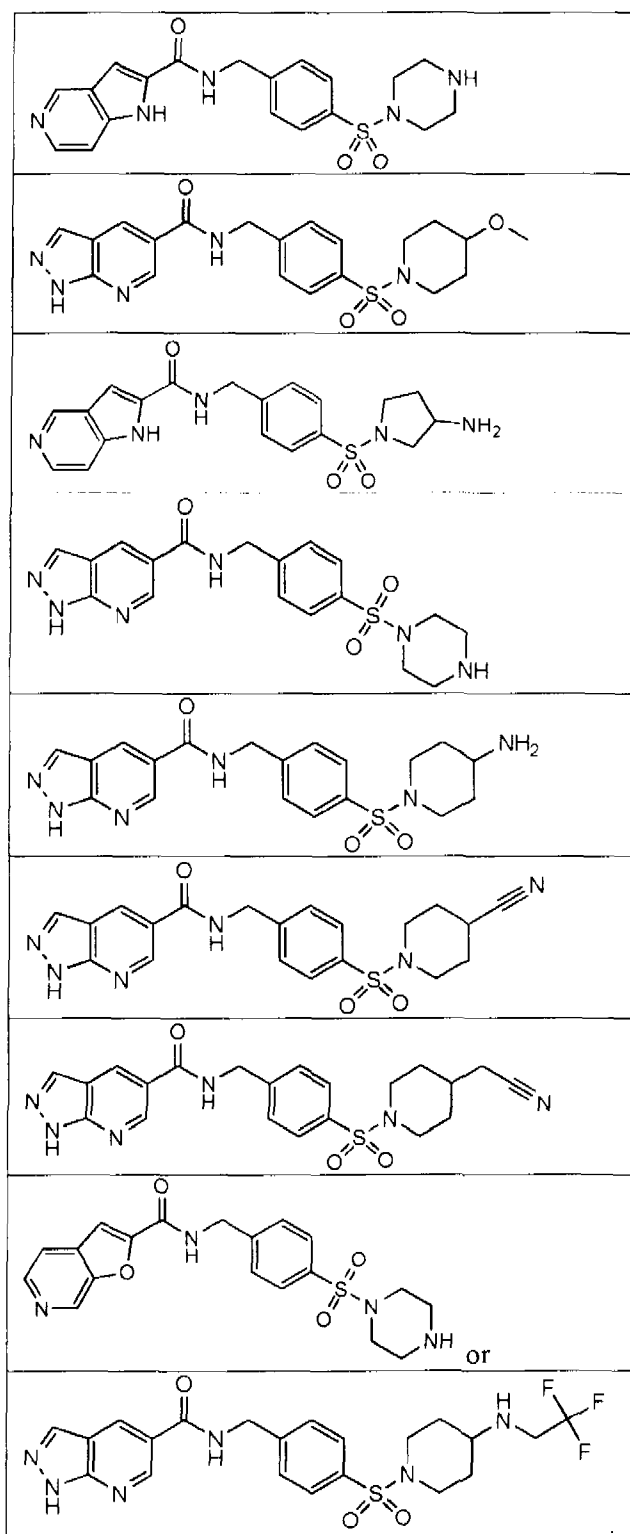












2. The compound of claim 1, wherein E is O.

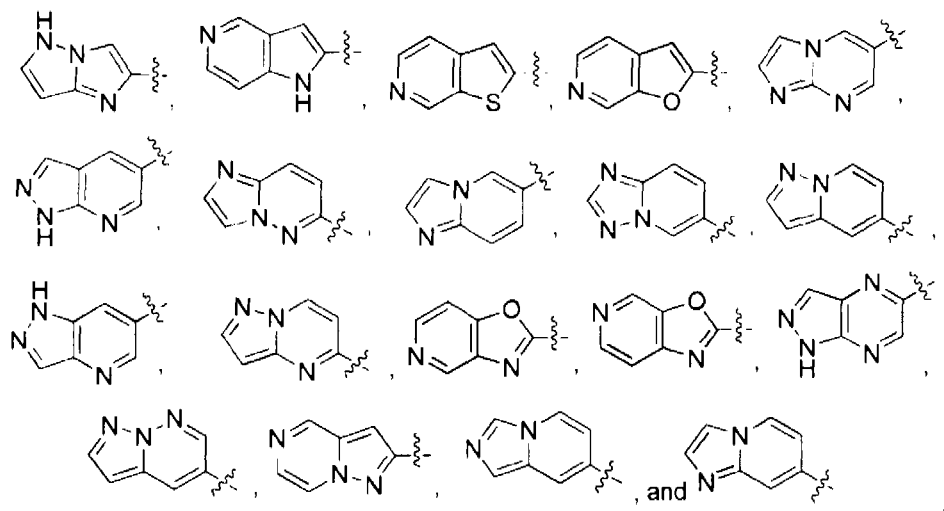
3. The compound of claim 1, wherein E is absent.

4. The compound of claim 1, wherein R is an unsubstituted or substituted bicyclic heteroaryl.

5. The compound of claim 1, wherein R is an unsubstituted or substituted 8- or 9-membered heteroaryl.

10

6. The compound of claim 1, wherein R is a bicyclic heteroaryl selected from the group consisting of:



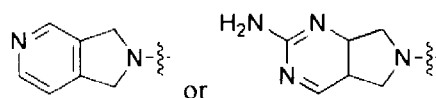
each unsubstituted or substituted as in claim 1.

15

7. The compound of claim 1, wherein R is a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to an unsubstituted or substituted phenyl or monocyclic heteroaryl.

20

8. The compound of claim 1, wherein R is



9. The compound of claim 1, wherein R¹ is a saturated, monocyclic, nitrogen-linked heterocycloalkyl, unsubstituted or substituted as in claim 1.

10. The compound of claim 9, wherein the saturated, monocyclic, nitrogen-linked
5 heterocycloalkyl is azetidiny, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, or diazepanyl, unsubstituted or substituted as in claim 9.

11. The compound of claim 9, wherein the saturated, monocyclic, nitrogen-linked
10 heterocycloalkyl is substituted with one or more R^x groups independently selected from the group consisting of: hydroxy, methoxy, cyano, cyanomethyl, amino, difluoroethylamino, methoxyethylamino, cyanoethylamino, hydroxymethyl, pyrrolidinyl, methyl, ethyl, isopropyl, isobutyl, trifluoroethyl, trifluoromethyl, cyclohexyl, tetrahydropyranyl, pyrrolidinyl, oxetanyl, fluoro, -C(O)(4-methyl-
15 piperazin-1-yl), 4-methylpiperazinyl, -NH(Boc), acetyl, hydroxyethyl, dimethylaminoethyl, cyanoethyl, methoxyethyl, -N(Me)(acetyl), dimethylamino, -C(O)(dimethylamino), and oxo, and where two adjacent substituents taken together form a phenyl ring.

12. The compound of claim 9, wherein the saturated, monocyclic, nitrogen-linked
20 heterocycloalkyl is substituted with 1, 2, or 3 R^x groups independently selected from the group consisting of: methyl, ethyl, isopropyl, hydroxy, methoxy, amino, cyano, fluoro, and trifluoromethyl.

13. The compound of claim 1, wherein R¹ is a saturated, monocyclic, carbon-linked
25 heterocycloalkyl, unsubstituted or substituted as in claim 1.

14. The compound of claim 13, wherein the saturated, monocyclic, carbon-linked
heterocycloalkyl is tetrahydropyranyl, pyrrolidinyl, piperidinyl, or tetrahydrofuranyl,
unsubstituted or substituted as described in claim 13.

30

15. The compound of claim 13, wherein the saturated, monocyclic, carbon-linked heterocycloalkyl is pyrrolidin-3-yl, tetrahydropyran-4-yl, tetrahydropyran-3-yl, piperidin-3-yl, piperidin-4-yl, or tetrahydrofuran-3-yl, unsubstituted or substituted as described in claim 13.

5

16. The compound of claim 13, wherein the saturated, monocyclic, carbon-linked heterocycloalkyl is substituted with one or more substituents independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, trifluoroethyl, acetyl, propionyl, butyryl, isobutyryl, benzoyl, methylsulfonyl, phenylsulfonyl, tert-butoxycarbonyl, tetrahydropyranyl, and oxetanyl.

10

17. The compound of claim 1, wherein R^1 is a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and is unsubstituted or substituted as described in claim 1.

15

18. The compound of claim 17, wherein R^1 is a bridged, bicyclic, nitrogen-linked heterocycloalkyl, unsubstituted or substituted as described for claim 17.

20 19. The compound of claim 17, wherein R^1 is an azetidine, pyrrolidine, piperidine, morpholine, azepane, 1,4-diazepane, or azocane ring, substituted with two substituents on the same or different carbons that together form a C_{1-6} alkylenyl group, wherein one carbon atom of the alkylenyl group is optionally replaced with one or two O, S, or NH groups, and the resulting bicyclic heterocycloalkyl is optionally further substituted as described for claim 17.

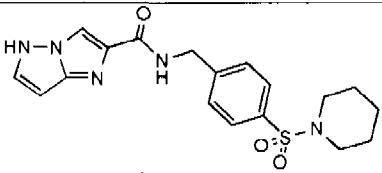
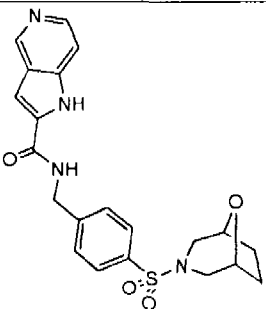
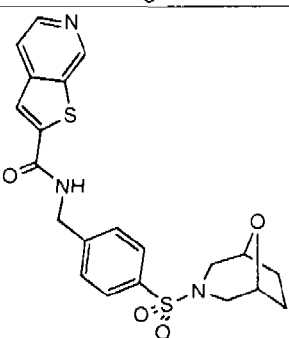
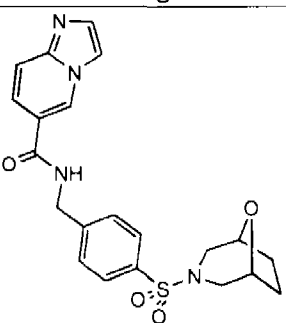
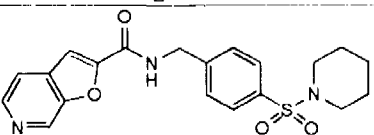
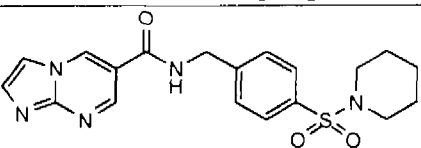
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20. The compound of claim 17, wherein R^1 is substituted with one or more substituents independently selected from the group consisting of: methyl, ethyl, isopropyl, acetyl, fluoro, oxo, hydroxy, tert-butoxycarbonyl, amino, aminomethyl, tert-butoxycarbonylamino, and tert-butoxycarbonyl-aminomethyl.

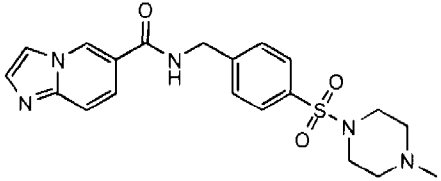
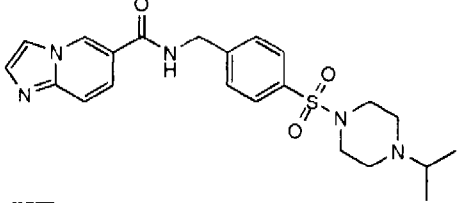
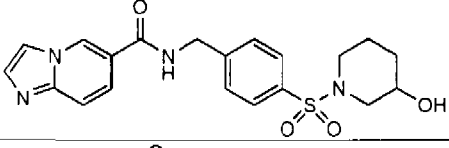
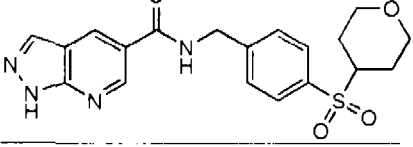
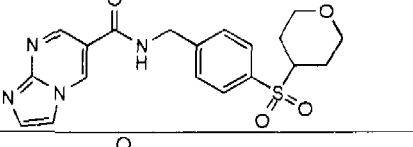
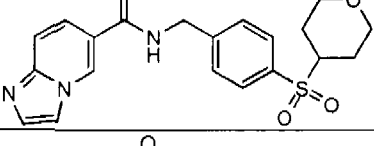
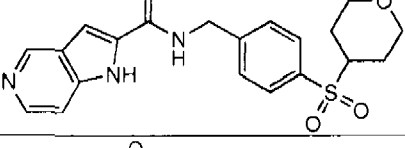
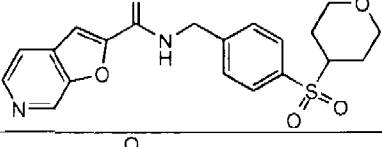
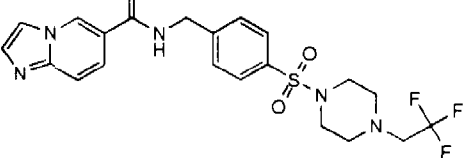
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21. The compound of claim 1, wherein both R^2 and R^3 are H.

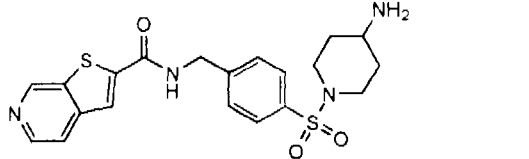
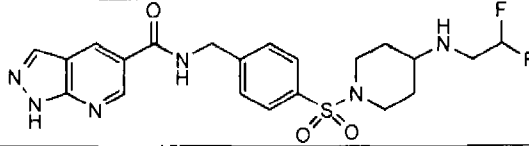
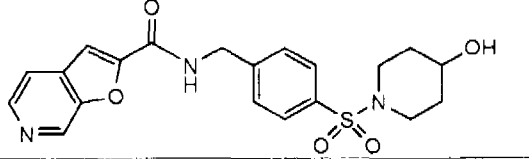
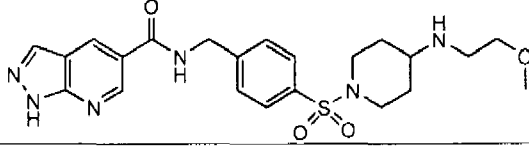
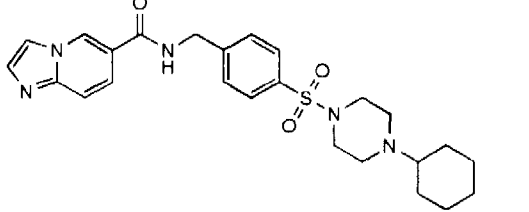
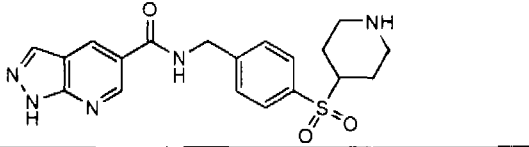
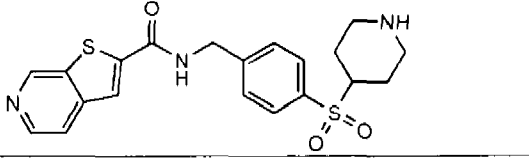
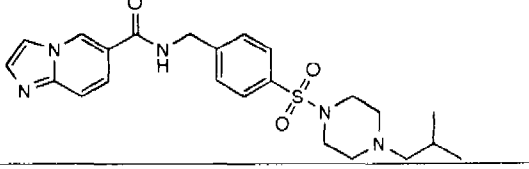
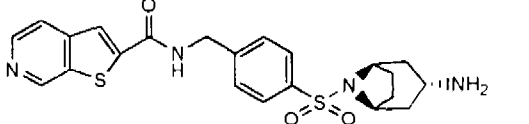
22. A compound selected from the group consisting of:

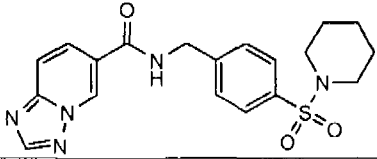
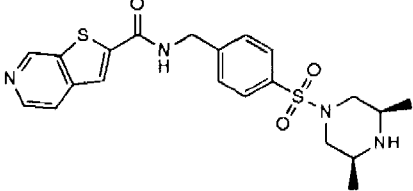
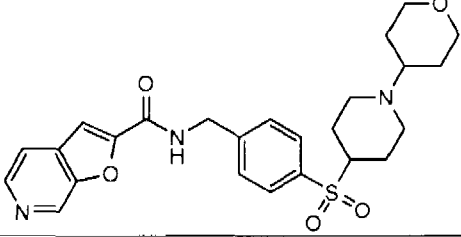
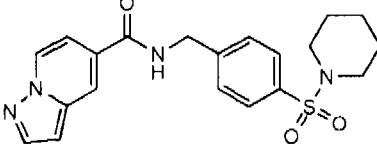
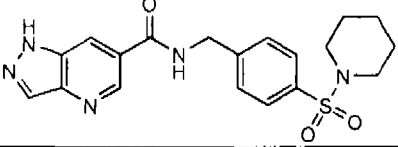
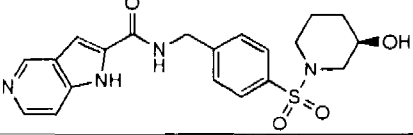
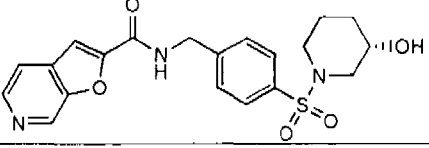
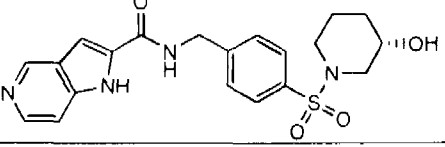
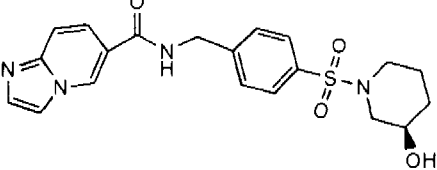
	<p>5H-Imidazo[1,2-b]pyrazole-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;</p>
	<p>1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;</p>
	<p>Thieno[2,3-c]pyridine-2-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;</p>
	<p>Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;</p>
	<p>Furo[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;</p>
	<p>Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;</p>

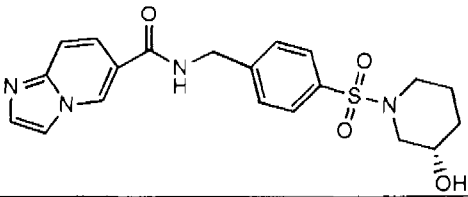
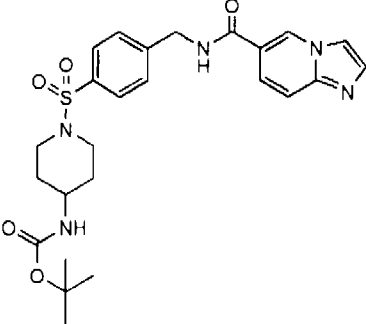
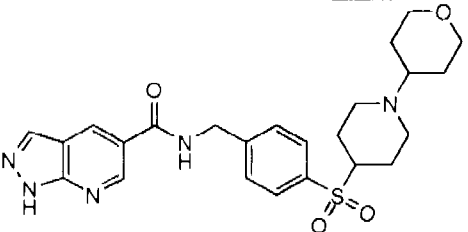
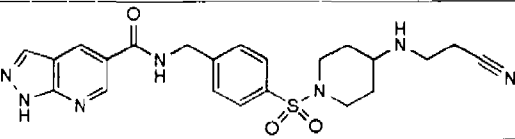
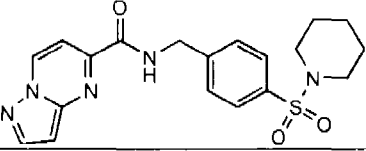
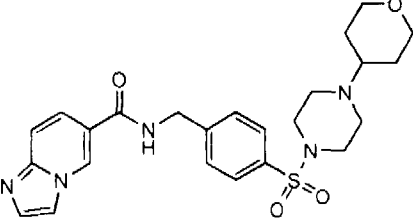
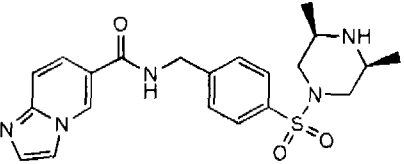
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	Furo[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	Thieno[2,3-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyano-piperidine-1-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-cyanomethyl-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(morpholine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-b]pyridazine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;

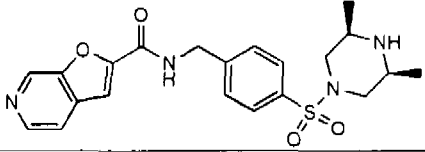
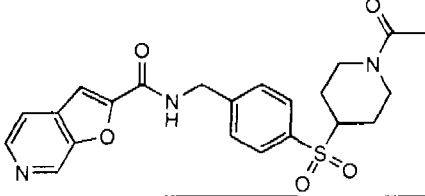
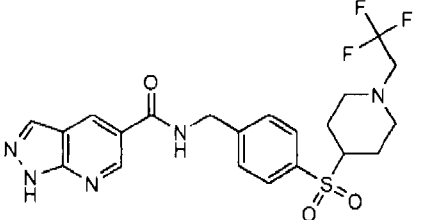
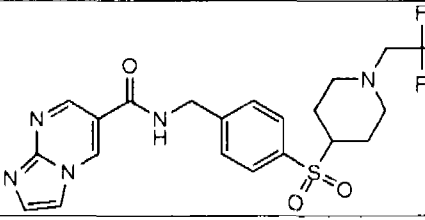
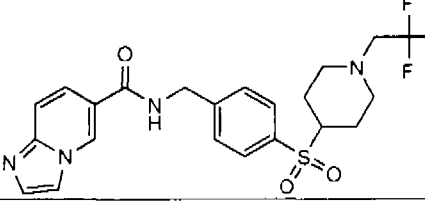
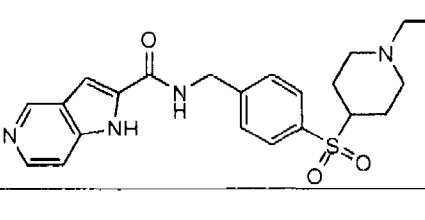
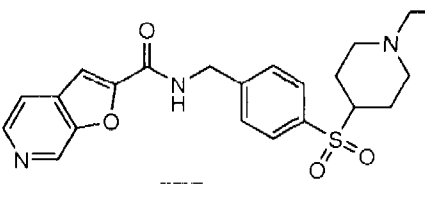
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-methylpiperazine-1-sulfonyl)-benzyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-isopropylpiperazine-1-sulfonyl)-benzyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxypiperidine-1-sulfonyl)-benzylamide (racemic);
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydropyran-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(tetrahydropyran-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydropyran-4-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydropyran-4-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydropyran-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2,2,2-trifluoroethyl)-piperazine-1-sulfonyl]-benzylamide;

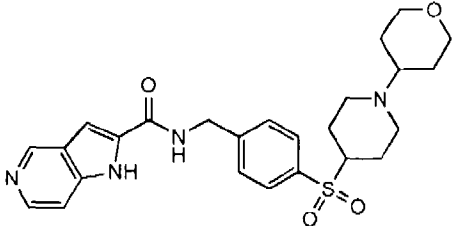
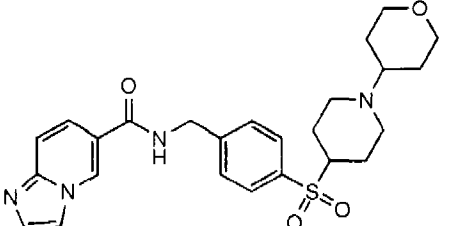
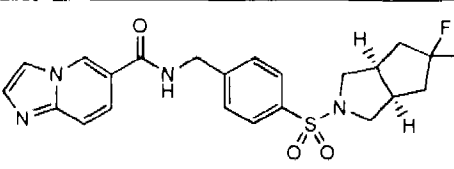
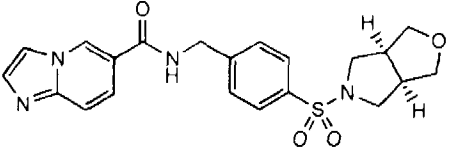
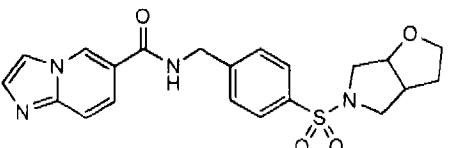
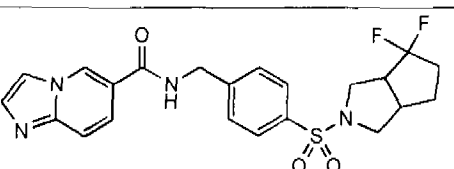
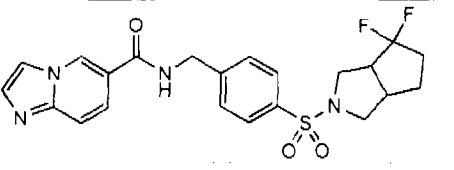
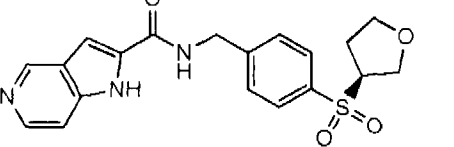
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(3-hydroxy-piperidine-1-sulfonyl)-benzylamide (racemic);

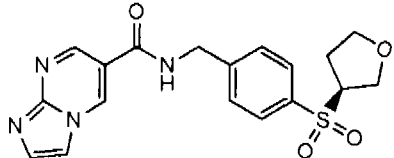
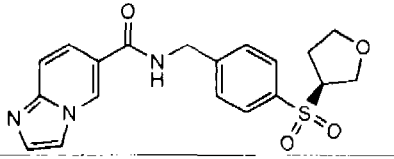
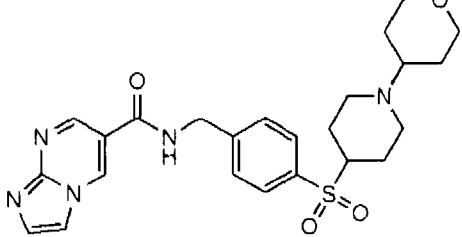
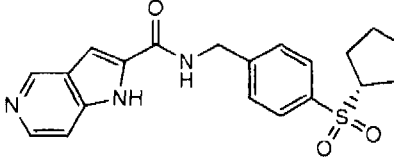
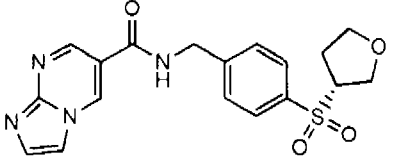
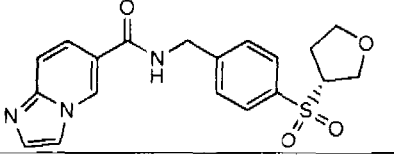
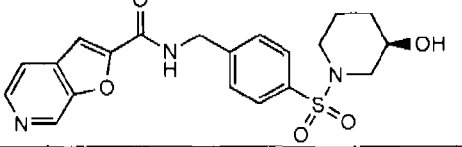
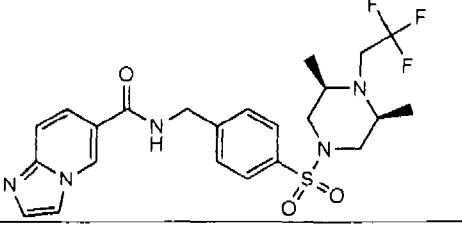
	Thieno[2,3-c]pyridine-2-carboxylic acid 4-(4-amino-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2,2-difluoroethylamino)-piperidine-1-sulfonyl]-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-methoxyethylamino)-piperidine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-cyclohexyl-piperazine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide;
	Thieno[2,3-c]pyridine-2-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-isobutyl-piperazine-1-sulfonyl)-benzylamide;
	Thieno[2,3-c]pyridine-2-carboxylic acid 4-((1R,3R,5S)-3-amino-8-azabicyclo[3.2.1]octane-8-sulfonyl)-benzylamide;

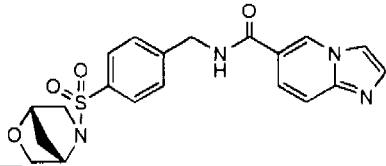
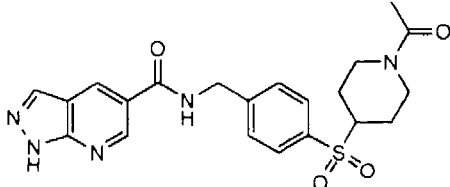
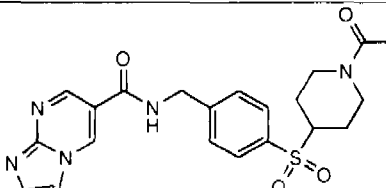
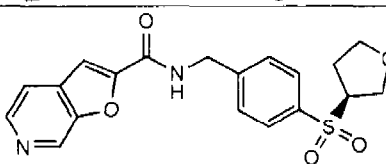
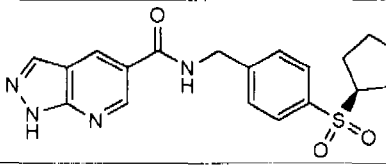
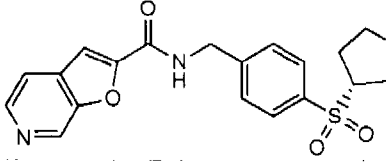
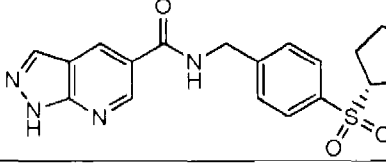
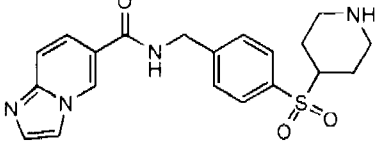
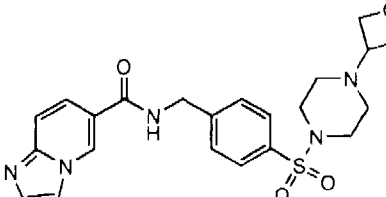
	[1,2,4]Triazolo[1,5-a]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
	Thieno[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(tetrahydro-pyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
	Pyrazolo[1,5-a]pyridine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[4,3-b]pyridine-6-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;

	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;
	[1-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-piperidin-4-yl]-carbamic acid tert-butyl ester;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[1-(tetrahydropyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-cyanoethylamino)-piperidine-1-sulfonyl]-benzylamide;
	Pyrazolo[1,5-a]pyrimidine-5-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(tetrahydropyran-4-yl)-piperazine-1-sulfonyl]-benzylamide;
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide;

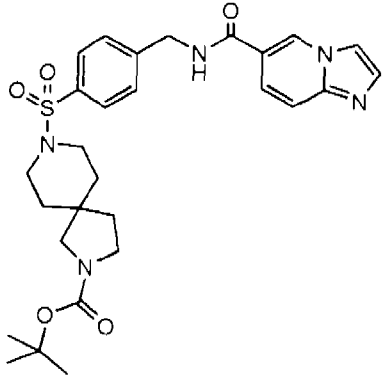
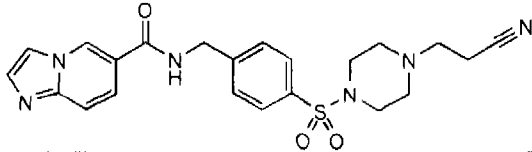
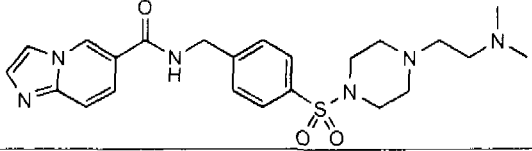
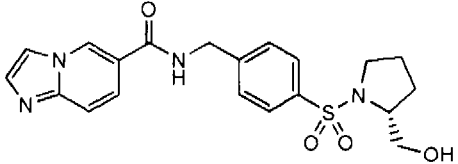
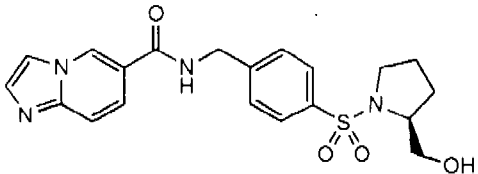
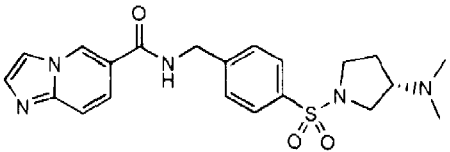
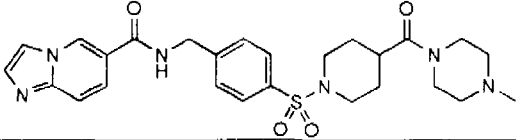
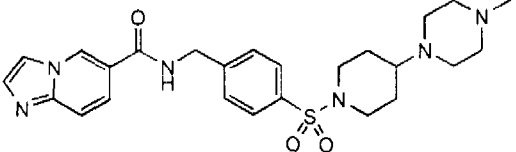
	cis-Furo[2,3-c]pyridine-2-carboxylic acid 4-((3R,5S)-3,5-dimethyl-piperazine-1-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyl]-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyl]-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[1-(2,2,2-trifluoro-ethyl)-piperidine-4-sulfonyl]-benzylamide;

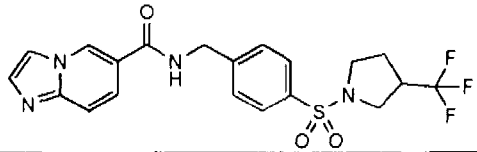
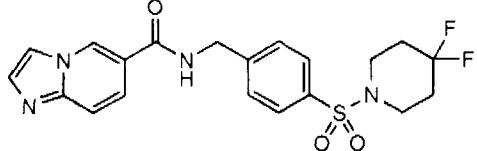
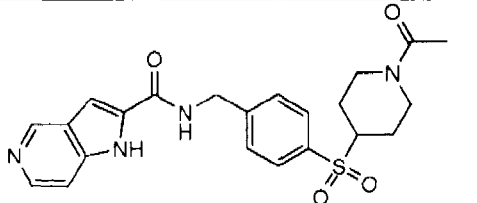
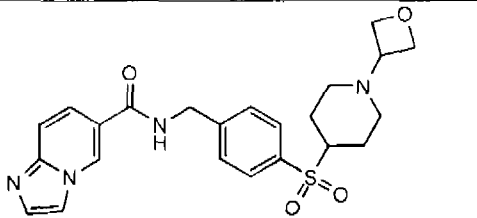
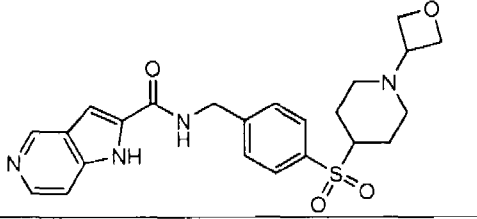
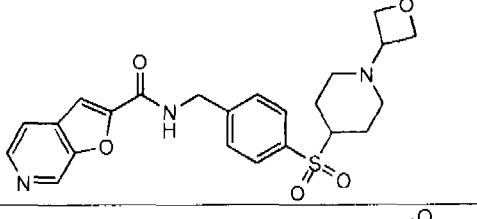
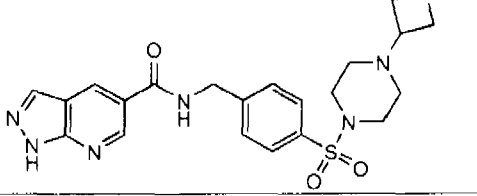
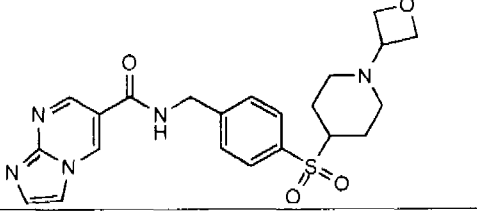
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[1-(tetrahydropyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[1-(tetrahydropyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((3aR,6aS)-5,5-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide;
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3aR,6aS)-(tetrahydro-furo[3,4-c]pyrrol-5-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[2,3-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (isomer A);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-hexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (isomer B);
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;

	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(S)-(tetrahydrofuran-3-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(S)-(tetrahydrofuran-3-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[1-(tetrahydropyran-4-yl)-piperidine-4-sulfonyl]-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydrofuran-3-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-[(R)-(tetrahydrofuran-3-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(R)-(tetrahydrofuran-3-yl)sulfonyl]-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[(R)-3-hydroxy-piperidine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoro-ethyl)-piperazine-1-sulfonyl]-benzylamide;

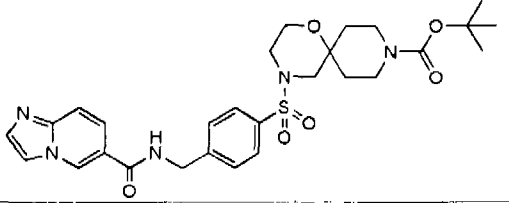
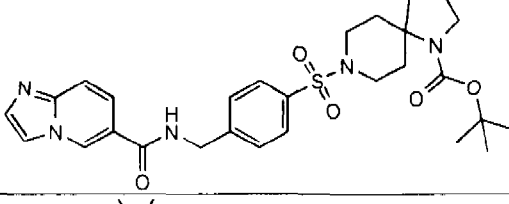
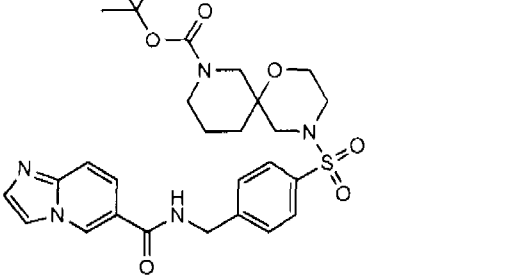
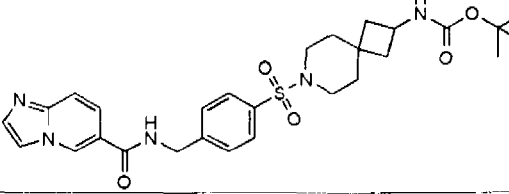
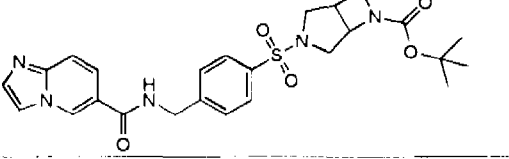
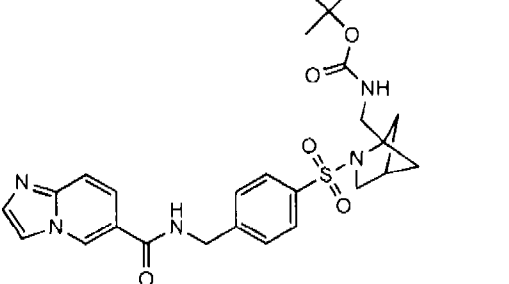
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[(1S,4S)-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)sulfonyl]-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(S)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[(R)-(tetrahydro-furan-3-yl)sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(piperidine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;

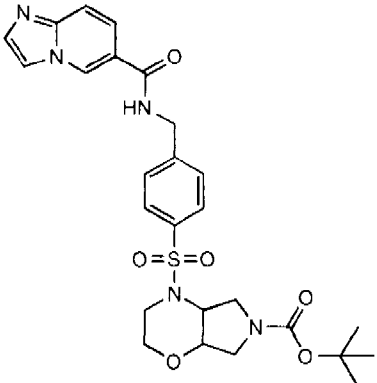
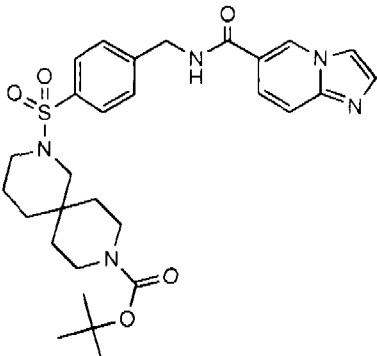
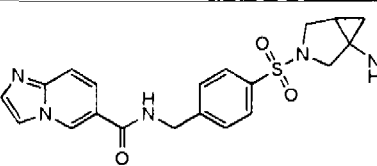
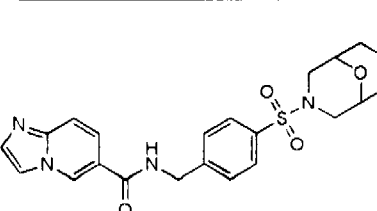
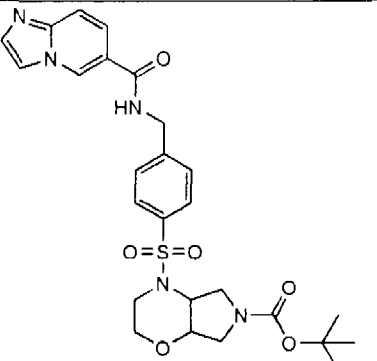
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-acetyl-piperazine-1-sulfonyl)-benzylamide);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-hydroxyethyl)-piperazine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-cyano-piperidine-1-sulfonyl)-benzylamide);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-methoxyethyl)-piperazine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3,3-difluoro-pyrrolidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-(4-acetyl-[1,4]diazepane-1-sulfonyl)-benzylamide);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[3-(acetyl-methyl-amino)-pyrrolidine-1-sulfonyl]-benzylamide (racemic);
	7-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-2,7-diazaspiro[4.5]decane-2-carboxylic acid tert-butyl ester (racemic);

	8-(4- {[(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl}-benzenesulfonyl)-2,8-diazaspiro[4.5]decane-2-carboxylic acid tert-butyl ester;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-cyanoethyl)-piperazine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(2-dimethylaminoethyl)-piperazine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((R)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-2-hydroxymethyl-pyrrolidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-((S)-3-dimethylamino-pyrrolidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methylpiperazine-1-carbonyl)-piperidine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-[4-(4-methylpiperazin-1-yl)-piperidine-1-sulfonyl]-benzylamide;

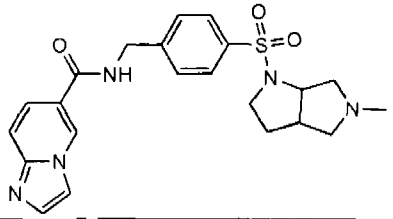
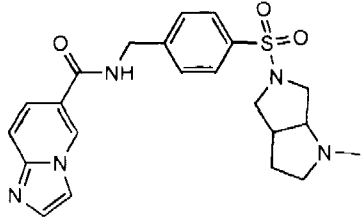
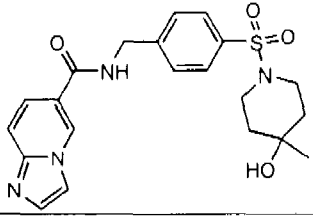
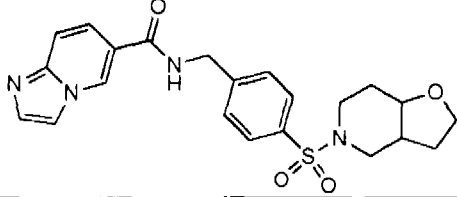
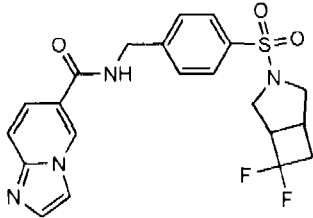
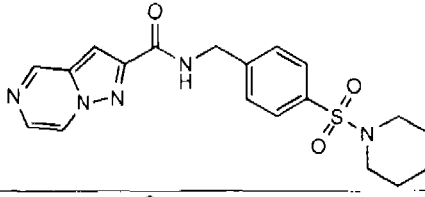
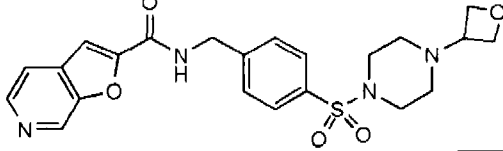
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-trifluoromethyl-pyrrolidine-1-sulfonyl)-benzylamide (racemic);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4,4-difluoro-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide;
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide;

	<p>Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;</p>
	<p>Thieno[2,3-c]pyridine-2-carboxylic acid 4-(1-oxetan-3-yl-piperidine-4-sulfonyl)-benzylamide;</p>
	<p>9-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-3,9-diazaspiro[5.5]undecane-3-carboxylic acid tert-butyl ester;</p>
	<p>9-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-2,9-diazaspiro[5.5]undecane-2-carboxylic acid tert-butyl ester;</p>
	<p>8-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-1,8-diazaspiro[5.5]undecane-1-carboxylic acid tert-butyl ester (racemic);</p>

	<p>4-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylic acid tert-butyl ester;</p>
	<p>8-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-1,8-diazaspiro[4.5]decane-1-carboxylic acid tert-butyl ester;</p>
	<p>4-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylic acid tert-butyl ester (racemic);</p>
	<p>[7-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-7-azaspiro[3.5]non-2-yl]-carbamic acid tert-butyl ester;</p>
	<p>cis-3-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-3,6-diazabicyclo[3.2.0]heptane-6-carboxylic acid tert-butyl ester (racemic);</p>
	<p>[2-(4-{{{(Imidazo[1,2-a]pyridine-6-carbonyl)-amino}-methyl}-benzenesulfonyl})-2-azabicyclo[2.1.1]hex-1-ylmethyl]-carbamic acid tert-butyl ester;</p>

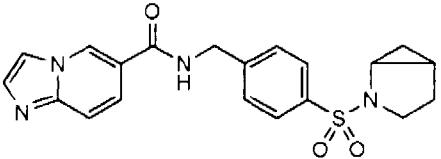
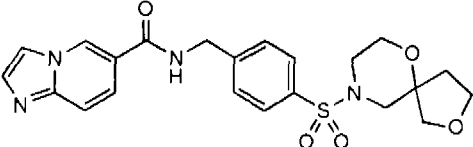
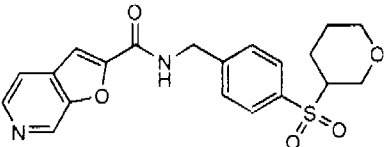
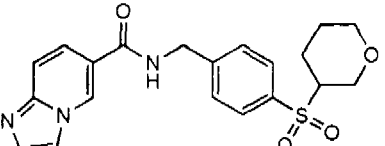
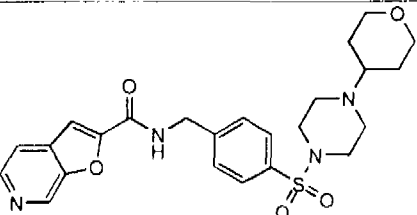
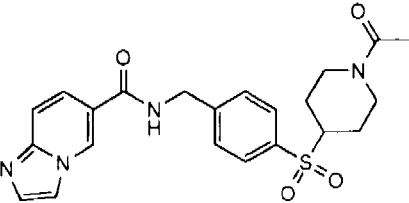
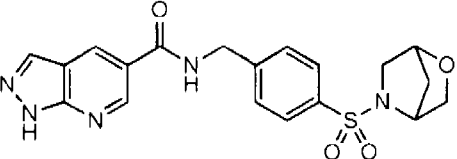
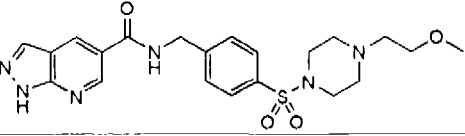
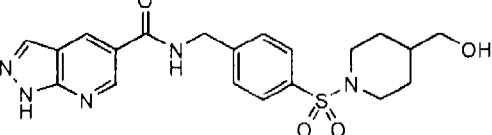
	<p>cis-4-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic);</p>
	<p>2-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-2,9-diaza-spiro[5.5]undecane-9-carboxylic acid tert-butyl ester;</p>
	<p>cis-[3-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-3-azabicyclo[3.1.0]hex-1-yl]-carbamic acid tert-butyl ester (racemic);</p>
	<p>cis-7-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester (racemic);</p>
	<p>cis-4-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b][1,4]oxazine-6-carboxylic acid tert-butyl ester (racemic);</p>

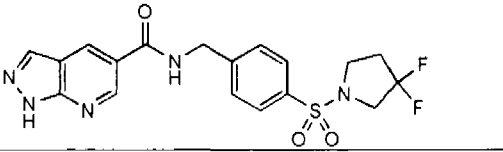
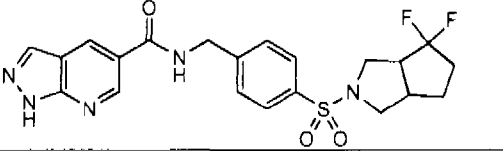
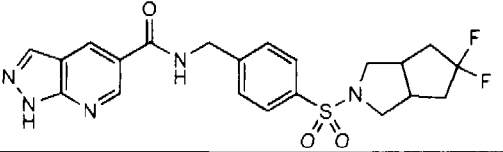
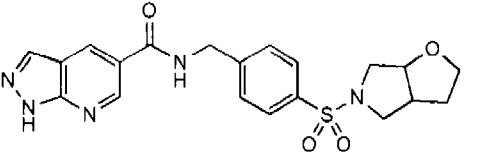
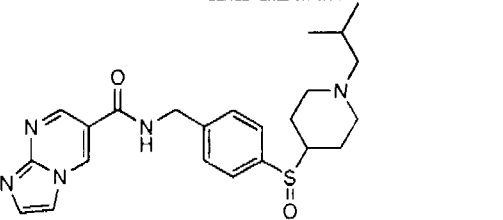
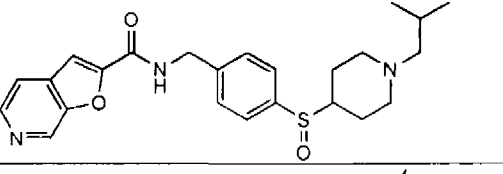
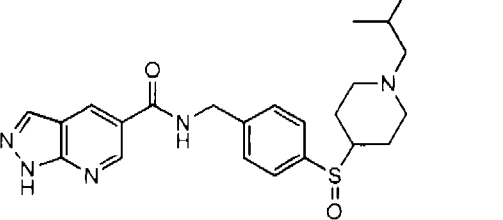
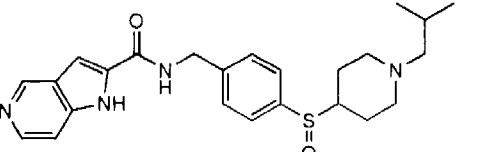
	<p>cis-1-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-5-carboxylic acid tert-butyl ester (racemic);</p> <p>cis-5-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-b]pyrrole-1-carboxylic acid tert-butyl ester (racemic);</p>
	<p>cis-5-(4-(((Imidazo[1,2-a]pyridine-6-carbonyl)-amino)-methyl)-benzenesulfonyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid tert-butyl ester (racemic).</p>
	<p>Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-hydroxy-3-oxa-7-aza-bicyclo[3.3.1]nonane-7-sulfonyl)-benzylamide (mixture of diastereomers);</p>
	<p>trans-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-4-methyl-pyrrolidine-1-sulfonyl)-benzylamide (racemic);</p>
	<p>cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-hydroxy-3-oxa-9-aza-bicyclo[3.3.1]nonane-9-sulfonyl)-benzylamide (racemic);</p>
	<p>cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5,5-difluoro-2-aza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic);</p>
	<p>cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(7-methyl-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-sulfonyl)-benzylamide (racemic);</p>

	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-1-sulfonyl)-benzylamide (racemic);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-methyl-hexahydro-pyrrolo[3,4-b]pyrrole-5-sulfonyl)-benzylamide (racemic);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(4-hydroxy-4-methyl-piperidine-1-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(hexahydro-furo[3,2-c]pyridine-5-sulfonyl)-benzylamide (mixture of diastereomers);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(6,6-difluoro-3-aza-bicyclo[3.2.0]heptane-3-sulfonyl)-benzylamide (racemic);
	Pyrazolo[1,5-a]pyrazine-2-carboxylic acid 4-(piperidine-1-sulfonyl)-benzylamide;
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-oxetan-3-yl-piperazine-1-sulfonyl)-benzylamide;

	<p>Furo[2,3-c]pyridine-2-carboxylic acid 4-((S)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;</p>
	<p>Furo[2,3-c]pyridine-2-carboxylic acid 4-((R)-3-hydroxy-piperidine-1-sulfonyl)-benzylamide;</p>
	<p>Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,8-diazaspiro[4.5]decane-8-sulfonyl)-benzylamide;</p>
	<p>Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-furo[3,4-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);</p>
	<p>1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(tetrahydropyran-3-sulfonyl)-benzylamide (racemic);</p>
	<p>1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydropyran-3-sulfonyl)-benzylamide (racemic);</p>
	<p>1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide;</p>

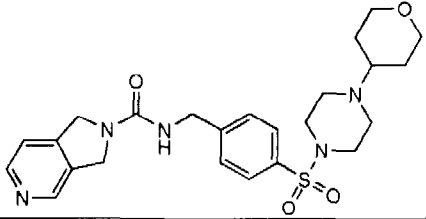
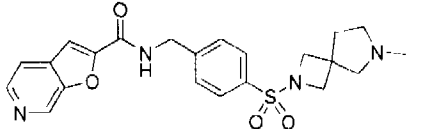
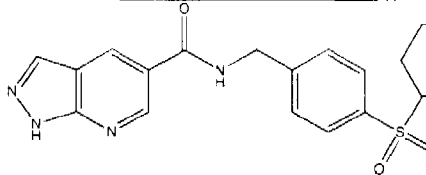
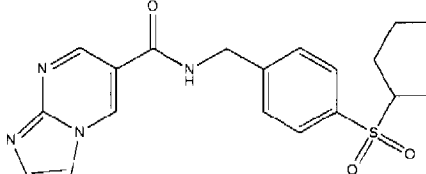
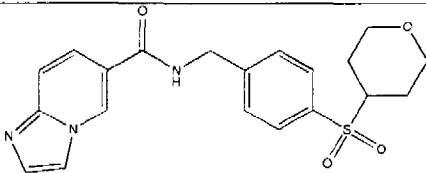
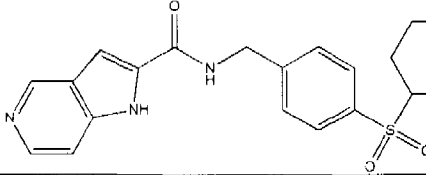
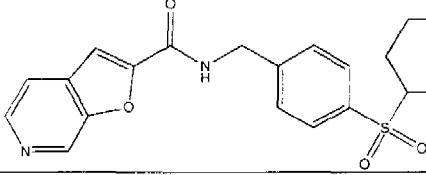
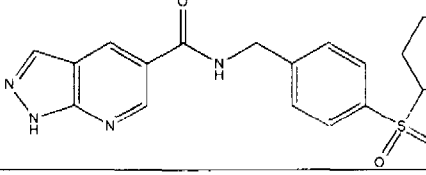
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(4-pyrrolidin-1-yl-piperidine-1-sulfonyl)-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(tetrahydrofuro[3,4-c]pyrrole-5-sulfonyl)-benzylamide (mixture of diastereomers);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-azabicyclo[2.1.1]hexane-2-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-azabicyclo[3.1.0]hexane-3-sulfonyl)-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-hydroxy-3-methyl-pyrrolidine-1-sulfonyl)-benzylamide (racemic);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(9-methyl-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-7-sulfonyl)-benzylamide (racemic);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-acetyl-2,5-diaza-bicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic)
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(5-fluoro-2-azabicyclo[2.2.1]heptane-2-sulfonyl)-benzylamide (racemic);
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(3-methyl-3,6-diaza-bicyclo[3.2.1]octane-6-sulfonyl)-benzylamide (racemic);

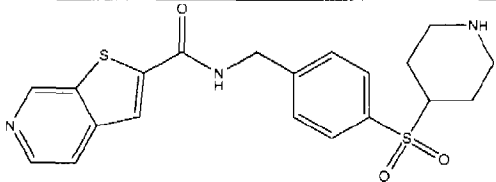
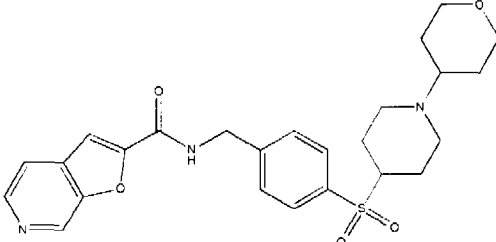
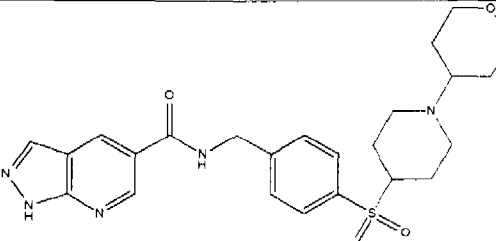
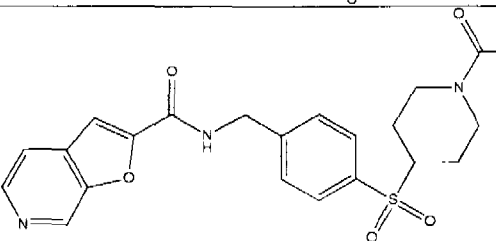
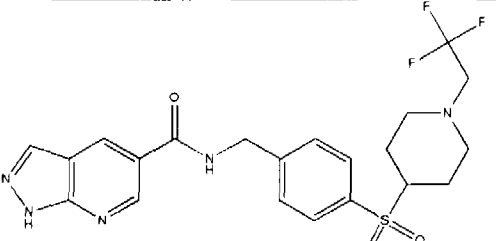
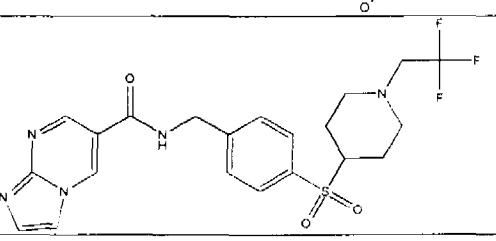
	cis-Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2-aza-bicyclo[3.1.0]hexane-2-sulfonyl)-benzylamide (racemic);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(2,6-dioxo-9-aza-spiro[4.5]decane-9-sulfonyl)-benzylamide (racemic);
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(tetrahydro-pyran-3-sulfonyl)-benzylamide (racemic);
	Furo[2,3-c]pyridine-2-carboxylic acid 4-[4-(tetrahydro-pyran-4-yl)-piperazine-1-sulfonyl]-benzylamide;
	Imidazo[1,2-a]pyridine-6-carboxylic acid 4-(1-acetyl-piperidine-4-sulfonyl)-benzylamide;
	cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(2-oxa-5-aza-bicyclo[2.2.1]heptane-5-sulfonyl)-benzylamide (racemic);
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-[4-(2-methoxy-ethyl)-piperazine-1-sulfonyl]-benzylamide;
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4-hydroxymethyl-piperidine-1-sulfonyl)-benzylamide;

	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(3,3-difluoropyrrolidine-1-sulfonyl)-benzylamide;
	cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(4,4-difluorohexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic);
	cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(5,5-difluorohexahydro-cyclopenta[c]pyrrole-2-sulfonyl)-benzylamide (racemic);
	cis-1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(hexahydro-furo[2,3-c]pyrrole-5-sulfonyl)-benzylamide (racemic);
	Imidazo[1,2-a]pyrimidine-6-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic);
	Furo[2,3-c]pyridine-2-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic);
	1H-Pyrazolo[3,4-b]pyridine-5-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic);
	1H-Pyrrolo[3,2-c]pyridine-2-carboxylic acid 4-(1-isobutylpiperidine-4-sulfinyl)-benzylamide (racemic);

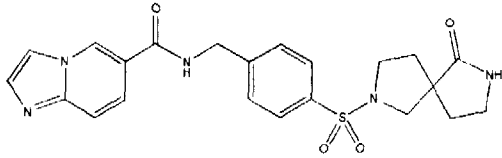
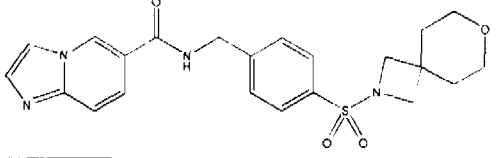
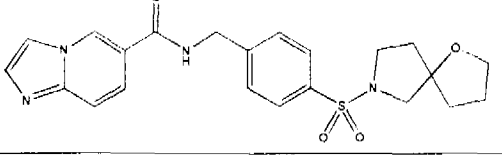
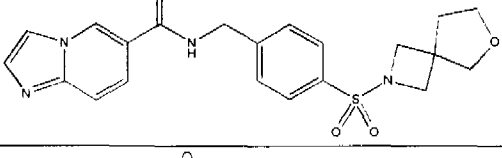
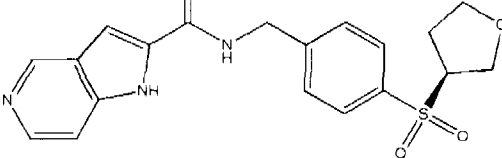
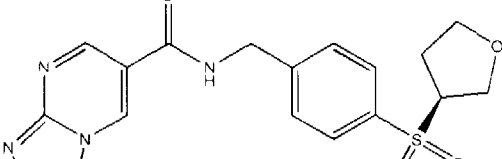
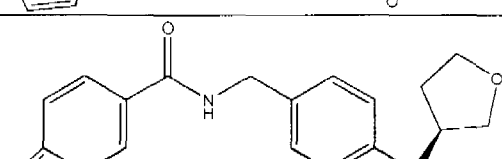
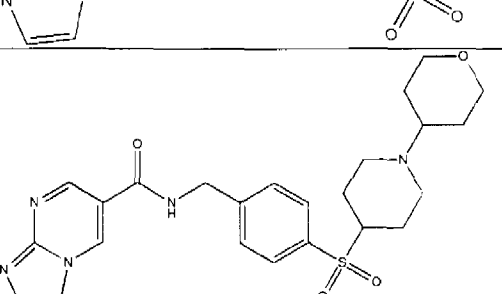
	<p>8-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-1,8-diazaspiro[4.6]undecane-1-carboxylic acid tert-butyl ester (racemic);</p>
	<p>3-[(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonylamino)-methyl]-1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester (racemic);</p>
	<p>1-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-1,8-diazaspiro[4.5]decane-8-carboxylic acid tert-butyl ester;</p>
	<p>3-[1-(4-([(Imidazo[1,2-a]pyridine-6-carbonyl)-amino]-methyl)-benzenesulfonyl)-2,3-dihydro-1H-indol-3-yl]-piperidine-1-carboxylic acid tert-butyl ester (mixture of diastereomers);</p>
	<p>N-(4-(1-isobutylpiperidin-4-ylsulfinyl)benzyl)H-imidazo[1,2-a]pyridine-6-carboxamide (racemic);</p>

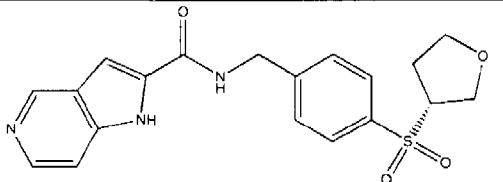
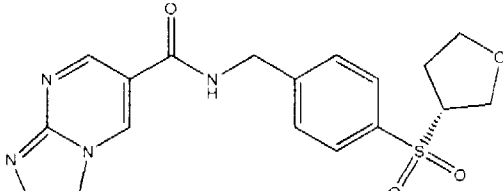
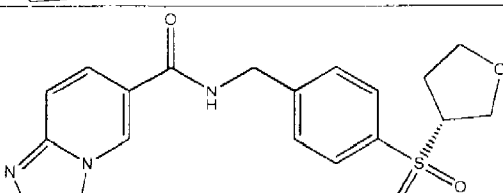
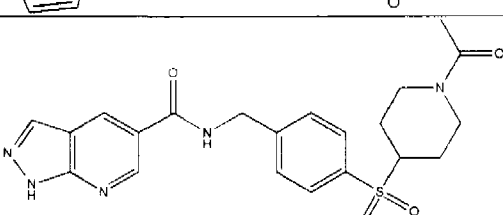
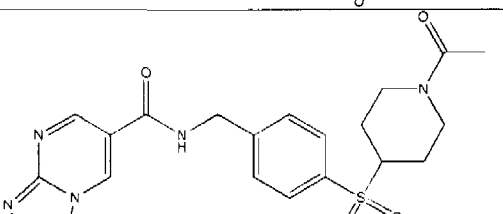
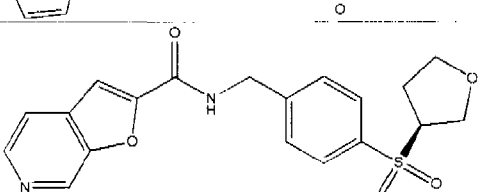
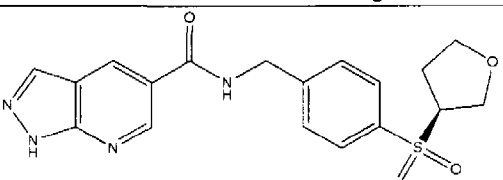
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer);
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide (single isomer);
	N-[[4-(8-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(2,8-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

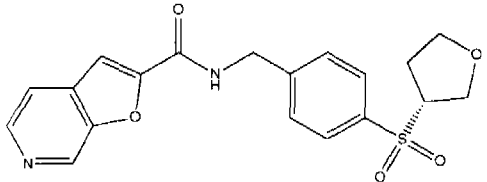
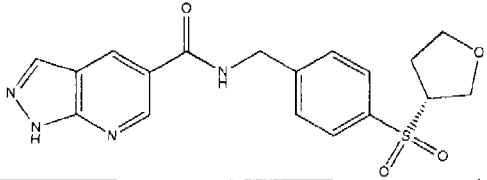
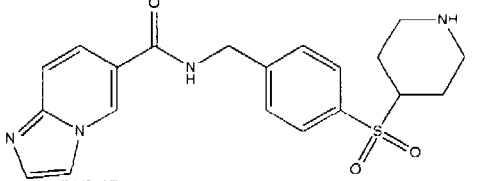
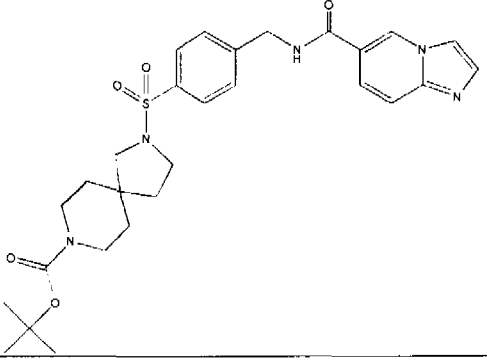
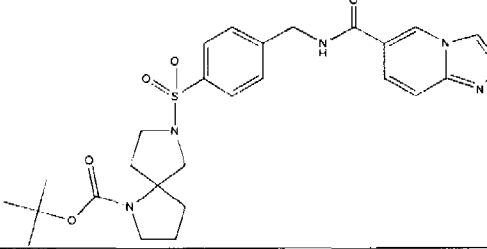
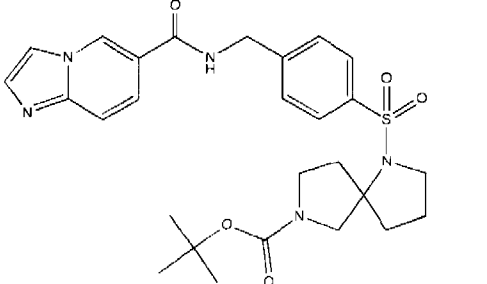
	N-[[4-(4-tetrahydropyran-4-yl)piperazin-1-yl)sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(6-methyl-2,6-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonylphenyl)methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(4-piperidylsulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	N-[[4-(4-piperidylsulfonyl)phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;

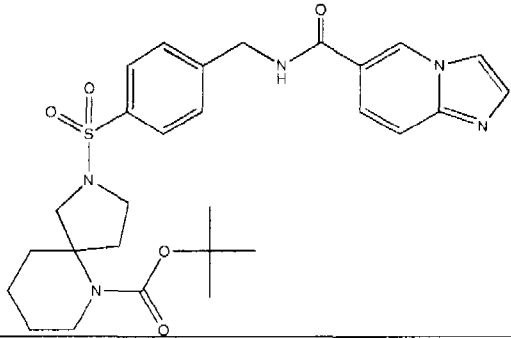
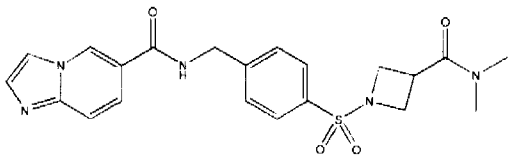
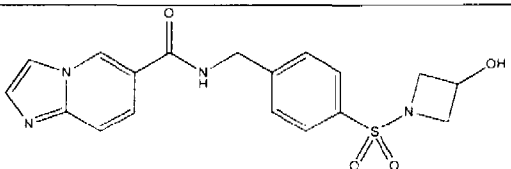
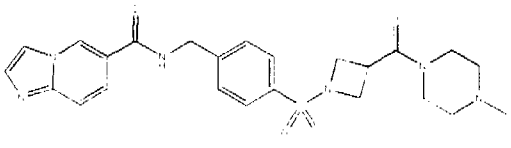
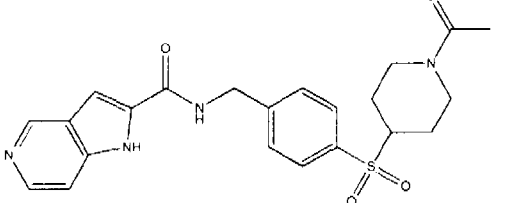
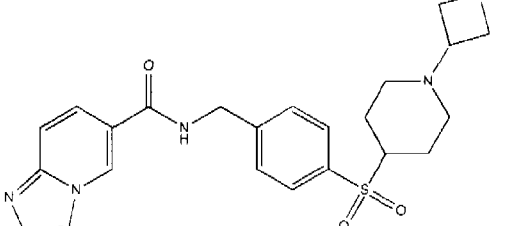
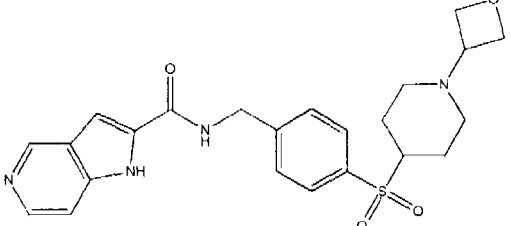
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(2,6-diazaspiro[3.4]octan-6-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

	N-[[4-[(1-oxo-2,7-diazaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide
	N-[[4-(6-oxa-2-azaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(3S)-tetrahydrofuran-3-yl)sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[(3S)-tetrahydrofuran-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
	N-[[4-[(3S)-tetrahydrofuran-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;

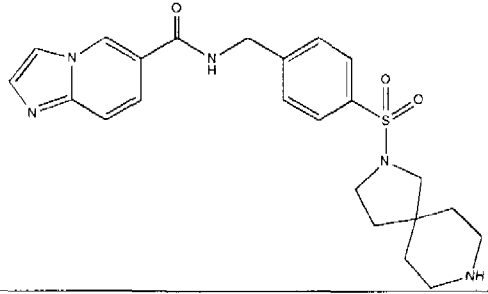
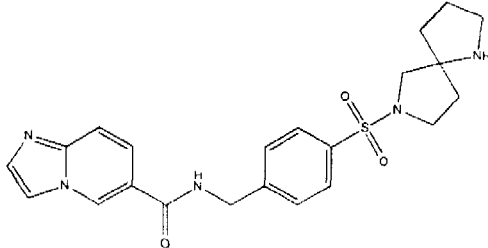
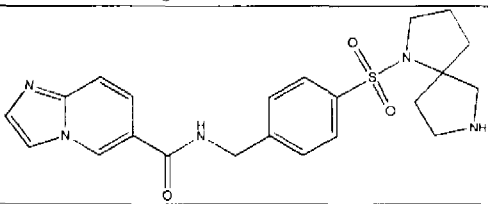
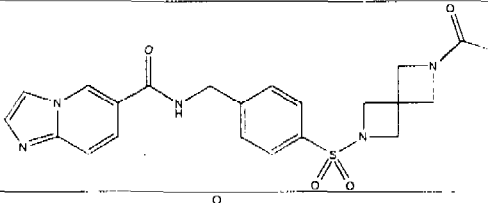
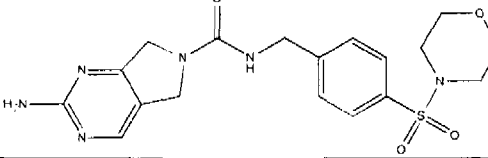
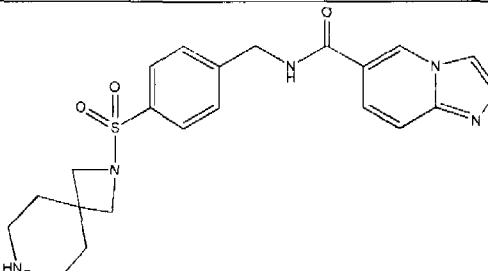
	N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
	N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;
	N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(3S)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

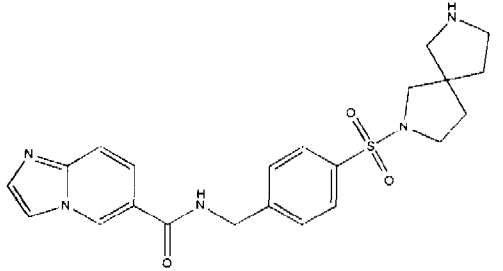
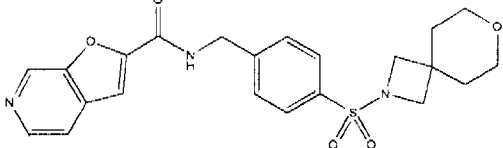
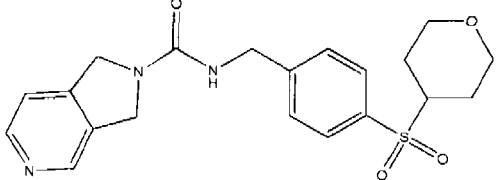
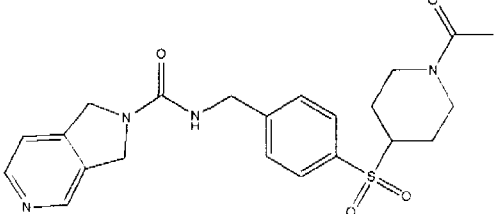
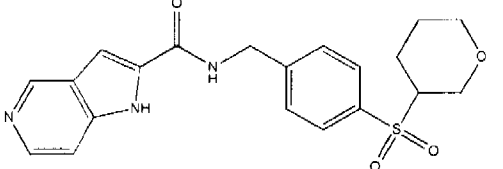
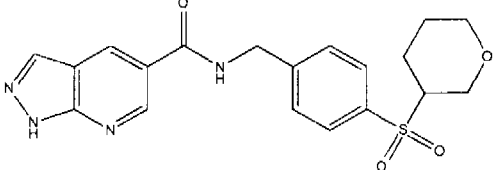
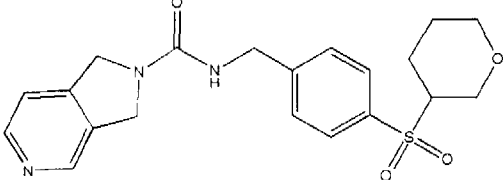
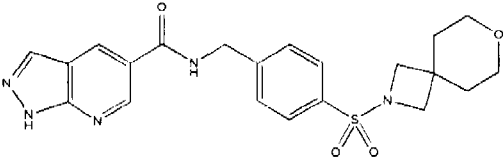
	N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(3R)-tetrahydrofuran-3-yl]sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(4-piperidyl)sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,8-diazaspiro[4.5]decane-8-carboxylate;
	tert-butyl 7-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-1,7-diazaspiro[4.4]nonane-1-carboxylate;
	tert-butyl 1-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-1,7-diazaspiro[4.4]nonane-7-carboxylate;

	<p>tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,8-diazaspiro[3.5]nonane-8-carboxylate;</p>
	<p>N-[[4-(3,3-difluoroazetidin-1-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;</p>
	<p>N-[[4-(azetidin-1-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;</p>
	<p>tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,7-diazaspiro[4.4]nonane-7-carboxylate;</p>
	<p>tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carboxylamino)methyl]phenyl]sulfonyl-2,9-diazaspiro[4.5]decane-9-carboxylate;</p>

	tert-butyl 2-[4-[(imidazo[1,2-a]pyridine-6-carbonylamino)methyl]phenyl]sulfonyl-2,6-diazaspiro[4.5]decane-6-carboxylate;
	N-[[4-[3-(dimethylcarbamoyl)azetidin-1-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(3-hydroxyazetidin-1-yl)sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[3-(4-methylpiperazine-1-carbonyl)azetidin-1-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

	<p>N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyrimidine-6-carboxamide;</p>
	<p>N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonyl]phenyl]methyl]thieno[2,3-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-(2,8-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;</p>
	<p>N-[[4-(1,7-diazaspiro[4.4]nonan-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;</p>
	<p>N-[[4-(1,7-diazaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;</p>

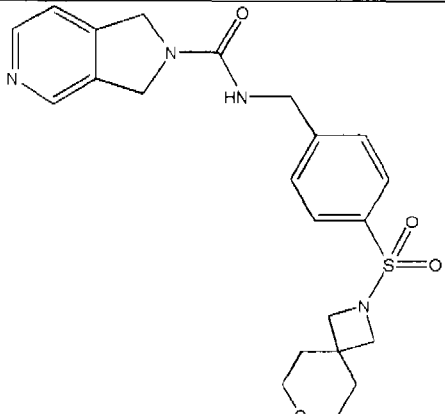
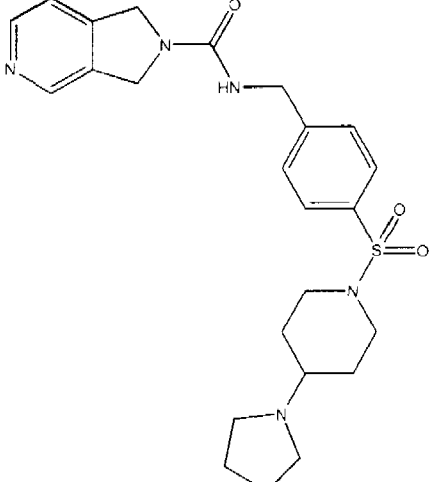
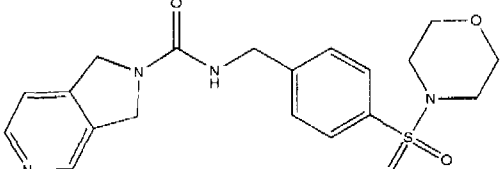
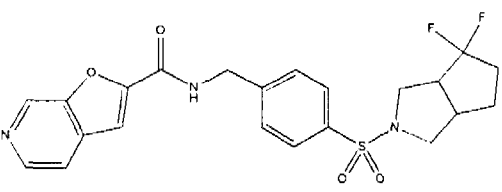
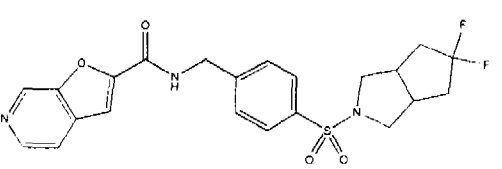
	N-[[4-(2,8-diazaspiro[4.5]decan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1,7-diazaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1,7-diazaspiro[4.4]nonan-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(6-acetyl-2,6-diazaspiro[3.3]heptan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	2-amino-N-[(4-morpholinosulfonyl)phenyl]methyl-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide;
	N-[[4-(2,7-diazaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

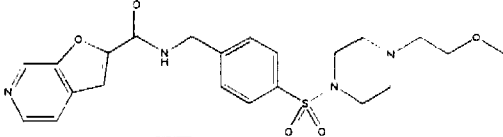
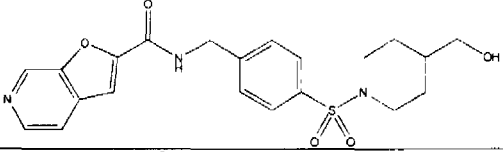
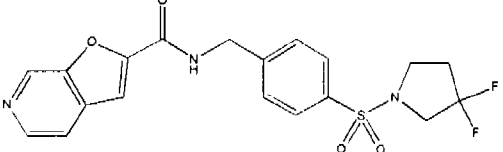
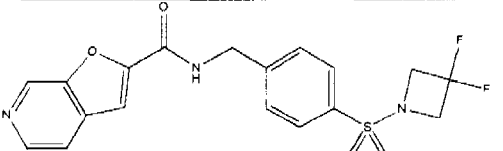
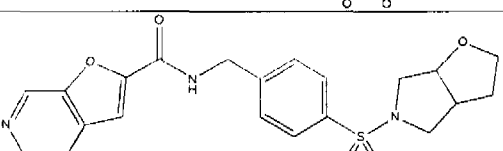
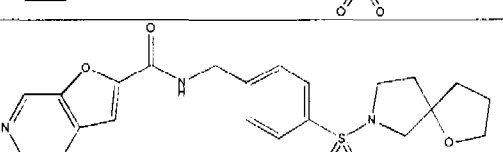
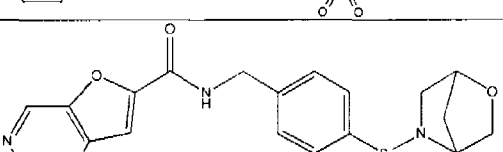
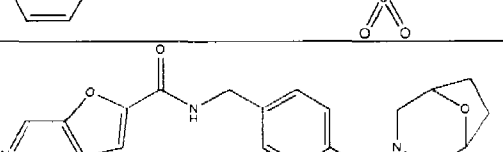
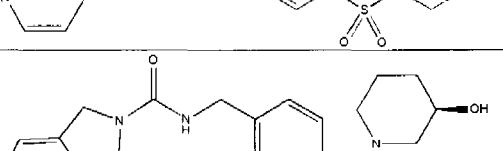
	N-[[4-(2,7-diazaspiro[4.4]nonan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-4-ylsulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[(4-tetrahydropyran-3-ylsulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	N-[[4-[(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(7-methyl-2,7-diazaspiro[3.5]nonan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(8-methyl-5-oxa-2,8-diazaspiro[3.5]nonan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(5-methyl-2,5-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(5-oxa-2-azaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[(4-tetrahydropyran-3-yl)sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[(4-tetrahydropyran-3-yl)sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	2-amino-N-[(4-tetrahydropyran-4-yl)sulfonylphenyl]methyl]-5,7-dihydropyrrolo[3,4-d]pyrimidine-6-carboxamide;

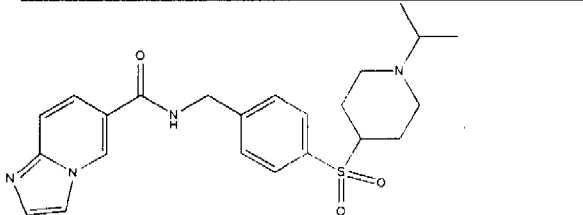
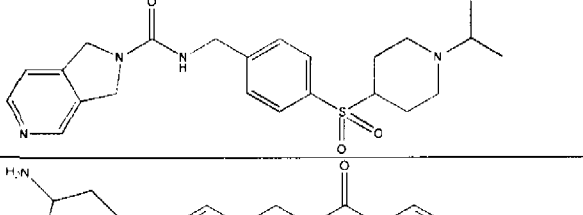
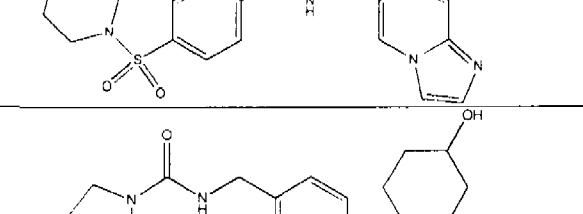
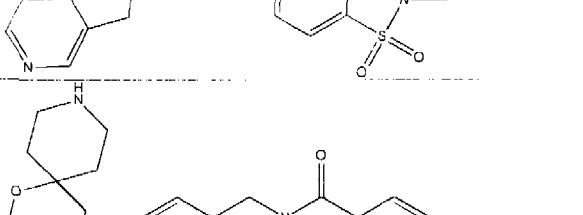
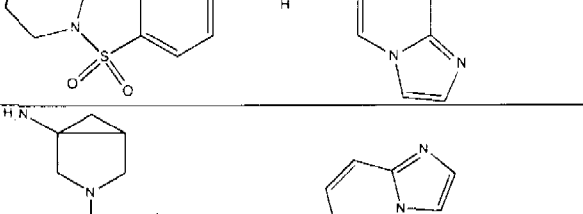
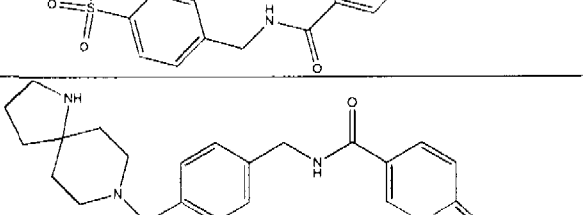
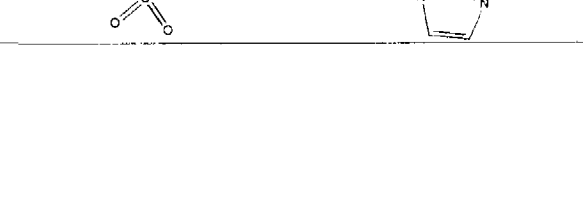
	N-[[4-(4-tetrahydropyran-4-yl)piperazin-1-yl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-acetyl-4-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[4-(oxetan-3-yl)piperazin-1-yl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-(3,3-difluoroazetidin-1-yl)sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-oxo-2,7-diazaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(6-oxa-1-azaspiro[3.3]heptan-1-yl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	<p>N-[[4-[(3S,5R)-3,5-dimethyl-4-(oxetan-3-yl)piperazin-1-yl]sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[[1-(oxetan-3-yl)-4-piperidyl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-(4-methylpiperazin-1-yl)sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfonylphenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[(7-methyl-2,7-diazaspiro[3.4]octan-2-yl)sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;</p>

	<p>N-[[4-(7-oxa-2-azaspiro[3.5]nonan-2-ylsulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[(4-pyrrolidin-1-yl)-1-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[(4-morpholinosulfonyl)phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[(4,4-difluoro-1,3,3a,5,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;</p>
	<p>N-[[4-[(5,5-difluoro-1,3,3a,4,6,6a-hexahydrocyclopenta[c]pyrrol-2-yl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;</p>

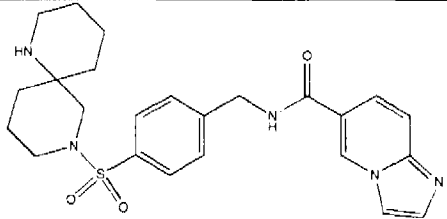
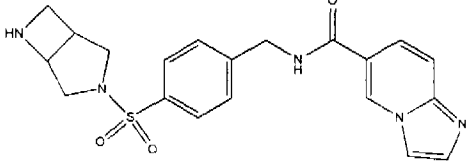
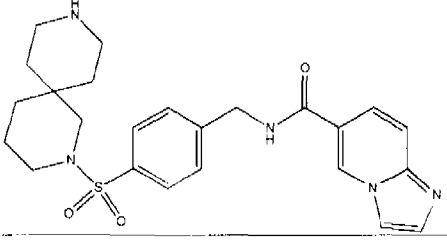
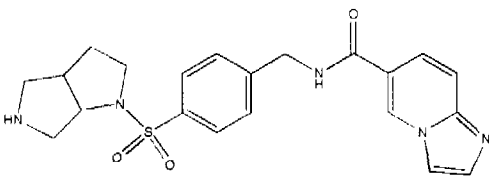
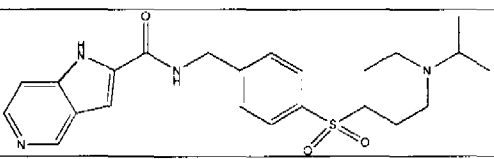
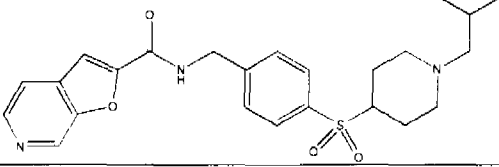
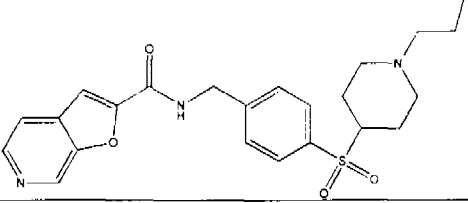
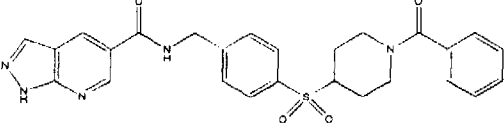
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	N-[[4-[4-(hydroxymethyl)-1-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(3,3-difluoropyrrolidin-1-yl)sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(3,3-difluoroazetidin-1-yl)sulfonylphenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(2,3,3a,4,6,6a-hexahydrofuro[2,3-c]pyrrol-5-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(1-oxa-7-azaspiro[4.4]nonan-7-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-(8-oxa-3-azabicyclo[3.2.1]octan-3-ylsulfonyl)phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(3R)-3-hydroxy-1-piperidyl]sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;

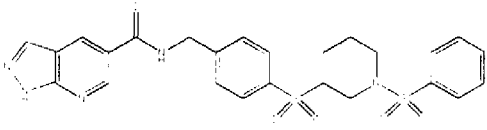
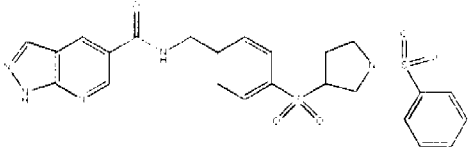
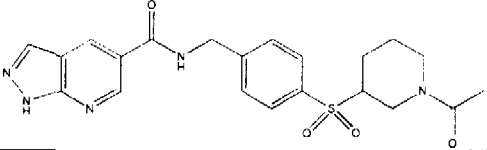
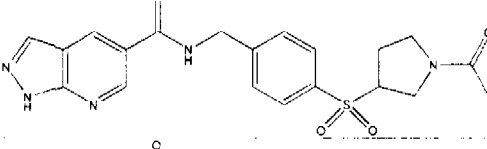
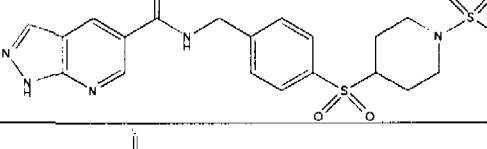
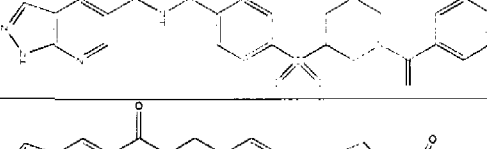
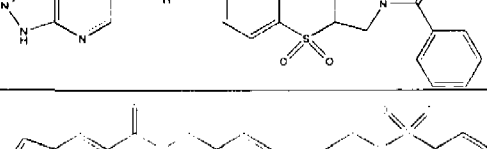
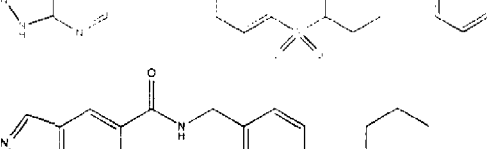
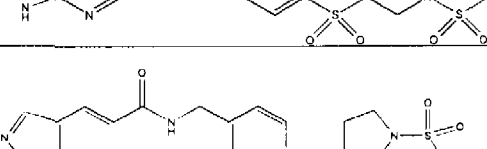
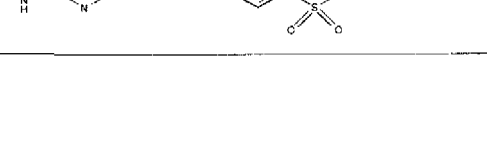
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	N-[[4-(1-piperidylsulfonyl)phenyl]methyl]imidazo[1,5-a]pyridine-7-carboxamide;
	N-[[4-[(1-methyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-propanoyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-propanoyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[[1-(2-methylpropanoyl)-4-piperidyl]sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-butanoyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;

	N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(4-amino-1-piperidyl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(4-hydroxy-1-piperidyl)sulfonyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(5-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1,8-diazaspiro[4.5]decan-8-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

	N-[[4-(1-oxa-4,8-diazaspiro[5.5]undecan-4-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(2-amino-7-azaspiro[3.5]nonan-7-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(3,9-diazaspiro[5.5]undecan-3-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
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	N-[[4-(1,8-diazaspiro[5.5]undecan-8-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-yl)sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[[4-(aminomethyl)-3-azabicyclo[2.1.1]hexan-3-yl]sulfonyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

	N-[[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[3-(3-piperidyl)indolin-1-yl]sulfonylphenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1,8-diazaspiro[4.5]decan-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-b]pyrrol-5-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(1,9-diazaspiro[4.6]undecan-9-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(3,4a,5,6,7,7a-hexahydro-2H-pyrrolo[3,4-b][1,4]oxazin-4-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;

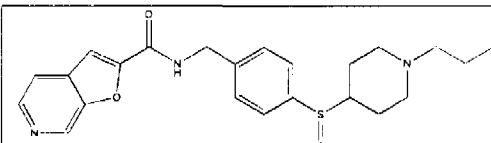
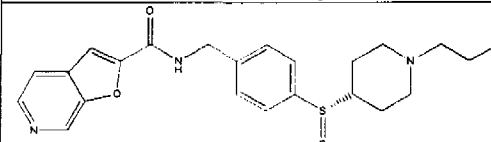
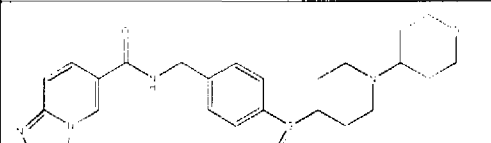
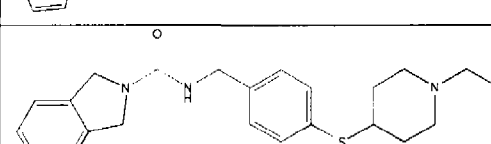
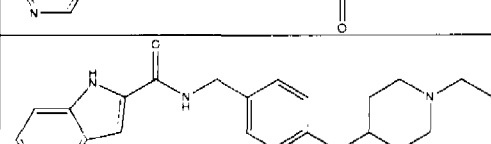
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	N-[[4-(2,9-diazaspiro[5.5]undecan-2-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-(3,3a,4,5,6,6a-hexahydro-2H-pyrrolo[2,3-c]pyrrol-1-ylsulfonyl)phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-propyl-4-piperidyl)sulfonyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-benzoyl-4-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	N-[[4-[[1-(benzenesulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[1-(benzenesulfonyl)pyrrolidin-3-yl]sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-acetyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(1-acetylpyrrolidin-3-yl)sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-methylsulfonyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-benzoyl-3-piperidyl)sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(1-benzoylpyrrolidin-3-yl)sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[[1-(benzenesulfonyl)-4-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-methylsulfonyl)-3-piperidyl]sulfonyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-(1-methylsulfonylpyrrolidin-3-yl)sulfonylphenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;

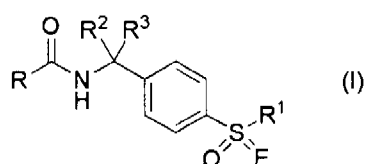
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(R)-(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-methyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-methyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;

	N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-isobutyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[[1-(2,2,2-trifluoroethyl)-4-piperidyl]sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide;
	N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;
	N-[[4-[(1-methyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]methyl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl)-4-piperidyl]sulfinyl]phenyl]methyl]-1H-pyrazolo[3,4-b]pyridine-5-carboxamide;

	N-[[4-[(1-propyl-4-piperidyl)sulfinyl]phenyl]meth-yl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(S)-(1-propyl-4-piperidyl)sulfinyl]phenyl]meth-yl]furo[2,3-c]pyridine-2-carboxamide;
	N-[[4-[(1-tetrahydropyran-4-yl-4-piperidyl)sulfinyl]phenyl]meth-yl]imidazo[1,2-a]pyridine-6-carboxamide;
	N-[[4-[(1-ethyl-4-piperidyl)sulfinyl]phenyl]meth-yl]-1,3-dihydropyrrolo[3,4-c]pyridine-2-carboxamide; and
	N-[[4-[(1-isopropyl-4-piperidyl)sulfinyl]phenyl]meth-yl]-1H-pyrrolo[3,2-c]pyridine-2-carboxamide;

and pharmaceutically acceptable salts thereof, stereoisomers thereof, and pharmaceutically acceptable salts of stereoisomers thereof.

- 5 23. A pharmaceutical composition comprising:
(a) an effective amount of at least one compound of Formula I:



wherein:

E is O or is absent:

- 10 R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium,

amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or

- (b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

- 10 R^1 is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R^x ;
- wherein each R^x substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, cyano, $-NR^aR^b$, $-alkylenyl-NR^aR^b$, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, $-S$ -alkyl, alkenyl, alkynyl, aryl, arylalkyl-, aryloxy-, arylalkoxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-, $-C(O)alkyl$, $-CO_2alkyl$, $-CO_2H$, $-C(O)cycloalkyl$, $-C(O)heterocycloalkyl$, $-S(O)-alkyl$, $-SO_2-alkyl$, $-SO_2-aryl$, $-SO_2-(haloalkyl)$, $-CONH_2$, $C(O)NH(alkyl)$, $-C(O)NH(haloalkyl)$, $-C(O)N(alkyl)_2$, $-C(O)NH(cycloalkyl)$, heteroaryl, (heteroaryl)alkyl-, $-N(R^c)-C(O)-alkyl$, $-N(R^c)-C(O)-aryl$, $-N(R^c)-CO_2-alkyl$, $-SO_2NH_2$, $-SO_2NH(alkyl)$, $-SO_2N(alkyl)_2$, $-SO_2NH(cycloalkyl)$, and $-N(H)(SO_2alkyl)$, or two adjacent R^x substituents taken together form a phenyl ring,
- 25 wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and phenyl substituents within R^x is independently unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino, $-C(O)alkyl$, and $-CO_2alkyl$;
- 30 wherein R^a and R^b are each independently H, alkyl, alkoxy,

alkoxyalkyl, cyanoalkyl, or haloalkyl; and

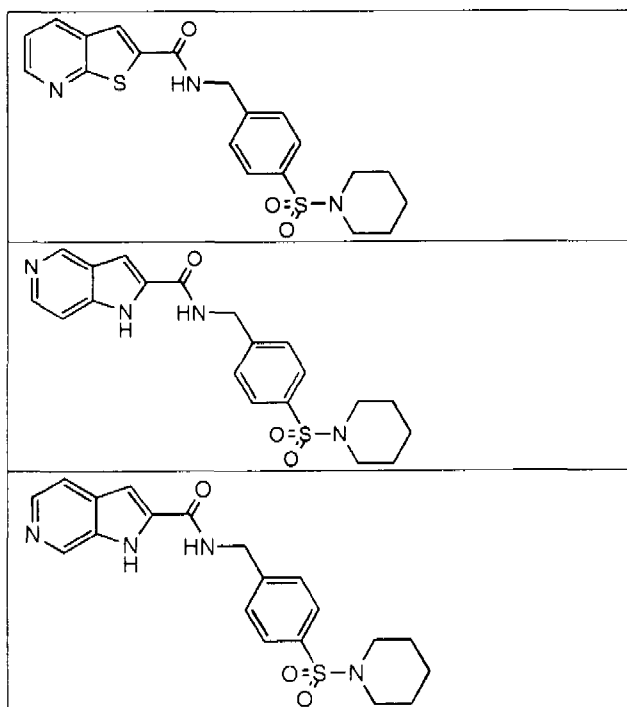
R^c is H or alkyl; or

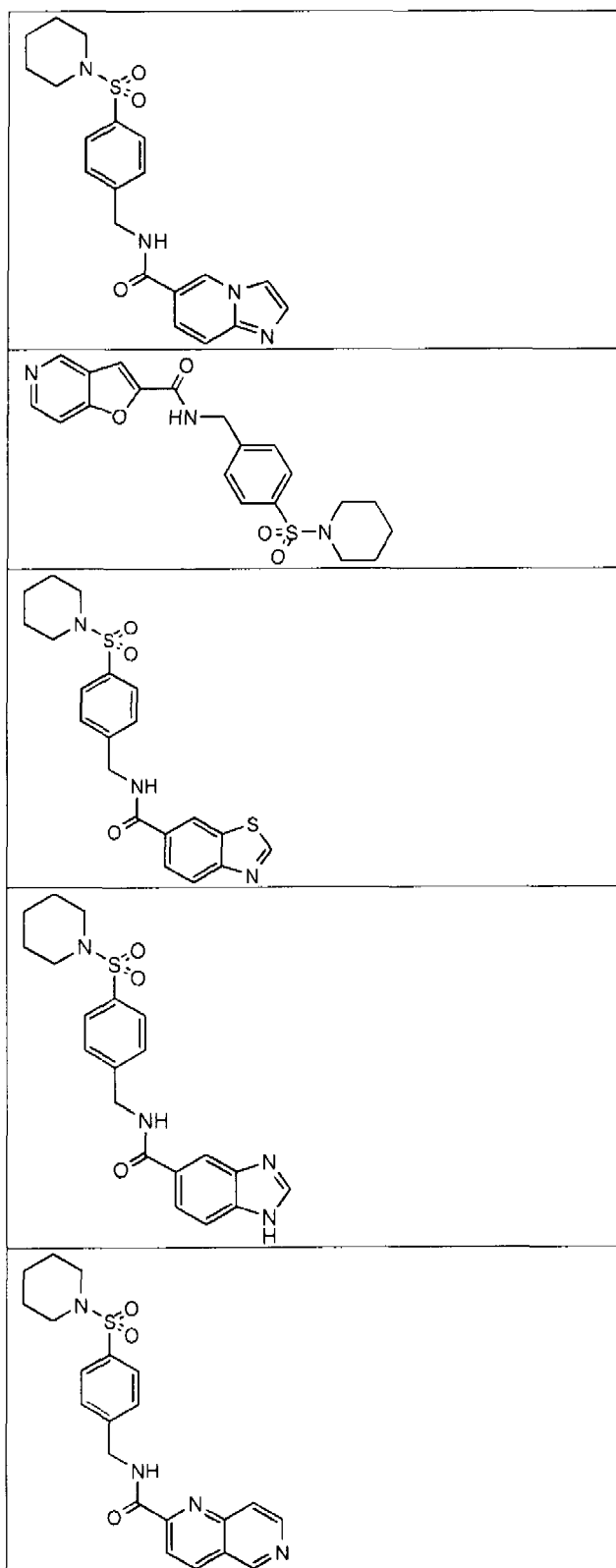
- (2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system, and said heterocycloalkyl is unsubstituted or substituted with one or more substituents independently selected from the group consisting of: alkyl, halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo, $-NR^dR^e$, $-alkylenyl-NR^dR^e$, $-C(O)alkyl$, $-CO_2alkyl$, and $-SO_2alkyl$; wherein R^d is H or alkyl and R^e is H, alkyl, haloalkyl, $-C(O)alkyl$, $-CO_2alkyl$, or $-SO_2alkyl$; and

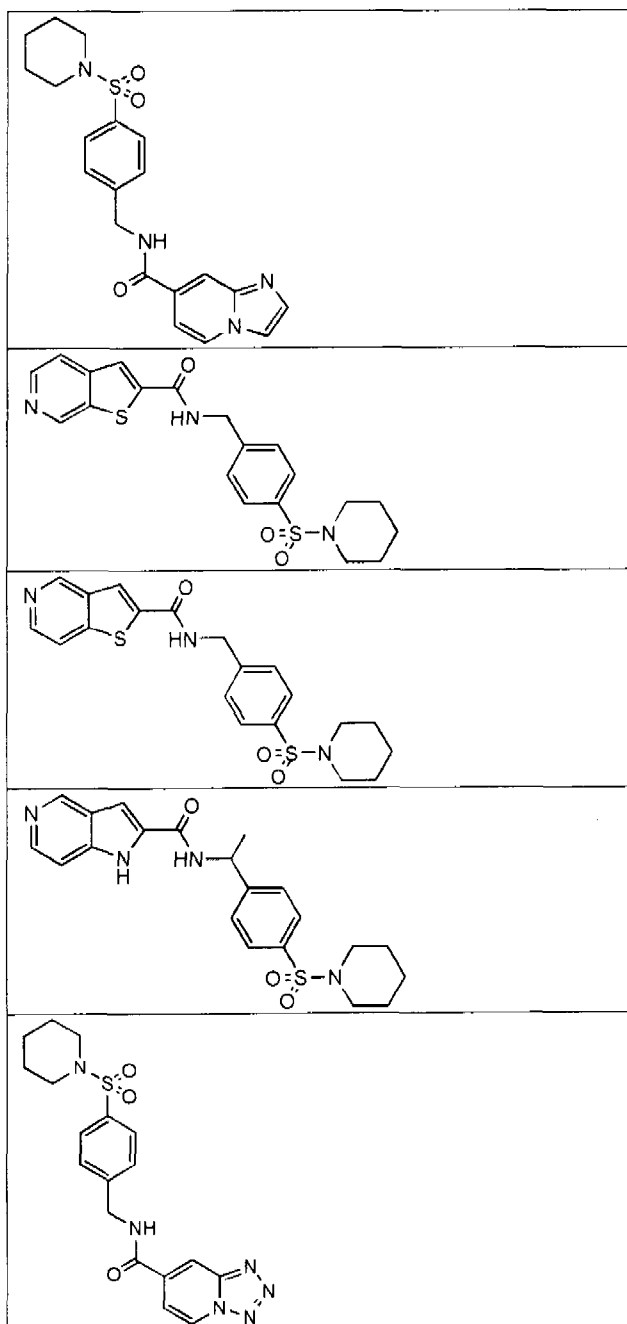
R^2 and R^3 are each independently H or deuterium;

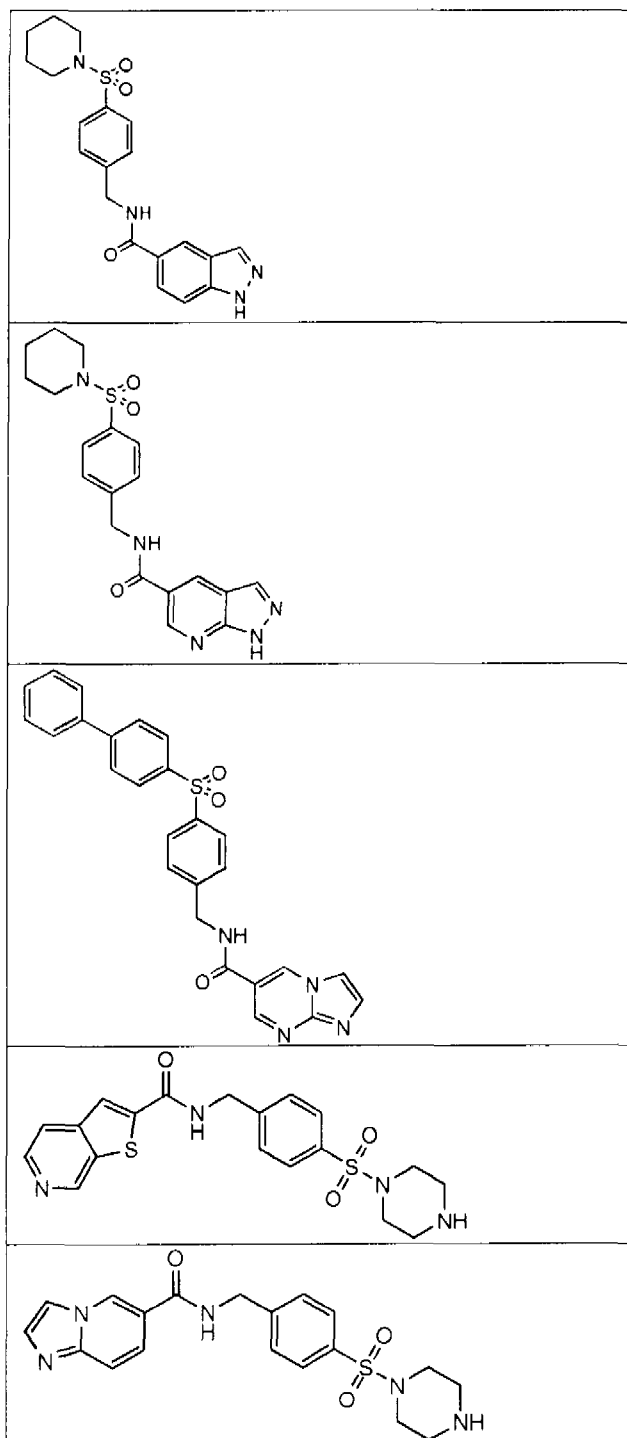
or a pharmaceutically acceptable salt thereof,

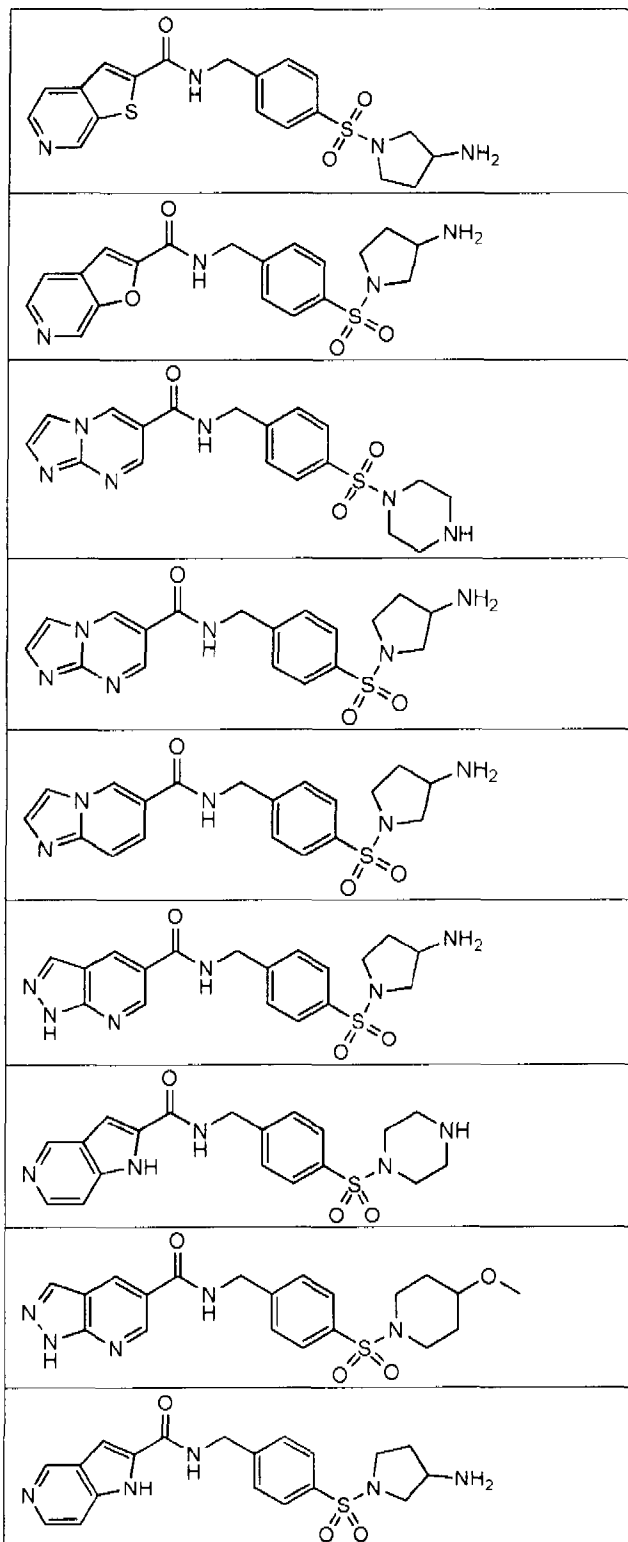
with the proviso that the compound of Formula I is not one of the following compounds:

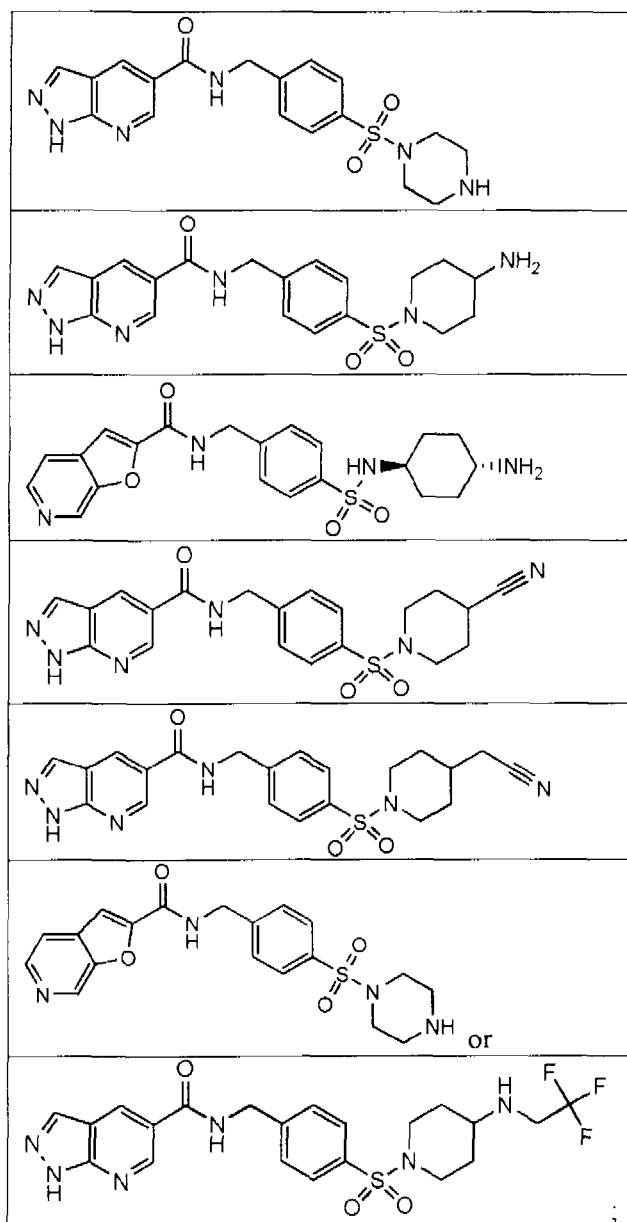












and (b) a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, further comprising therapeutically effective amounts of one or more additional adjunctive active agents.

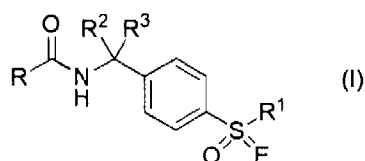
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25. The pharmaceutical composition of claim 24, wherein said one or more additional adjunctive active agents are selected from the group consisting of cytotoxic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar,

- topotecan, paclitaxel, docetaxel, the epothilones, tamoxifen, 5-fluorouracil, methotrexate, temozolomide, cyclophosphamide, SCH 66336, tipifarnib (Zarnestra[®]), R115777, L778,123, BMS 214662, Iressa[®], Tarceva[®], C225, GLEEVEC[®], intron[®], Peg-Intron[®], aromatase combinations, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovorin, oxaliplatin (ELOXATIN[®]), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, MithramycinTM, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrol acetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrozole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Ifosfomide, Rituximab, C225, Campath, leucovorin, and dexamethasone, bicalutamide, carboplatin, chlorambucil, cisplatin, letrozole, megestrol, valrubicin, vinblastine, and NIASPAN[®].
26. The pharmaceutical composition of claim 23 further comprising a rescuing agent.
27. The pharmaceutical composition of claim 26, wherein the rescuing agent is selected from the group consisting of nicotinamide, nicotinic acid, and nicotinamide mononucleotide (NMN).

28. A method of treating a subject suffering from or diagnosed with a disease or medical condition mediated by NAMPT activity, comprising administering to the subject in need of such treatment an effective amount of at least one compound of

5 Formula I:



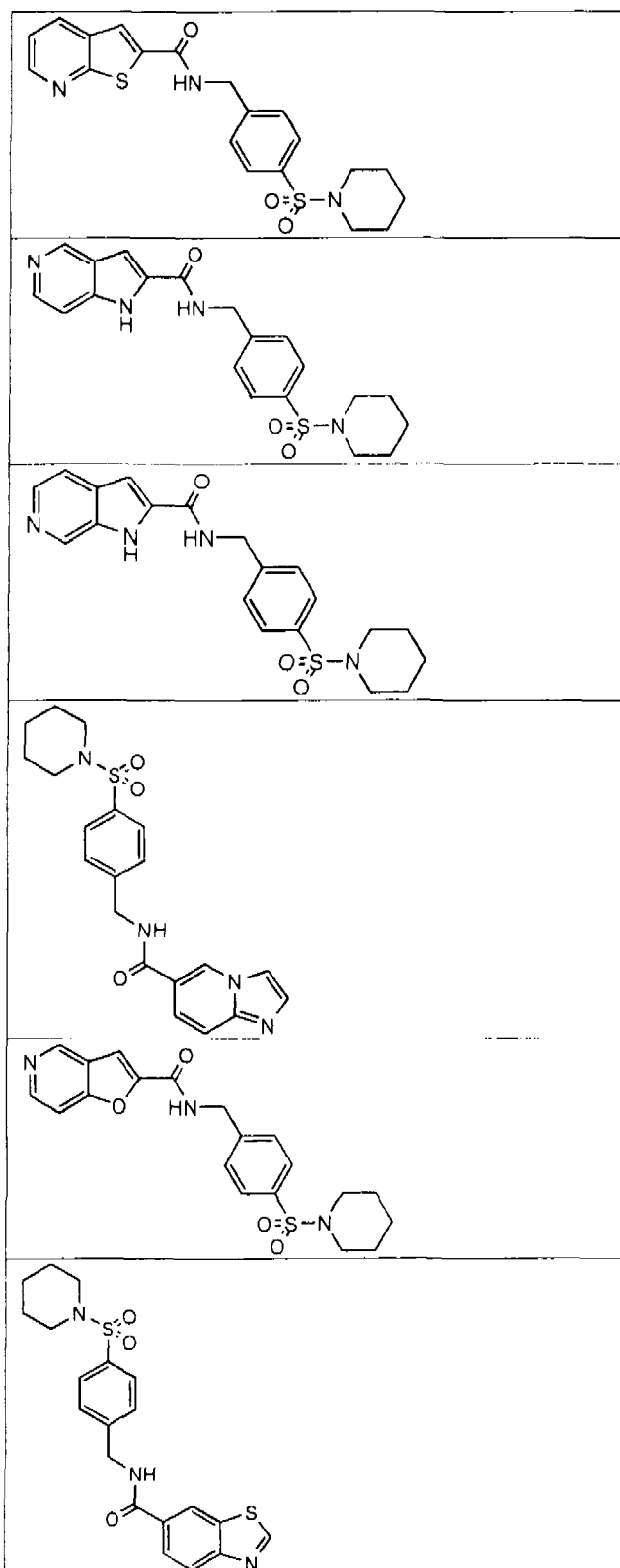
wherein:

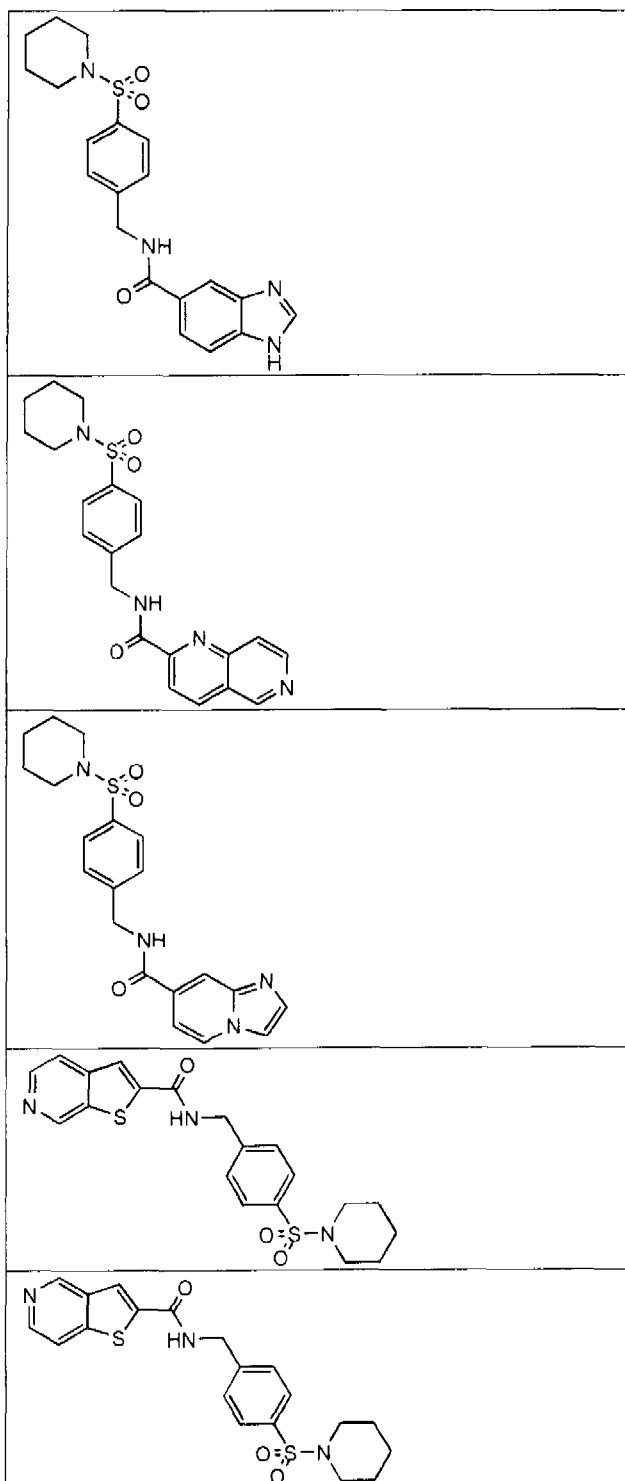
E is O or is absent;

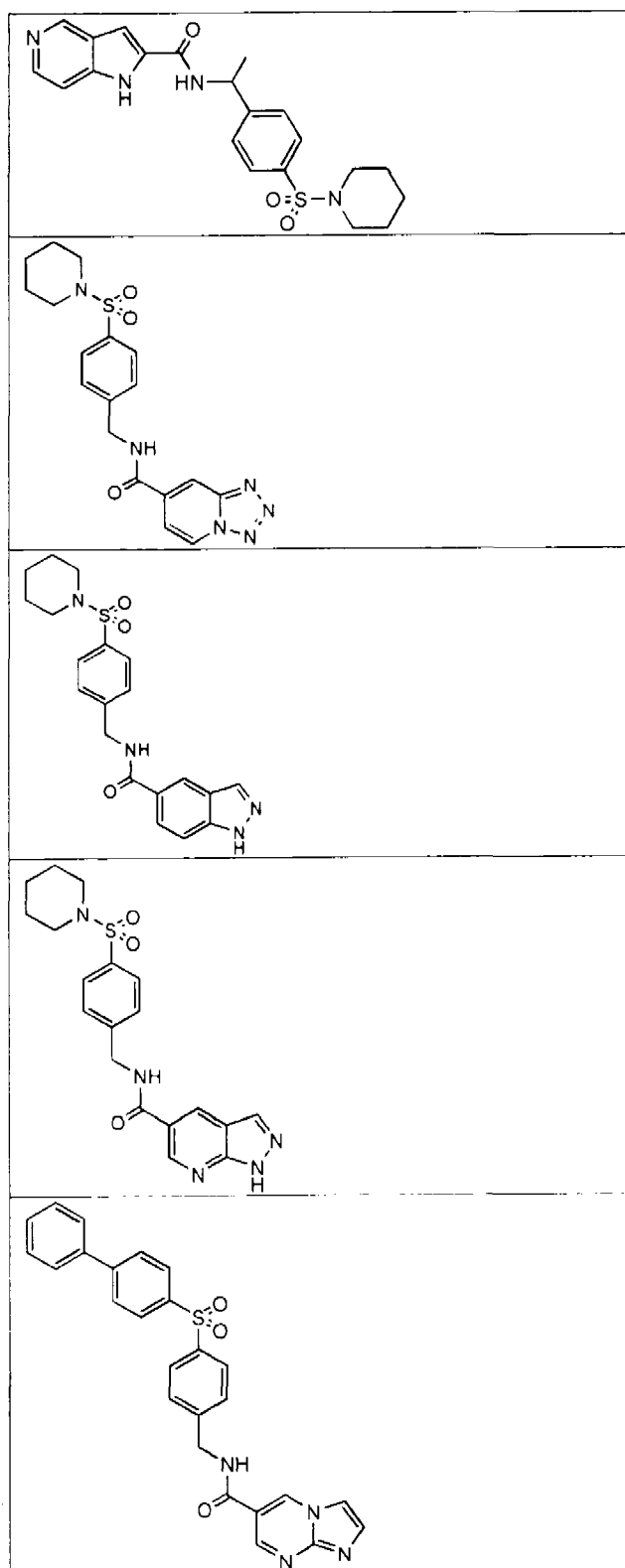
- R is (a) an 8-, 9-, or 10-membered bicyclic heteroaryl comprising one heteroatom selected from N, S, and O, and one, two, or three additional N atoms, wherein said bicyclic heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy, and wherein one or more N atoms of said bicyclic heteroaryl is optionally an N-oxide; or
- (b) a five- or six-membered nitrogen-linked heterocycloalkyl ring fused to a phenyl or monocyclic six-membered heteroaryl, wherein said phenyl or heteroaryl is unsubstituted or is substituted with one or more substituents selected from the group consisting of deuterium, amino, alkylamino, dialkylamino, alkyl, halo, cyano, haloalkyl, hydroxy, hydroxyalkyl, and alkoxy;

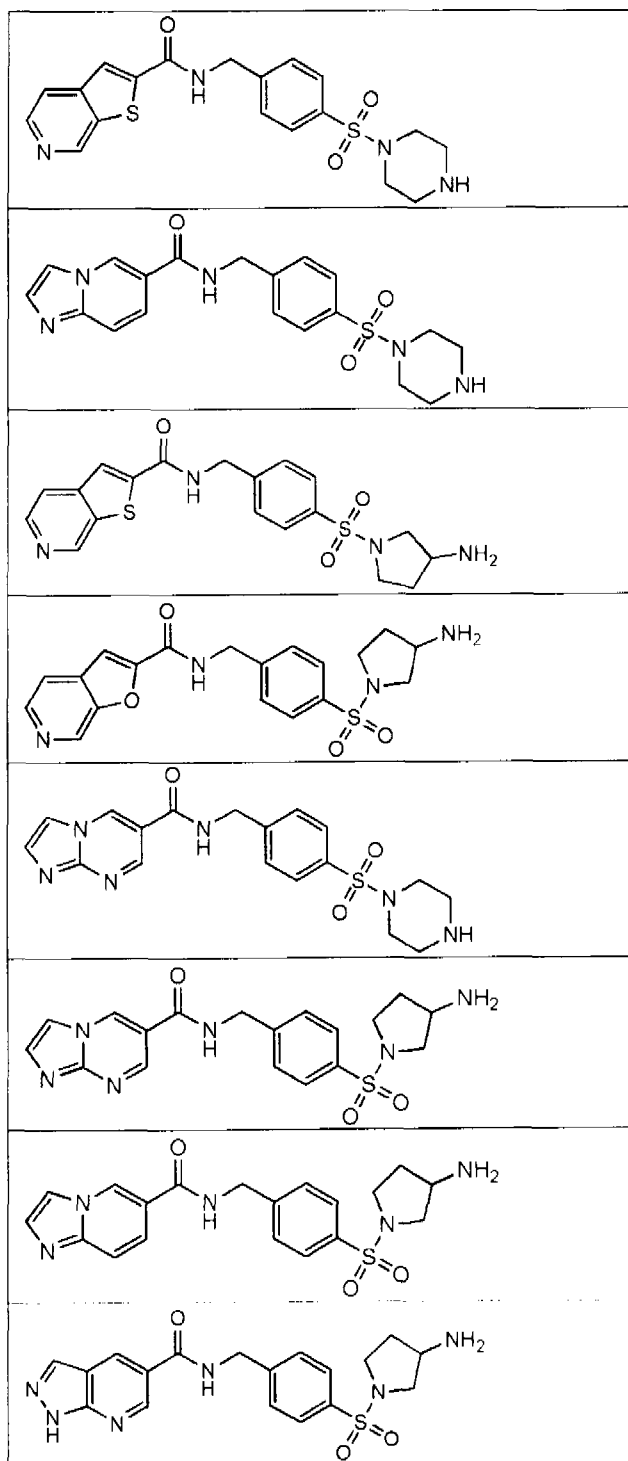
- R¹ is (1) a saturated, monocyclic heterocycloalkyl, which is unsubstituted or substituted with one or more substituents R^x; wherein each R^x substituent is independently selected from the group consisting of: deuterium, halo, hydroxy, cyano, -NR^aR^b, -alkylenyl-NR^aR^b, oxo, alkyl, hydroxyalkyl, cyanoalkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl-, -S-alkyl, alkenyl, alkynyl, aryl, arylalkyl-, aryloxy-, arylalkoxy-, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl-, heterocycloalkyl, (heterocycloalkyl)alkyl-, (heterocycloalkyl)alkoxy-,

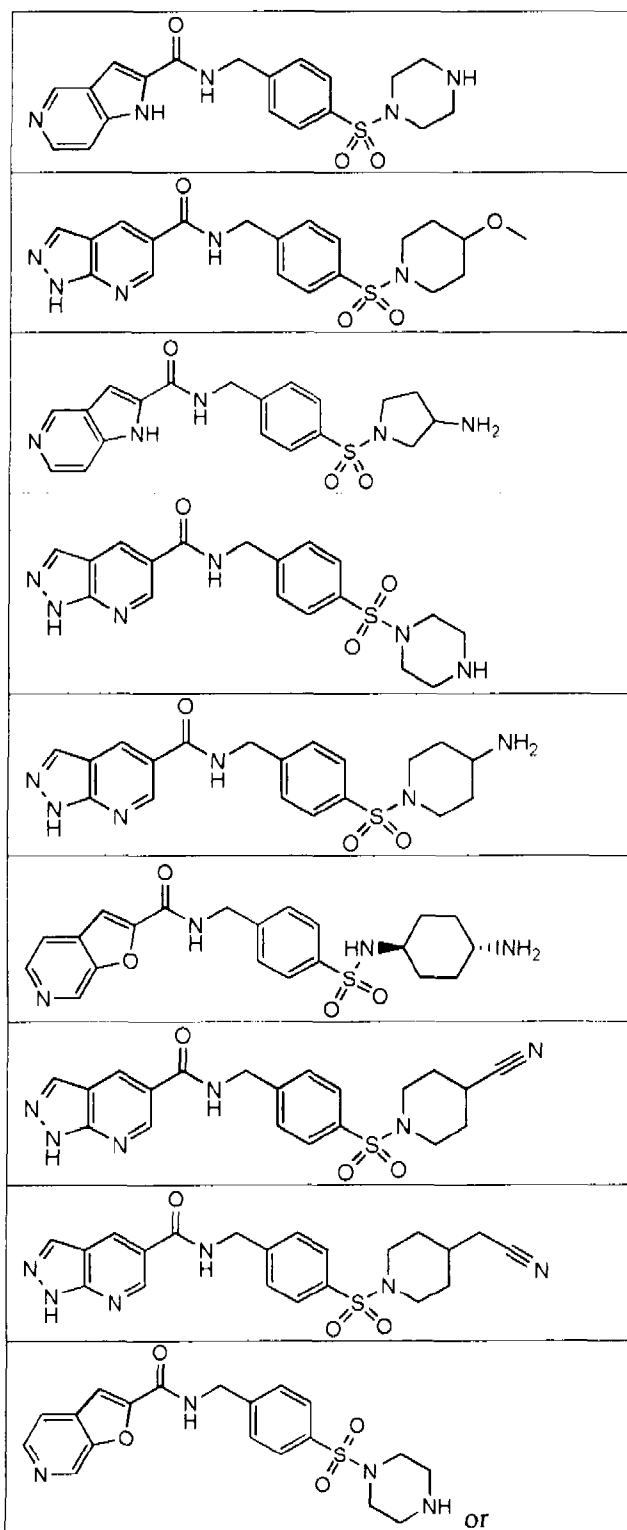
- C(O)alkyl, -CO₂alkyl, -CO₂H, -C(O)cycloalkyl,
 -C(O)heterocycloalkyl, -S(O)-alkyl, -SO₂-alkyl, -SO₂-aryl, -SO₂-
 (haloalkyl), -CONH₂, C(O)NH(alkyl), -C(O)NH(haloalkyl),
 -C(O)N(alkyl)₂, -C(O)NH(cycloalkyl), heteroaryl, (heteroaryl)alkyl-,
 -N(R^c)-C(O)-alkyl, -N(R^c)-C(O)-aryl, -N(R^c)-CO₂-alkyl, -SO₂NH₂,
 -SO₂NH(alkyl), -SO₂N(alkyl)₂, -SO₂NH(cycloalkyl), and
 -N(H)(SO₂alkyl), or two adjacent R^x substituents taken together form a
 phenyl ring,
 wherein each of said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and
 phenyl substituents within R^x is independently unsubstituted or
 substituted with one or more substituents selected from the group
 consisting of alkyl, halo, hydroxy, cyano, alkoxy, amino,
 -C(O)alkyl, and -CO₂alkyl;
 wherein R^a and R^b are each independently H, alkyl, alkoxy,
 alkoxyalkyl, cyanoalkyl, or haloalkyl; and
 R^e is H or alkyl; or
 (2) a saturated, bicyclic or tricyclic, nitrogen-linked heterocycloalkyl, wherein
 said heterocycloalkyl comprises a fused, bridged, or spiro bicyclic system,
 and said heterocycloalkyl is unsubstituted or substituted with one or more
 substituents independently selected from the group consisting of: alkyl,
 halo, haloalkyl, hydroxy, hydroxyalkyl, alkoxy, cyano, cyanoalkyl, oxo,
 -NR^dR^e, -alkylenyl-NR^dR^e, -C(O)alkyl, -CO₂alkyl, and -SO₂alkyl;
 wherein R^d is H or alkyl and R^e is H, alkyl, haloalkyl, -C(O)alkyl,
 -CO₂alkyl, or -SO₂alkyl; and
 R² and R³ are each independently H or deuterium;
 or a pharmaceutically acceptable salt thereof,
 with the proviso that the compound of Formula I is not one of the following
 compounds:

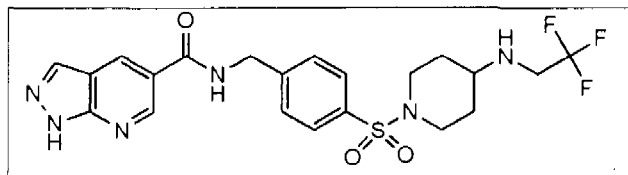












29. The method of claim 28, wherein the disease or medical condition is a solid or liquid tumor, non-small cell lung cancer, leukemia, lymphoma, ovarian cancer, glioma, breast cancer, uterine cancer, colon cancer, cervical cancer, lung cancer, prostate cancer, skin cancer, rhino-gastric tumors, colorectal cancer, CNS cancer, bladder cancer, pancreatic cancer, Hodgkin's disease, rheumatoid arthritis, diabetes, atherosclerosis, sepsis, aging, inflammation.
30. The method of claim 28, further comprising administering to the subject an effective amount of at least one compound selected from the group consisting of: a cytotoxic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, the epothilones, tamoxifen, 5-fluorouracil, methotrexate, temozolomide, cyclophosphamide, SCH 66336, tipifarnib (Zarnestra[®]), R115777, L778,123, BMS 214662, Iressa[®], Tarceva[®], C225, GLEEVEC[®], intron[®], Peg-Intron[®], aromatase combinations, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, leucovirin, oxaliplatin (ELOXATIN[®]), Pentostatine, vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, MithramycinTM, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 α -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrol acetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole,

Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Ifosfomide, Rituximab, C225, Campath, leucovorin, 5 dexamethasone, bicalutamide, chlorambucil, letrozole, megestrol, valrubicin, vinblastine, and NIASPAN[®].

31. The method of claim 28 further comprising administering an effective amount of a rescuing agent.

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32. The pharmaceutical composition of claim 31, wherein the rescuing agent is selected from the group consisting of nicotinamide, nicotinic acid, and nicotinamide mononucleotide (NMN).

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