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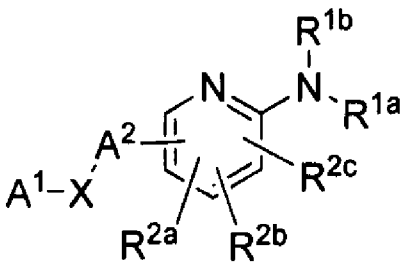
(54) **Title**: SUBSTITUTED PYRIDINES AS SODIUM CHANNEL BLOCKERS



I

(57) **Abstract**: The invention relates to substituted pyridine compounds of Formula I: (I) and the pharmaceutically acceptable salts, prodrugs, and solvates thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{2c}, A^1, A^2, and X are defined as set forth in the specification. The invention is also directed to the use of compounds of Formula I to treat a disorder responsive to the blockade of sodium channels. Compounds of the present invention are especially useful for treating pain.

SUBSTITUTED PYRIDINES AS SODIUM CHANNEL BLOCKERS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is in the field of medicinal chemistry. The invention relates to novel substituted pyridine compounds and the use of these compounds as blockers of voltage-gated sodium (Na^+) channels.

Background Art

Voltage-gated sodium channels (VGSCs) are found in all excitable cells. In neuronal cells of the central nervous system (CNS) and peripheral nervous system (PNS) sodium channels are primarily responsible for generating the rapid upstroke of the action potential. In this manner sodium channels are essential to the initiation and propagation of electrical signals in the nervous system. Proper function of sodium channels is therefore necessary for normal function of the neuron. Consequently, aberrant sodium channel function is thought to underlie a variety of medical disorders (See Hubner *et al.*, *Hum. Mol. Genet. 11*:2435-2445 (2002) for a general review of inherited ion channel disorders) including epilepsy (Yogeeswari *et al, Curr. Drug Target 5*:589-602 (2004)), arrhythmia (Noble, *Proc. Natl. Acad. Sci. USA 99*:5755-5756 (2002)), myotonia (Cannon, *Kidney Int. 57*:772-779 (2000)), and pain (Wood *et al.*, *J. Neurobiol., 61*:55-71 (2004)).

VGSCs are composed of one α-subunit, which forms the core of the channel and is responsible for voltage-dependent gating and ion permeation, and several auxiliary β-subunits (see, *e.g.,* Chahine *et al.*, *CNS & Neurological Disorders-Drug Targets 7*:144-158 (2008) and Kyle and Ilyin, *J. Med. Chem. 50*:2583-2588 (2007)). α-Subunits are large proteins composed of four homologous domains. Each domain contains six α-helical transmembrane spanning segments. There are currently nine known members of the family of voltage-gated sodium channel α-subunits. Names for this family include SCNx, SCNAx, and Na_vx.x (see Table 1, below). The VGSC family has been phylogenetically divided into two subfamilies Na_v1.x (all but SCN6A) and Na_v2.x (SCN6A). The Na_v1.x subfamily can be functionally subdivided into two groups, those which are sensitive to blocking by

tetrodotoxin (TTX-sensitive or TTX-s) and those which are resistant to blocking by tetrodotoxin (TTX-resistant or TTX-r).

There are three members of the subgroup of TTX-resistant sodium channels. The SCN5A gene product ($Na_v1.5$, Hl) is almost exclusively expressed in cardiac tissue and has been shown to underlie a variety of cardiac arrhythmias and other conduction disorders (Liu *et al.*, *Am. J. Pharmacogenomics* 3:173-179 (2003)). Consequently, blockers of $Na_v1.5$ have found clinical utility in treatment of such disorders (Srivatsa *et al.*, *Curr. Cardiol. Rep.* 4:401-410 (2002)). The remaining TTX-resistant sodium channels, $Na_v1.8$ (SCNl0A, PN3, SNS) and $Na_v1.9$ (SCN11A, NaN, SNS2) are expressed in the peripheral nervous system and show preferential expression in primary nociceptive neurons. Human genetic variants of these channels have not been associated with any inherited clinical disorder. However, aberrant expression of $Na_v1.8$ has been found in the CNS of human multiple sclerosis (MS) patients and also in a rodent model of MS (Black *et al.*, *Proc. Natl. Acad. Sci. USA* 97:11598-115602 (2000)). Evidence for involvement in nociception is both associative (preferential expression in nociceptive neurons) and direct (genetic knockout). $Na_v1.8$-null mice exhibited typical nociceptive behavior in response to acute noxious stimulation but had significant deficits in referred pain and hyperalgesia (Laird *et al.*, *J. Neurosci.* 22:8352-8356 (2002)).

TABLE 1

Voltage-gated sodium channel gene family

Type	Gene Symbol	Tissue Distribution	TTX IC_{50} (nM)	Disease Association	Indications
$Na_v1.1$	SCN1A	CNS/PNS	10	Epilepsy	Pain, seizures, neurodegeneration
$Na_v1.2$	SCN2A	CNS	10	Epilepsy	Epilepsy, neurodegeneration
$Na_v1.3$	SCN3A	CNS	15	-	Pain
$Na_v1.4$	SCN4A	Skeletal muscle	25	Myotonia	Myotonia
$Na_v1.5$	SCN5A	Heart muscle	2,000	Arrhythmia	Arrhythmia
$Na_v1.6$	SCN8A	CNS/PNS	6	-	Pain, movement disorders
$Na_v1.7$	SCN9A	PNS	25	Erythermalgia	Pain
$Na_v1.8$	SCN10A	PNS	50,000	-	Pain
$Na_v1.9$	SCN11A	PNS	1,000	-	Pain

The $Na_v1.7$ (PNl, SCN9A) VGSC is sensitive to blocking by tetrodotoxin and is preferentially expressed in peripheral sympathetic and sensory neurons. The SCN9A gene has been cloned from a number of species, including human, rat, and rabbit and shows ~90 % amino acid identity between the human and rat genes (Toledo-Aral *et al.*, *Proc. Natl. Acad. Sci. USA 94*:1527-1532 (1997)).

An increasing body of evidence suggests that $Na_v1.7$ plays a key role in various pain states, including acute, inflammatory and/or neuropathic pain. Deletion of the SCN9A gene in nociceptive neurons of mice led to an increase in mechanical and thermal pain thresholds and reduction or abolition of inflammatory pain responses (Nassar *et al.*, *Proc Natl. Acad. Sci. USA 101*:12706-12711 (2004)).

Sodium channel-blocking agents have been reported to be effective in the treatment of various disease states, and have found particular use as local anesthetics, *e.g.*, lidocaine and bupivacaine, and in the treatment of cardiac arrhythmias, *e.g.*, propafenone and amiodarone, and epilepsy, *e.g.*, lamotrigine, phenytoin and carbamazepine (see Clare *et al.*, *Drug Discovery Today 5*:506-510 (2000); Lai *et al.*, *Annu. Rev. Pharmacol. Toxicol. 44*:371-397 (2004); Anger *et al.*, *J. Med. Chem. 44*:115-137 (2001), and Catterall, *Trends Pharmacol. Sci. 8*:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of sodium ions.

Other sodium channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia (Graham *et al., J. Pharmacol. Exp. Ther. 269*:854-859 (1994); Brown *et al., British J. Pharmacol. 115*:1425-1432 (1995)). It has also been reported that sodium channel-blocking agents can be useful in the treatment of pain, including acute, chronic, inflammatory, neuropathic, and other types of pain such as rectal, ocular, and submandibular pain typically associated with paroxysmal extreme pain disorder; see, for example, Kyle and Ilyin., *J. Med. Chem. 50*:2583-2588 (2007); Wood *et al., J. Neurobiol. 61*:55-71 (2004); Baker *et al.*, *TRENDS in Pharmacological Sciences 22*:27-31 (2001); and Lai *et al.*, *Current Opinion in Neurobiology 13*:291-297 (2003); the treatment of neurological disorders such as epilepsy, seizures, epilepsy with febrile seizures, epilepsy with benign familial neonatal infantile seizures, inherited pain disorders, *e.g.*, primary erythermalgia and paroxysmal extreme pain disorder, familial hemiplegic migraine, and movement disorder; and the treatment of other psychiatric disorders such as autism, cerebellar atrophy, ataxia, and mental retardation; see, for example, Chahine *et al.*, *CNS &*

Neurological Disorders-Drug Targets 7:144-158 (2008) and Meisler and Kearney, *J. Clin. Invest.* *115*:2010-2017 (2005). In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are used to treat neuropathic pain, such as from trigeminal neuralgia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci.* *16*:309-316 (1995)). Furthermore, based on a number of similarities between chronic pain and tinnitus, (Moller, *Am. J. Otol.* *18*:577-585 (1997); Tonndorf, *Hear. Res.* *28*:271-275 (1987)) it has been proposed that tinnitus should be viewed as a form of chronic pain sensation (Simpson, *et al., TiP.* *20*:12-18 (1999)). Indeed, lidocaine and carbamazepine have been shown to be efficacious in treating tinnitus (Majumdar, B. *et al., Clin. Otolaryngol.* *8*:175-180 (1983); Donaldson, *Laryngol. Otol.* *95*:947-951 (1981)).

Many patients with either acute or chronic pain disorders respond poorly to current pain therapies, and the development of resistance or insensitivity to opiates is common. In addition, many of the currently available treatments have undesirable side effects.

In view of the limited efficacy and/or unacceptable side-effects of the currently available agents, there is a pressing need for more effective and safer analgesics that work by blocking sodium channels.

BRIEF SUMMARY OF THE INVENTION

The present invention is related to the use of substituted pyridine compounds represented by Formulae **I-XVI**, below, and the pharmaceutically acceptable salts, prodrugs and solvates thereof (collectively referred to herein as "Compounds of the Invention"), as blockers of sodium (Na^+) channels.

The present invention is also related to treating a disorder responsive to the blockade of sodium channels in a mammal suffering from excess activity of said channels by administering an effective amount of a Compound of the Invention as described herein.

Some compounds useful in the present invention have not been heretofore reported. Thus, one aspect of the present invention is directed to novel compounds of Formula **I-XVI**, as well as their pharmaceutically acceptable salts, prodrugs and solvates.

Another aspect of the present invention is directed to the use of the novel compounds of Formulae **I-XVI**, and their pharmaceutically acceptable salts, prodrugs and solvates, as blockers of sodium channels.

A further aspect of the present invention is to provide a method for treating pain (*e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain) by administering an effective amount of a Compound of the Invention to a mammal in need of such treatment. Specifically, the present invention provides a method for preemptive or palliative treatment of pain by administering an effective amount of a Compound of the Invention to a mammal in need of such treatment.

A further aspect of the present invention is to provide a method for treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, by administering an effective amount of a Compound of the Invention to a mammal in need of such treatment.

A further aspect of the present invention is to provide a pharmaceutical composition useful for treating a disorder responsive to the blockade of sodium ion channels, said pharmaceutical composition containing an effective amount of a Compound of the Invention in a mixture with one or more pharmaceutically acceptable carriers.

Also, an aspect of the present invention is to provide a method of modulating sodium channels in a mammal, wherein said method comprises administering to the mammal an effective amount of at least one Compound of the Invention.

A further aspect of the present invention is to provide a Compound of the Invention for use in treating pain in a mammal, *e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain.

A further aspect of the present invention is to provide a Compound of the Invention for use in treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS),

or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, in a mammal.

A further aspect of the present invention is to provide radiolabeled Compounds of the Invention and the use of such compounds as radioligands in any appropriately selected competitive binding assays and screening methodologies. Thus, the present invention further provides a method for screening a candidate compound for its ability to bind to a sodium channel or sodium channel subunit using a radiolabeled Compound of the Invention. In certain embodiments, the compound is radiolabeled with ^{3}H, ^{11}C, or ^{14}C. This competitive binding assay can be conducted using any appropriately selected methodology. In one embodiment, the screening method comprises: i) introducing a fixed concentration of the radiolabeled compound to an in vitro preparation comprising a soluble or membrane-associated sodium channel, subunit or fragment under conditions that permit the radiolabeled compound to bind to the channel, subunit or fragment, respectively, to form a conjugate; ii) titrating the conjugate with a candidate compound; and iii) determining the ability of the candidate compound to displace the radiolabeled compound from said channel, subunit or fragment.

A further aspect of the present invention is to provide the use of a Compound of the Invention in the manufacture of a medicament for treating pain in a mammal. In one embodiment, the invention provides the use of a Compound of the Invention in the manufacture of a medicament for palliative or preemptive treatment of pain, such as acute pain, chronic pain, or surgical pain.

A further aspect of the present invention is to provide the use of a Compound of the Invention in the manufacture of a medicament for treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia, in a mammal.

Additional embodiments and advantages of the invention will be set forth in part in the description that follows, and will flow from the description, or can be learned by practice of

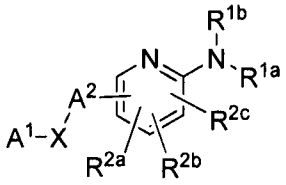
the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

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

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is based on the use of compounds of Formula **I**, and the pharmaceutically acceptable salts, prodrugs and solvates thereof, as blockers of Na^+ channels. In view of this property, compounds of Formula **I**, and the pharmaceutically acceptable salts, prodrugs and solvates thereof, are useful for treating disorders responsive to the blockade of sodium ion channels.

In one embodiment, compounds useful in this aspect of the invention are compounds represented by Formula **I**:



I

wherein:

A^1 is selected from the group consisting of:

optionally substituted cycloalkyl;

optionally substituted heterocyclo;

optionally substituted aryl; and

optionally substituted heteroaryl;

X is selected from the group consisting of:

-O-;

-S-;

-SO-;

$-SO_2-$

$-(CR^3R^4)_m-$;

$-NR^5-$;

$-SO_2NH-$; and

$-NHSO_2-$

wherein:

each R^3 and R^4, which can be identical or different, are selected from the group consisting of:

hydrogen;

halo; and

optionally substituted alkyl; or

each R^3 and R^4 taken together with the carbon atom to which they are attached form a 3- to 8-membered optionally substituted cycloalkyl or optionally substituted heterocyclo;

m is 0, 1, 2, or 3; and

R^5 is selected from the group consisting of hydrogen and optionally substituted alkyl;

A^2 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

R^{1a} is selected from the group consisting of:

optionally substituted alkyl;

(heterocyclo)alkyl;

(heteroaryl)alkyl;

(amino)alkyl;

(alkylamino)alkyl;

(dialkylamino)alkyl;

(carboxamido)alkyl;

(cyano)alkyl;

alkoxyalkyl;

hydroxyalkyl;

heteroalkyl;

optionally substituted heterocyclo;

$-SO_2R^6$; and

$-COR^7$;

wherein:

R^6 is selected from the group consisting of:

optionally substituted alkyl;

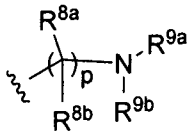
optionally substituted cycloalkyl;

optionally substituted aryl;
optionally substituted heteroaryl;
amino;
alkylamino;
dialkylamino;
cycloalkylamino;
heterocycloalkylamino;
heteroarylamino;
arylamino; and
optionally substituted alkenyl;

R^7 is selected from the group consisting of:

optionally substituted heteroaryl;

b)



; and

c) hydroxyalkyl;

wherein:

p is 0, 1, or 2;

each R^{8a} and R^{8b}, which can be identical or different, are selected from the group consisting of:

hydrogen;
optionally substituted alkyl;
aralkyl;
(heterocyclo)alkyl;
(heteroaryl)alkyl;
(amino)alkyl;
(alkylamino)alkyl;
(dialkylamino)alkyl;
(carboxamido)alkyl;
(cyano)alkyl;
alkoxyalkyl;

hydroxyalkyl;
optionally substituted cycloalkyl;
optionally substituted aryl;
optionally substituted heterocyclo; and
optionally substituted heteroaryl;

R^{9a} is selected from the group consisting of:

hydrogen;
optionally substituted alkyl;
$-COR^{10}$;
$-SO_2R^{11}$; and
$-R^{25}$;

wherein:

R^{10} is selected from the group consisting of:

optionally substituted alkyl;
aralkyl;
(heterocyclo)alkyl;
(heteroaryl)alkyl;
(amino)alkyl;
(alkylamino)alkyl;
(dialkylamino)alkyl;
(carboxamido)alkyl;
(cyano)alkyl;
alkoxyalkyl;
hydroxyalkyl;
heteroalkyl;
optionally substituted cycloalkyl;
optionally substituted aryl;
optionally substituted heterocyclo;
optionally substituted heteroaryl;
amino;
alkylamino;
dialkylamino;

cycloalkylamino;
heterocycloalkylamino;
heteroarylamino;
arylamino;
alkoxy; and
haloalkyl

R^{11} is selected from the group consisting of:
optionally substituted alkyl;
aralkyl;
(heterocyclo)alkyl;
(heteroaryl)alkyl;
(amino)alkyl;
(alkylamino)alkyl;
(dialkylamino)alkyl;
(carboxamido)alkyl;
(cyano)alkyl;
alkoxyalkyl;
hydroxyalkyl;
heteroalkyl;
optionally substituted cycloalkyl;
optionally substituted aryl;
optionally substituted heterocyclo;
optionally substituted heteroaryl;
amino;
alkylamino;
dialkylamino;
cycloalkylamino;
heterocycloalkylamino;
heteroarylamino; and
arylamino;

R^{9b} is selected from the group consisting of hydrogen and optionally substituted alkyl; or

R^{9a} and R^{9b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo;

R^{1b} is selected from the group consisting of:

hydrogen;

optionally substituted alkyl;

(heterocyclo)alkyl;

(heteroaryl)alkyl;

(amino)alkyl;

(alkylamino)alkyl;

(dialkylamino)alkyl;

(carboxamido)alkyl;

(cyano)alkyl;

alkoxyalkyl; and

hydroxyalkyl; or

R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo;

R^{2a}, R^{2b}, and R^{2c}, which can be identical or different, are selected from the group consisting of:

hydrogen;

halo;

nitro;

cyano;

hydroxy;

amino;

alkylamino;

dialkylamino;

haloalkyl;

hydroxyalkyl;

alkoxy;

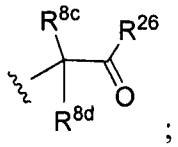
haloalkoxy;

aryloxy;

aralkyloxy;

alkylthio;
carboxamido;
sulfonamido;
alkylcarbonyl;
arylcarbonyl;
alkylsulfonyl;
arylsulfonyl;
ureido;
guanidino;
carboxy;
carboxyalkyl;
optionally substituted alkyl,
(amino)alkyl; and
(diamino)alkyl; and

R^{25} is:



;

R^{8c} and R^{8d}, which can be identical or different, are selected from the group consisting of:

hydrogen;
optionally substituted alkyl;
aralkyl;
(heterocyclo)alkyl;
(heteroaryl)alkyl;
(amino)alkyl;
(alkylamino)alkyl;
(dialkylamino)alkyl;
(carboxamido)alkyl;
(cyano)alkyl;
alkoxyalkyl;
hydroxyalkyl;

optionally substituted cycloalkyl;

optionally substituted aryl;

optionally substituted heterocyclo; and

optionally substituted heteroaryl; and

R^{26} is selected from the group consisting of:

hydroxy;

alkoxy;

amino;

alkylamino;

dialkylamino;

hydroxyalkylamino;

arylamino; and

cycloalkylamino,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

The A^1-X-A^2- group can be at any of the four available carbon atoms of the pyridine ring. In one embodiment, Compounds of the Invention are compounds having Formula **I**, with the proviso that when R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo or when R1a is alkoxyalkyl, alkyl or alkylaminoalkyl, then X is selected from the group consisting of:

-O-;

-S-;

-SO-;

$-SO_2-$

$-(CR^3R^4)_m-$;

$-SO_2NH-$; and

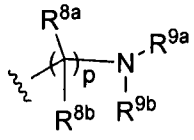
$-NHSO_2-$

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having Formula **I**, with the proviso that when A^2 pyrrolopyridine and X is X is $-(CR^3R^4)_m-$, then m is 1, 2, or 3,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having Formula **I**, with the proviso that when R^7 is:



,

and X is $-(CR^3R^4)_m-$, then m is 1, 2, or 3, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

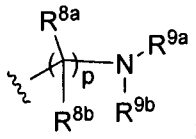
In one embodiment, Compounds of the Invention are compounds having Formula **I**, with the proviso that when R^7 is optionally substituted heteroaryl, then A^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having Formula **I**, wherein:

R^7 is selected from the group consisting of:

optionally substituted heteroaryl; and

b)



;

X is selected from the group consisting of:

-O-;

-S-;

-SO-;

$-SO_2-$

$-(CR^3R^4)_m-$;

$-NR^5-$; and

$-SO_2NH-$; and

R^{9a} is selected from the group consisting of:

hydrogen;

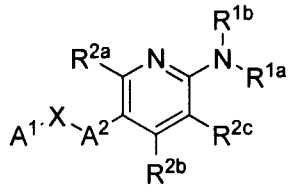
optionally substituted alkyl;

$-COR^{10}$; and

$-SO_2R^{11}$,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

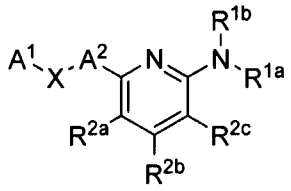
In one embodiment, Compounds of the Invention are compounds having Formula **II**:



II

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{2c}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having Formula **III**:

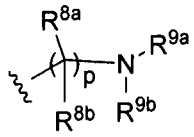


III

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{2c}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-III** wherein R^{1a} is $-SO_2R^6$, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-III** wherein R^{1a} is $-COR^7$, R^7 is:



,

and p is 1, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-III** wherein:

R^{1a} is $-COR^7$;

R^7 is hydroxyalkyl; and

X is selected from the group consisting of:

-O-;

-S-;

-SO-;

$-SO_2-$

$-(CR^3R^4)_m-$; and

$-NR^5-$,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-III** wherein:

R^{1a} is $-COR^7$;

R^7 a C_{2-4} dihydroxyalkyl; and

X is selected from the group consisting of:

-O-;

-S-;

-SO-;

$-SO_2-$

$-(CR^3R^4)_m-$; and

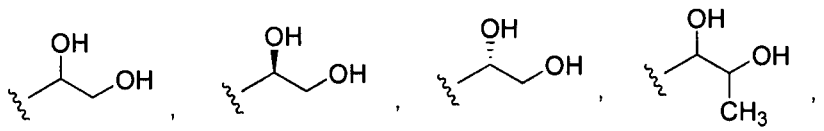
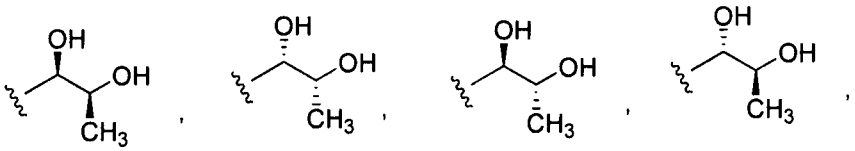
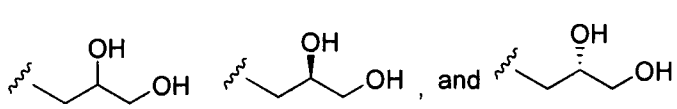
$-NR^5-$,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-III** wherein:

R^{1a} is $-COR^7$;

R^7 is selected from the group consisting of:

; and

X is selected from the group consisting of:

-O-;

-S-;

-SO-;

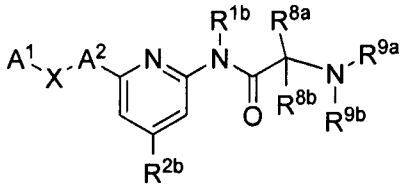
$-SO_2-$

$-(CR^3R^4)_m-$; and

$-NR^5-$,

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

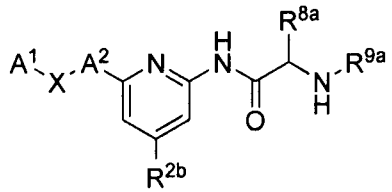
In one embodiment, Compounds of the Invention are compounds having Formula **IV**:



IV

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{1b}, R^{2b}, R^{8a}, R^{8b}, R^{9a}, R^{9b}, A^1, A^2, and X are as defined above in connection with Formula **I**.

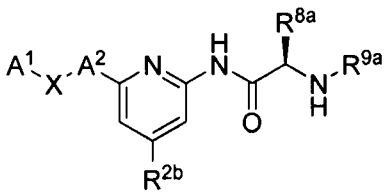
In one embodiment, Compounds of the Invention are compounds having Formula **V**:



V

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

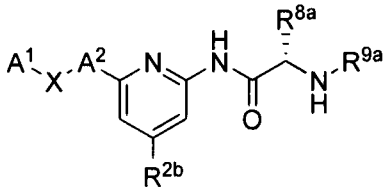
In one embodiment, Compounds of the Invention are compounds having Formula **VI**:



VI

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having Formula **VII**:



VII

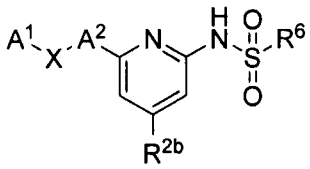
and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-VII** wherein R^{9a} is $-COR^{10}$, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof. In one embodiment, R^{10} is selected from the group consisting of C_1-C_4 alkyl, C_{1-4} haloalkyl, C_3-C_6 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, amino, and (amino)alkyl.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-VII** wherein R^{8a} is selected from the group consisting of hydrogen, C_{1-6} alkyl, hydroxyalkyl, (carboxamido)alkyl, aralkyl, and (heteroaryl)alkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-VII** wherein R^{9a} is $-SO_2R^{11}$, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof. In one embodiment, R^{11} is C_1-C_4 alkyl.

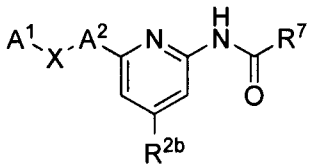
In one embodiment, Compounds of the Invention are compounds having Formula **VIII**:



VIII

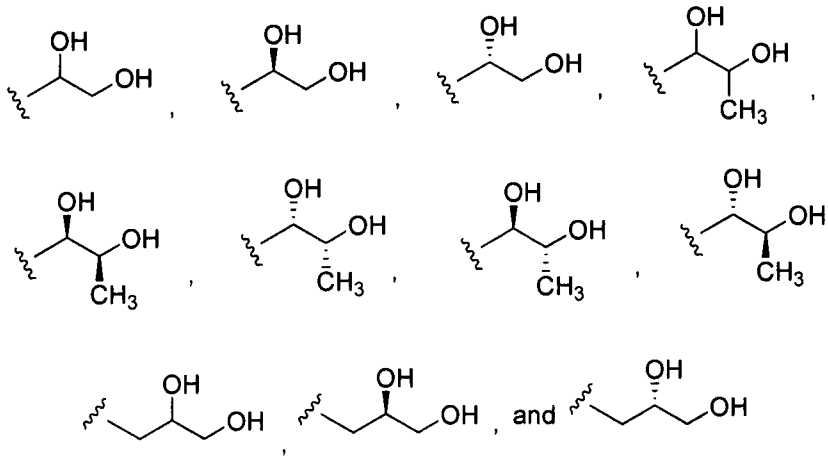
and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^6, A^1, A^2, and X are as defined above in connection with Formula **I**. In one embodiment, R^6 is selected from the group consisting of C_1-C_4 alkyl, C_3-C_6 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, amino, and (amino)alkyl.

In one embodiment, Compounds of the Invention are compounds having Formula **IX**:

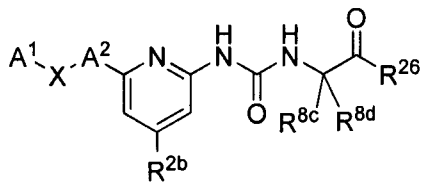


IX

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, A^1, and A^2 are as defined above in connection with Formula **I**, R^7 is hydroxyalkyl, and X is selected from the group consisting of -O-; -S-; -SO-; $-SO_2$-; $-(CR^3R^4)_m$-; and $-NR^5$-. In one embodiment, R^7 is monohydroxyalkyl. In one embodiment, R^7 is a dihydroxyalkyl. In one embodiment, R^7 is a C_{2-4} dihydroxyalkyl. In one embodiment, R^7 is selected from the group consisting of:



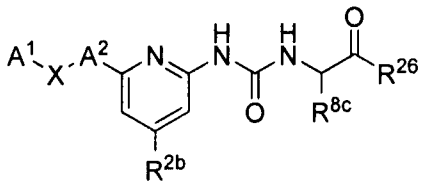
In one embodiment, Compounds of the Invention are compounds having Formula **X**:



X

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8c}, R^{8d}, R^{26}, A^1, A^2, and X are as defined above in connection with Formula **I**. In one embodiment, R^{26} is hydroxy. In one embodiment, R^{26} is alkoxy. In one embodiment, R^{26} is amino.

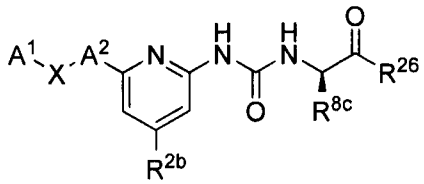
In one embodiment, Compounds of the Invention are compounds having Formula **XI**:



XI

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8c}, R^{26}, A^1, A^2, and X are as defined above in connection with Formula **I**. In one embodiment, R^{26} is hydroxy. In one embodiment, R^{26} is alkoxy. In one embodiment, R^{26} is amino.

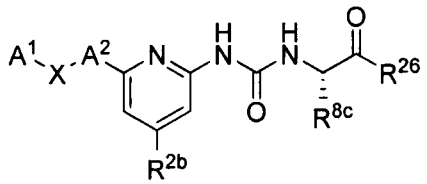
In one embodiment, Compounds of the Invention are compounds having Formula **XII**:



XII

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8c}, R^{26}, A^1, A^2, and X are as defined above in connection with Formula **I**. In one embodiment, R^{26} is hydroxy. In one embodiment, R^{26} is alkoxy. In one embodiment, R^{26} is amino.

In one embodiment, Compounds of the Invention are compounds having Formula **XIII**:

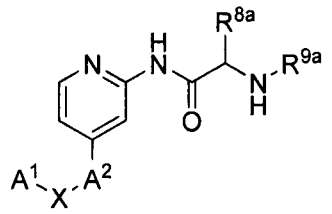


XIII

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{2b}, R^{8c}, R^{26}, A^1, A^2, and X are as defined above in connection with Formula **I**. In one embodiment, R^{26} is hydroxy. In one embodiment, R^{26} is alkoxy. In one embodiment, R^{26} is amino.

In one embodiment, Compounds of the Invention are compounds having any one of Formulae **X-XIII**, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{8c} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, and (carboxamido)alkyl, and R^{26} is amino.

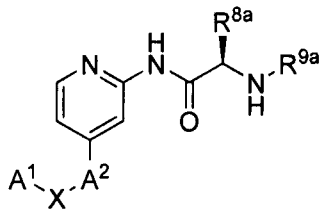
In one embodiment, Compounds of the Invention are compounds having Formula **XIV**:



XIV

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

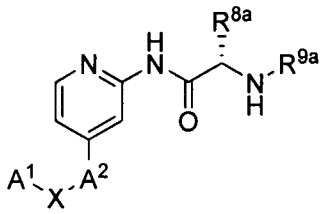
In one embodiment, Compounds of the Invention are compounds having Formula **XV**:



XV

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having Formula **XVI**:



XVI

and the pharmaceutically acceptable salts, solvates, and prodrugs thereof, wherein R^{8a}, R^{9a}, A^1, A^2, and X are as defined above in connection with Formula **I**.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **XIV-XVI** wherein R^{9a} is $-COR^{10}$, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof. In one embodiment, R^{10} is selected from the group consisting of C_1-C_4 alkyl, C_{1-4} haloalkyl, C_3-C_6 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, amino, and (amino)alkyl.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **XIV-XVI** wherein R^{8a} is selected from the group consisting of hydrogen, C_{1-6} alkyl, hydroxyalkyl, (carboxamido)alkyl, aralkyl, and (heteroaryl)alkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein X is -O-, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^2 is optionally substituted phenyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein R^{1b} is selected from the group consisting of hydrogen and hydroxyalkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

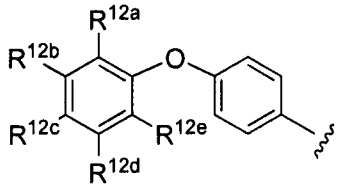
In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein R^{2b} is selected from the group consisting of hydrogen, halo, *e.g.,* chloro, C_{1-4} alkyl, and hydroxyalkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl; X is -O-; and A^2 is optionally substituted phenyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^1 selected from the group consisting of optionally substituted phenyl; optionally substituted 2-pyridyl (*i.e.*, pyridin-2-yl); optionally substituted 3-pyridyl (*i.e.*, pyridin-3-yl); and optionally substituted 4-pyridyl (*i.e.*, pyridin-4-yl), and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein the optional substituents of the A^1 group are selected from the group consisting of halo, cyano, haloalkyl, and C_{1-4} alkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^1-X-A^2- is:



wherein:

R^{12a}, R^{12b}, R^{12c}, R^{12d}, and R^{12e}, which can be identical or different, are selected from the group consisting of:

hydrogen;

halo;

nitro;

cyano;

hydroxy;

amino;

alkylamino;

dialkylamino;

haloalkyl;

hydroxyalkyl;

alkoxy;

haloalkoxy;

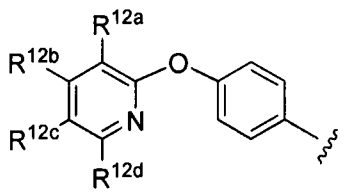
aryloxy;

aralkyloxy;

alkylthio;
carboxamido;
sulfonamido;
alkylcarbonyl;
arylcarbonyl;
alkylsulfonyl;
arylsulfonyl;
ureido;
guanidino;
carboxy;
carboxyalkyl;
alkyl;
optionally substituted cycloalkyl;
optionally substituted alkenyl;
optionally substituted alkynyl;
optionally substituted aryl;
optionally substituted heteroaryl; and
optionally substituted heterocyclo; or

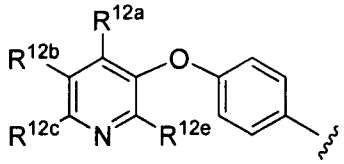
R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12c} and R^{12d}, or R^{12d} and R^{12e}, taken together with the carbon atoms to which they are attached form a 5- or 6-membered optionally substituted cycloalkyl or heterocyclo group, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI**, wherein A^1-X-A^2- is:



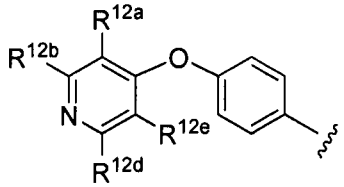
wherein R^{12a}, R^{12b}, R^{12c}, and R^{12d} are as defined above, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^1-X-A^2- is:



wherein R^{12a}, R^{12b}, R^{12c}, and R^{12e} are as defined above, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein A^1-X-A^2- is:

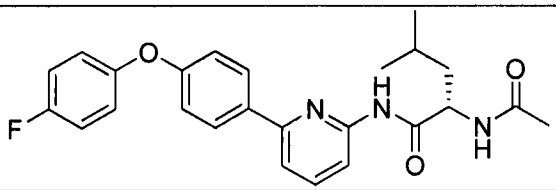


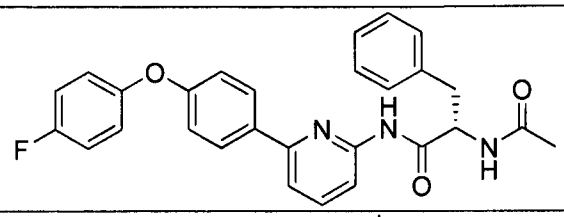
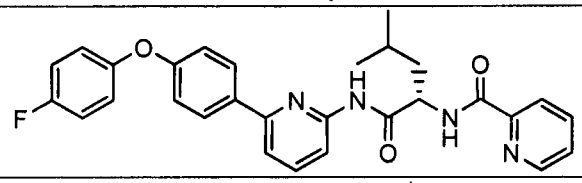
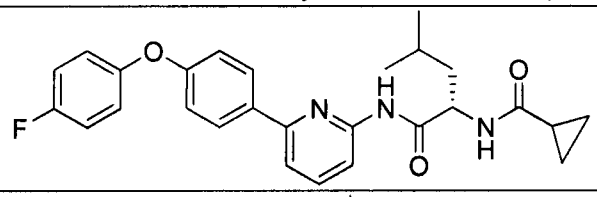
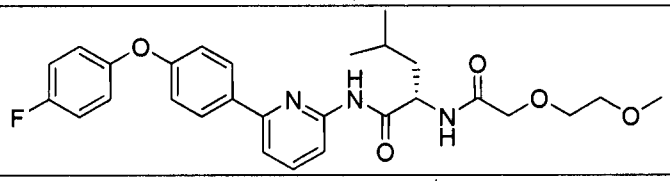
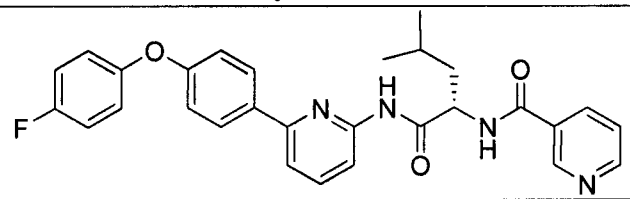
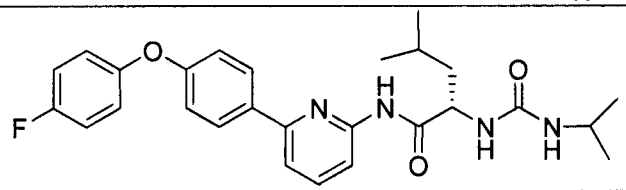
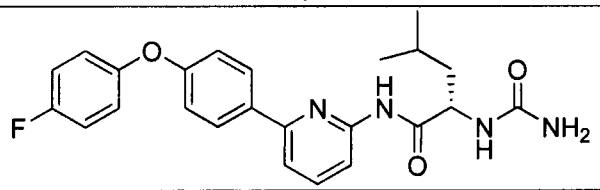
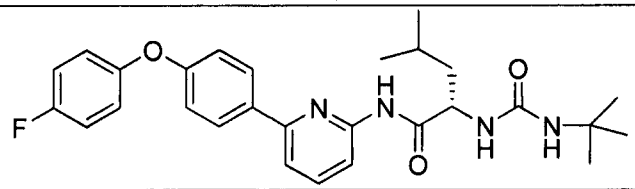
wherein R^{12a}, R^{12b}, R^{12d}, and R^{12e} are as defined above, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof.

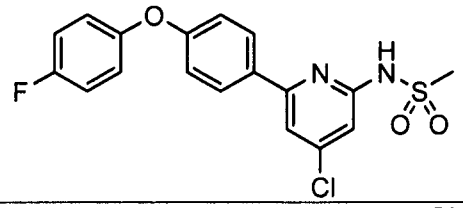
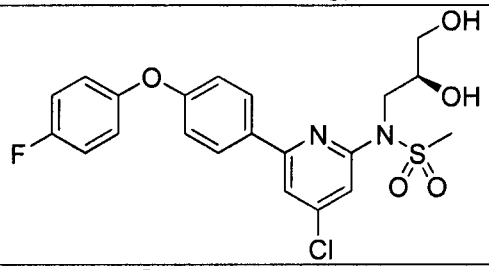
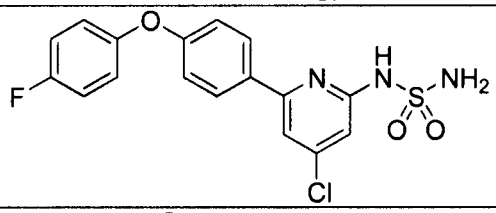
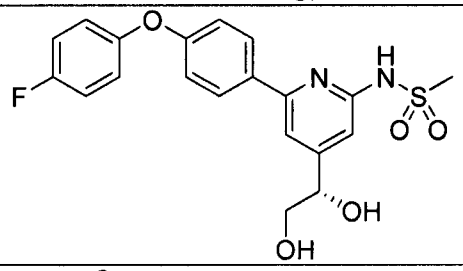
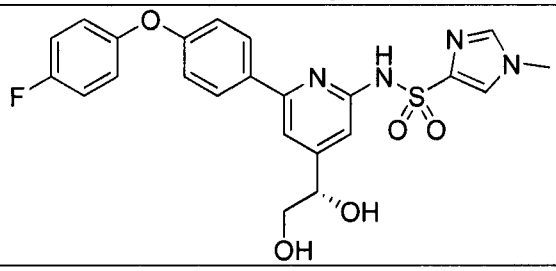
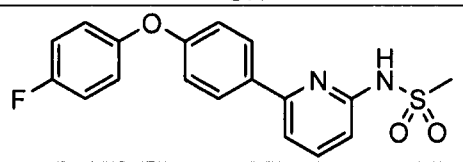
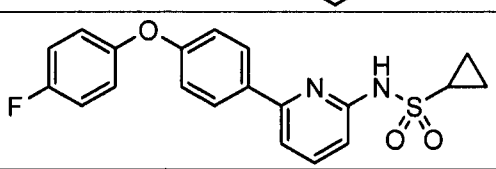
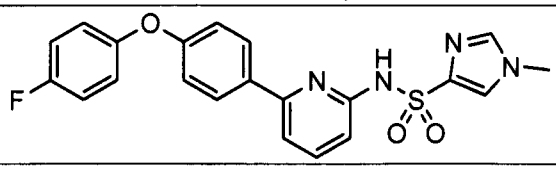
In one embodiment, Compounds of the Invention are compounds having any of Formulae **I-XVI** wherein R^{12a}, R^{12b}, R^{12c}, R^{12d}, and R^{12e}, which can be identical or different, are selected from the group consisting of hydrogen, halo, cyano, haloalkyl, and C_{1-4} alkyl, and the pharmaceutically acceptable salts, solvates, and prodrugs thereof. In one embodiment, one or two of R^{12a}, R^{12b}, R^{12c}, R^{12d}, and R^{12e} are halo, *e.g.*, fluoro or chloro, or haloalkyl, *e.g.*, trifluoromethyl, and the others are hydrogen. In one embodiment, R^{12c} is halo or haloalkyl.

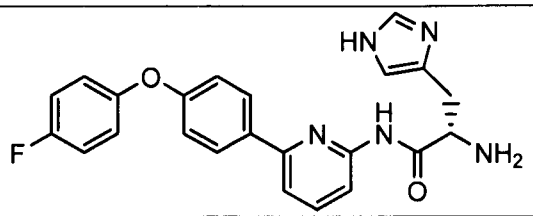
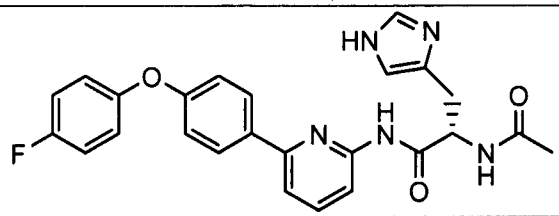
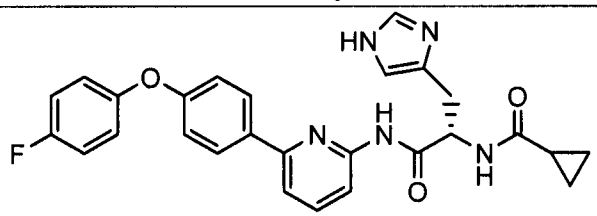
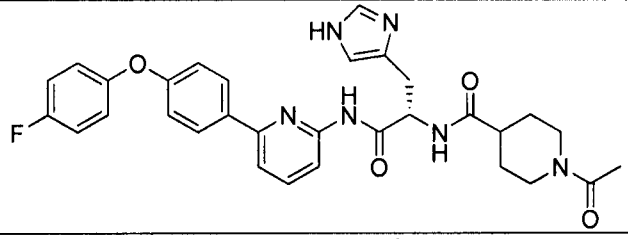
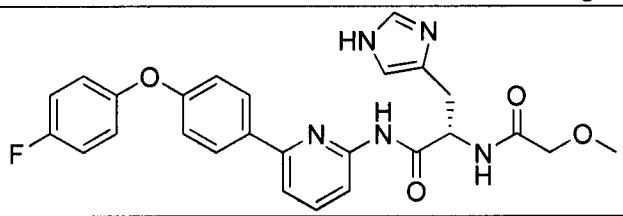
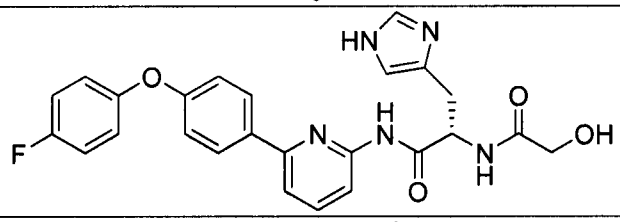
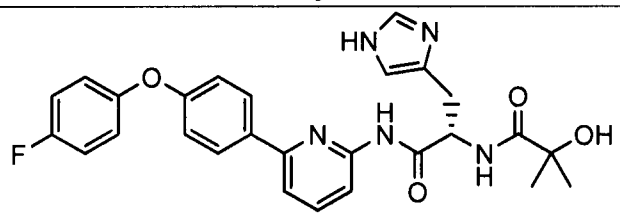
In another embodiment, Compounds of the Invention include the compound examples of TABLE 2, and the pharmaceutically acceptable salts, prodrugs, and solvates thereof. The chemical names of the compound examples are provided in TABLE 3.

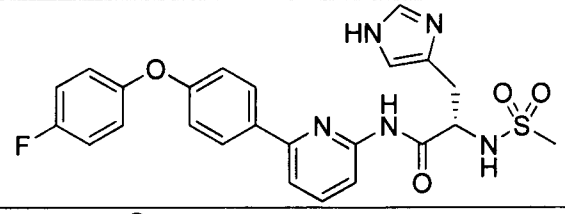
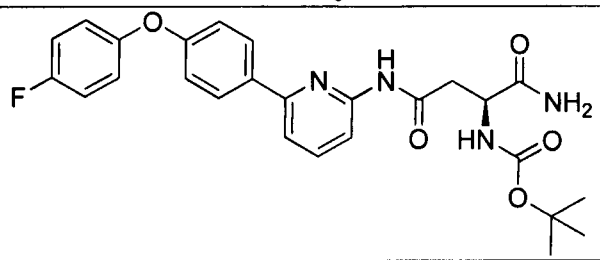
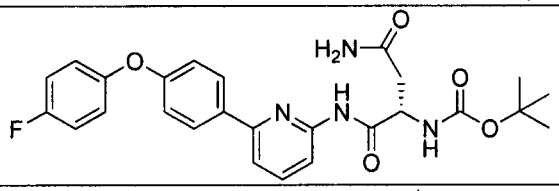
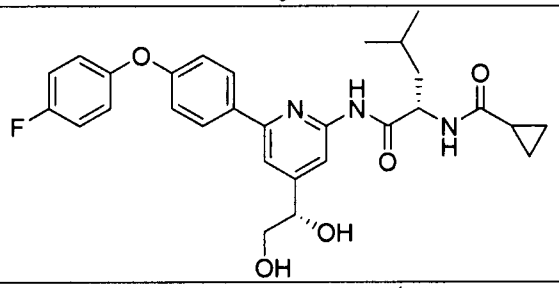
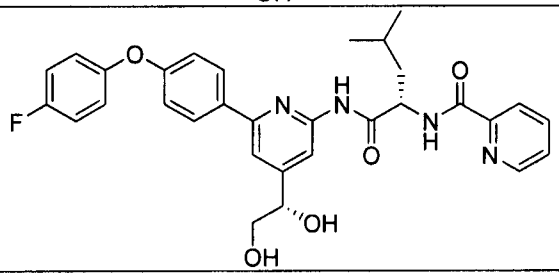
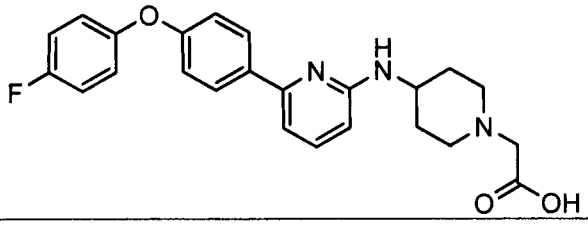
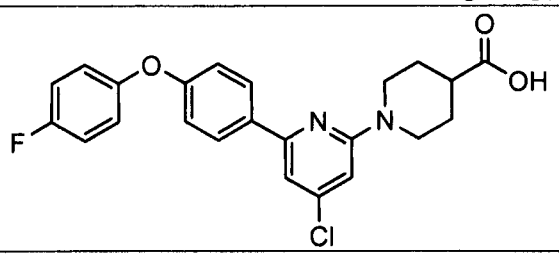
TABLE 2

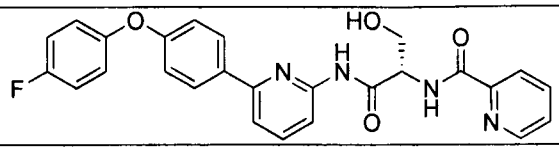
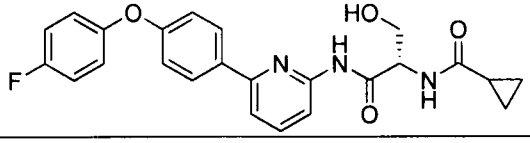
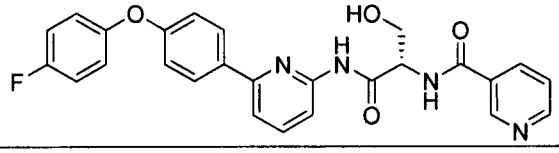
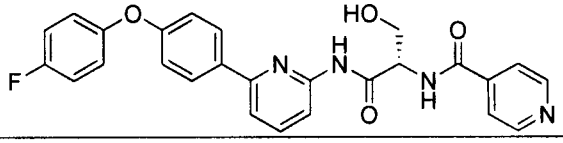
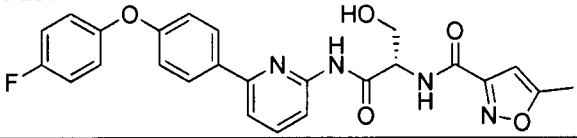
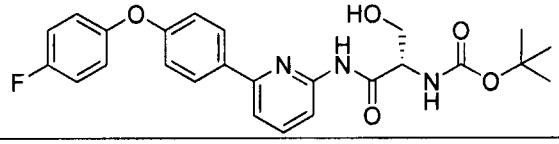
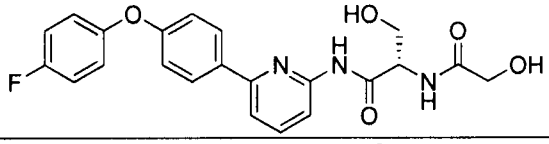
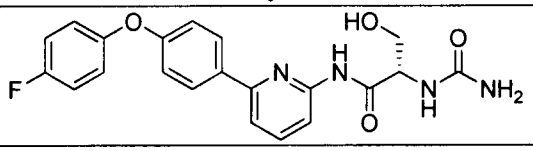
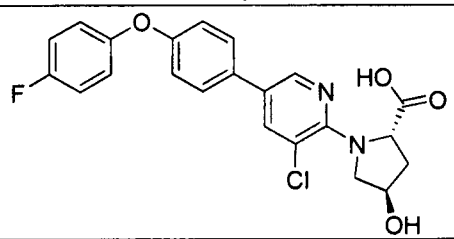
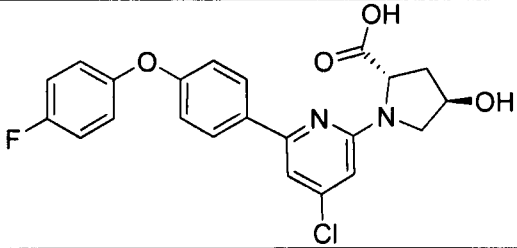
Compound Example No.	**Structure**
3	

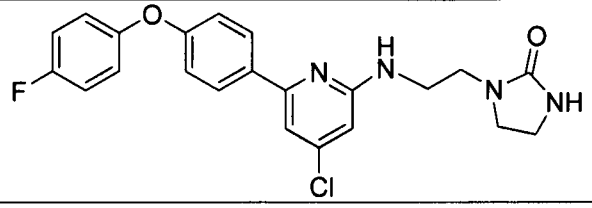
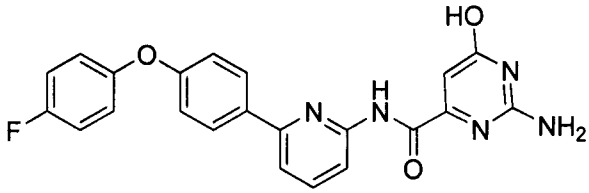
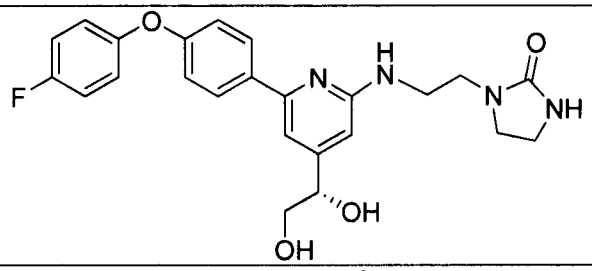
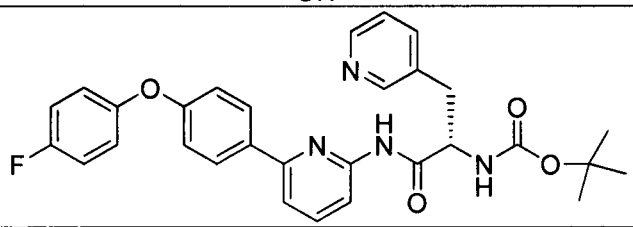
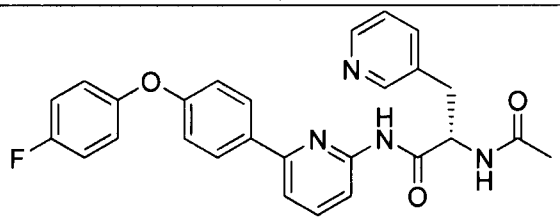
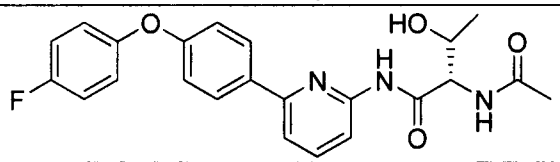
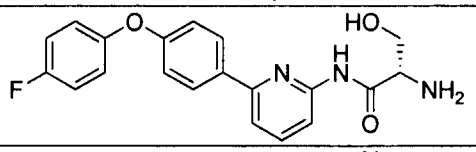
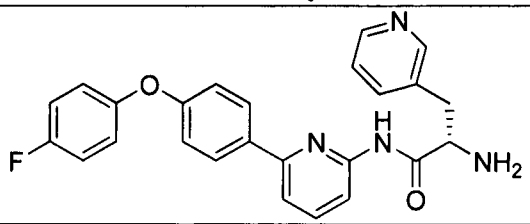
Compound Example No.	Structure
4	
7	
8	
9	
10	
11	
12	
13	

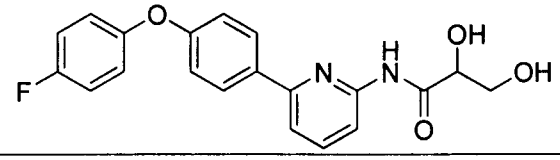
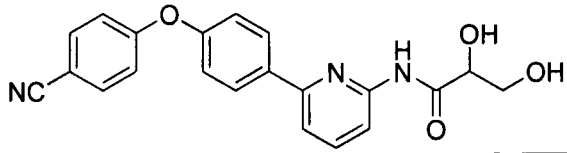
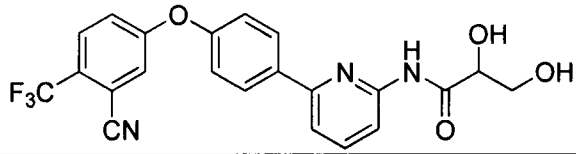
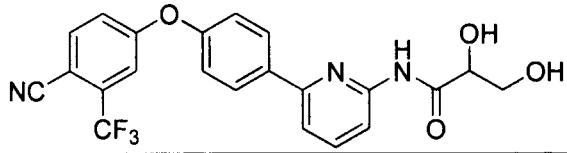
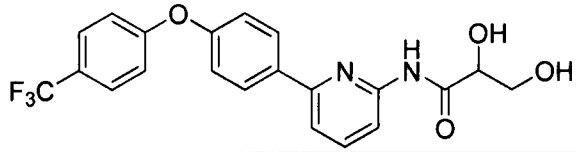
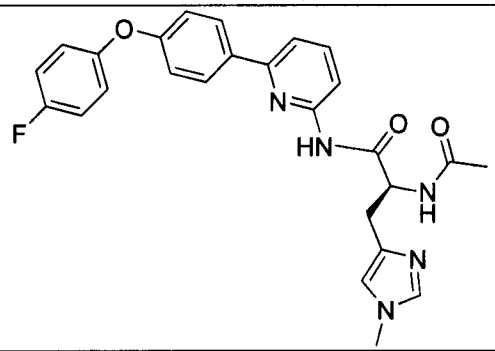
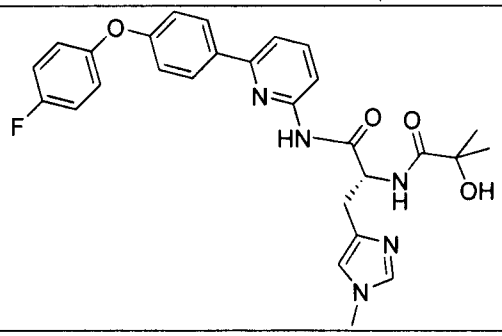
Compound Example No.	Structure
15	
17	
18	
24	
26	
27	
28	
29	

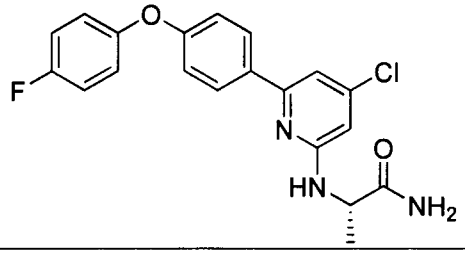
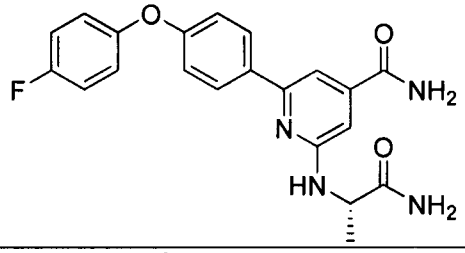
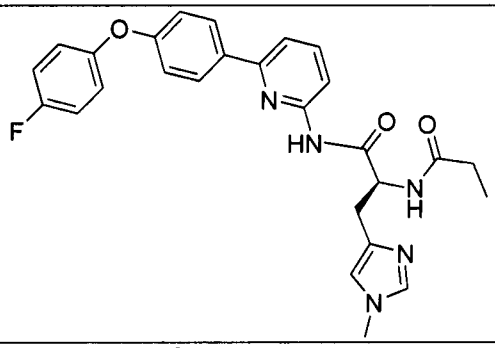
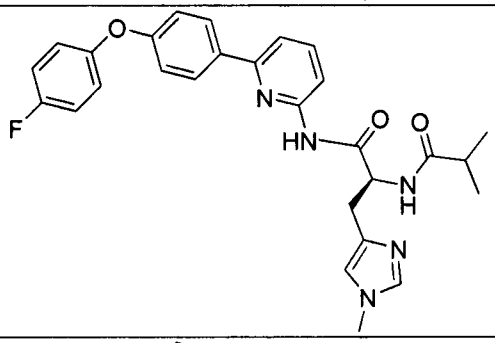
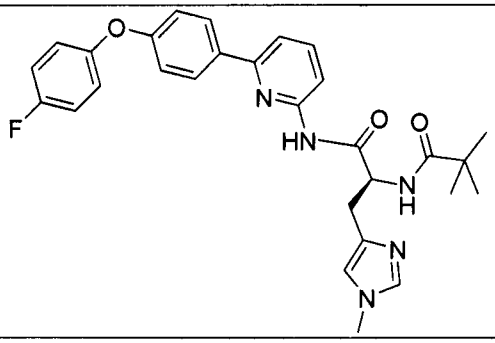
Compound Example No.	Structure
31	
32	
33	
34	
35	
36	
37	

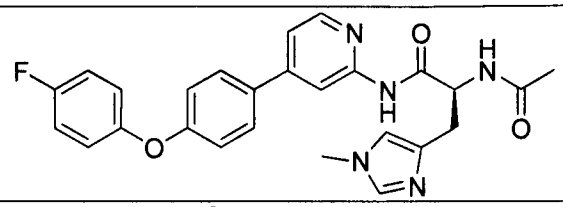
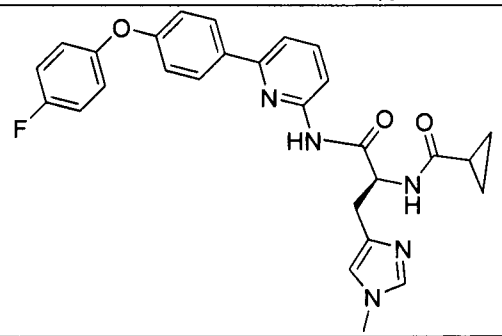
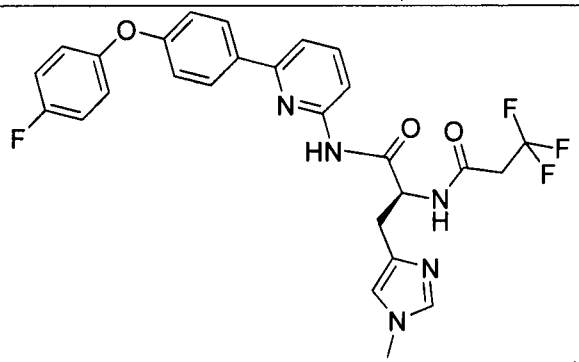
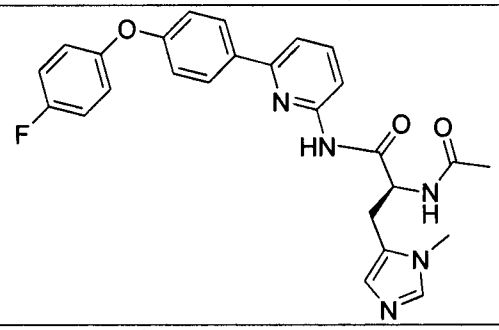
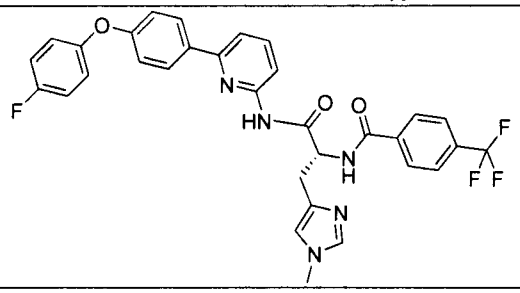
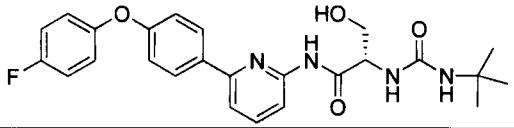
Compound Example No.	Structure
38	
40	
41	
44	
45	
50	
53	

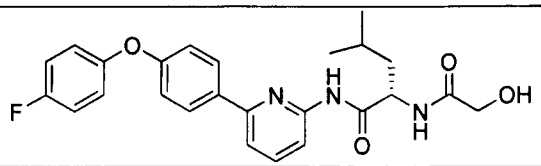
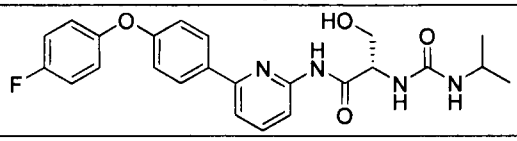
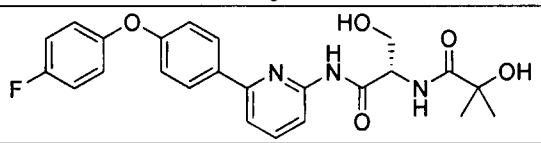
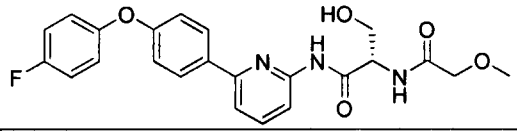
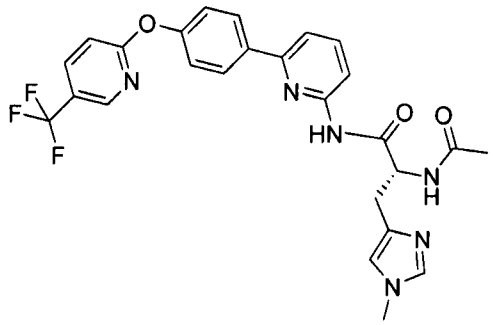
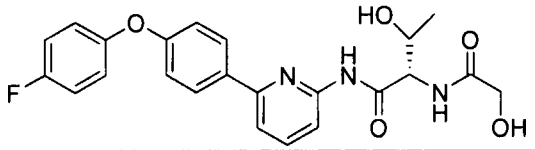
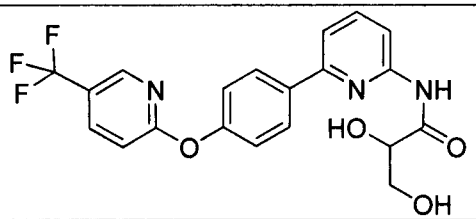
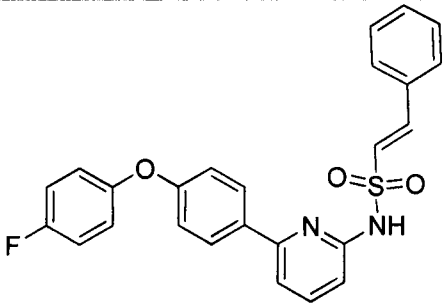
Compound Example No.	Structure
54	
55	
56	
57	
58	
59	
60	
61	
62	
63	

Compound Example No.	Structure
64	
65	
66	
67	
68	
69	
70	
71	

Compound Example No.	Structure
72	
73	
74	
75	
76	
77	
78	

Compound Example No.	Structure
79	
80	
81	
82	
83	

Compound Example No.	Structure
84	
85	
86	
87	
88	
89	

Compound Example No.	Structure
90	
91	
92	
93	
94	
95	
96	
97	

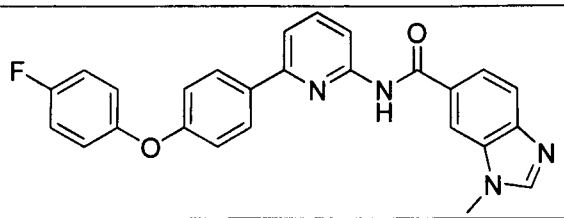
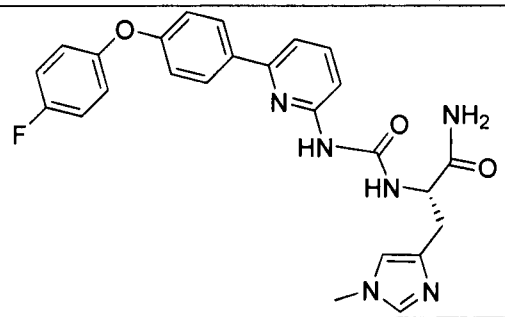
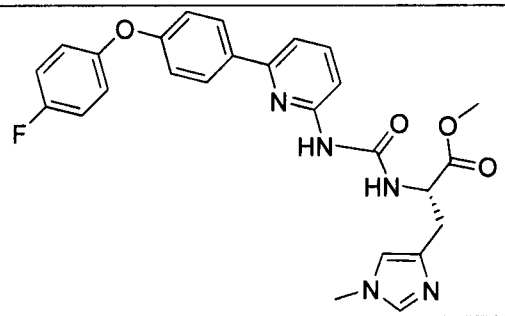
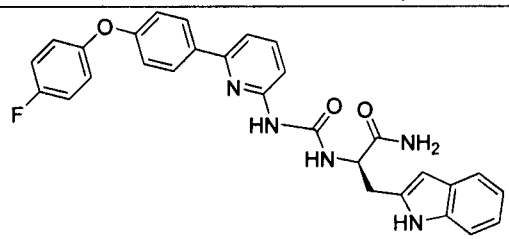
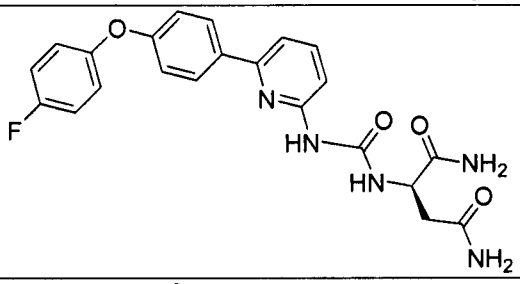
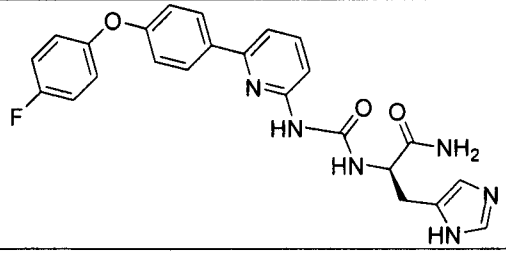
Compound Example No.	Structure
98	
99	
100	
101	
102	
103	

TABLE 3

Compound Example No.	Chemical Name
3	(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide
4	(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-phenylpropanamide
7	(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide
8	(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide
9	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-(2-methoxyethoxy)acetamido)-4-methylpentanamide
10	(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)nicotinamide
11	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(3-isopropylureido)-4-methylpentanamide
12	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methyl-2-ureidopentanamide
13	(S)-2-(3-(tert-butyl)ureido)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide
15	N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide
17	(S)-N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-N-(2,3-dihydroxypropyl)methanesulfonamide
18	N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)sulfamide
24	(S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide
26	(S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide
27	N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide
28	N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)cyclopropane sulfonamide
29	N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide
31	(S)-2-amino-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide
32	(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide
33	(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide

Compound Example No.	Chemical Name
34	(S)-1-acetyl-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)piperidine-4-carboxamide
35	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(2-methoxyacetamido)propanamide
36	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-3-(1H-imidazol-4-yl)propanamide
37	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1H-imidazol-4-yl)propanamide
38	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(methylsulfonamido)propanamide
40	(S)-tert-butyl (1-amino-4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate
41	(S)-tert-butyl (4-amino-1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate
44	N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide
45	N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide
50	2-(4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)piperidin-1-yl)acetic acid
53	1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)piperidine-4-carboxylic acid
54	Pyridine-2-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide
55	Cyclopropanecarboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide
56	N-((S)-1-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-nicotinamide
57	N-((S)-1-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-isonicotinamide
58	5-Methyl-isoxazole-3-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide
59	((S)-1-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-carbamic acid tert-butyl ester
60	(S)-N-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-(2-hydroxy-acetylamino)-propionamide

Compound Example No.	Chemical Name
61	(S)-N-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-ureido-propionamide
62	(2S,4R)-1-(3-chloro-5-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-hydroxypyrrolidine-2-carboxylic acid
63	(2S,4R)-1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-hydroxypyrrolidine-2-carboxylic acid
64	1-(2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)ethyl)imidazolidin-2-one
65	2-amino-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-6-hydroxypyrimidine-4-carboxamide
66	(S)-1-(2-((4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)ethyl)imidazolidin-2-one
67	((S)-1-{6-[4-(4-Fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-pyridin-3-yl-ethyl)-carbamic acid tert-butyl ester
68	(S)-2-Acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide
69	(S)-2-Acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-butyramide
70	(S)-2-Amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pridin-2-yl}-3-hydroxy-propionamide
71	(S)-2-Amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide
72	N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide
73	N-(6-(4-(4-cyanophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide
74	N-(6-(4-(3-cyano-4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide
75	N-(6-(4-(4-cyano-3-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide
76	2,3-dihydroxy-N-(6-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)propanamide
77	(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide
78	(R)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1-methyl-1H-imidazol-4-yl)propanamide
79	(S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide
80	(S)-2-((1-amino-1-oxopropan-2-yl)amino)-6-(4-(4-fluorophenoxy)phenyl)isonicotinamide

Compound Example No.	Chemical Name
81	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-propionamidopropanamide
82	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-isobutyramido-3-(1-methyl-1H-imidazol-4-yl)propanamide
83	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-pivalamidopropanamide
84	(S)-2-acetamido-N-(4-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide
85	(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide
86	(S)-3,3,3-trifluoro-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)propanamide
87	(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-5-yl)propanamide
88	(R)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)-4-(trifluoromethyl)benzamide
89	(S)-2-(3-(tert-butyl)ureido)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxypropanamide
90	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-4-methylpentanamide
91	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(3-isopropylureido)propanamide
92	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxy-2-methylpropanamido)propanamide
93	(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-methoxyacetamido)propanamide
94	(R)-2-acetamido-3-(1-methyl-1H-imidazol-4-yl)-N-(6-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyridin-2-yl)propanamide
95	(2S,3S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxyacetamido)butanamide
96	2,3-dihydroxy-N-(6-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyridin-2-yl)propanamide
97	(E)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-phenylethenesulfonamide
98	N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide
99	(S)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanamide
100	(S)-methyl 2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanoate

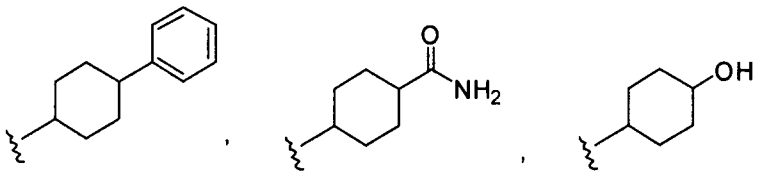
Compound Example No.	Chemical Name
101	(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-indol-2-yl)propanamide
102	(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido) succinamide
103	(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-imidazol-5-yl)propanamide

For the purpose of the present disclosure, the term "alkyl" as used by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms (*i.e.*, C_{1-12} alkyl) or the number of carbon atoms designated (*i.e.*, a C_1 alkyl such as methyl, a C_2 alkyl such as ethyl, a C_3 alkyl such as propyl or isopropyl, etc.). In one embodiment, the alkyl group is chosen from a straight chain C_{1-10} alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C_{1-10} alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C_{1-6} alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C_{3-6} alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C_{1-4} alkyl group. In another embodiment, the alkyl group is chosen from a straight chain C_{2-4} alkyl group. In another embodiment, the alkyl group is chosen from a branched chain C_{3-4} alkyl group. Non-limiting exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, decyl, and the like. Non-limiting exemplary C_{1-4} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, and *iso*-butyl.

For the purpose of the present disclosure, the term "optionally substituted alkyl" as used by itself or as part of another group means that the alkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from nitro, haloalkoxy, aryloxy, aralkyloxy, alkylthio, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, cycloalkyl, and the like. In one embodiment, the optionally substituted alkyl is substituted with two substituents. In another embodiment, the optionally substituted alkyl is substituted with one substituent. Non-limiting exemplary optionally substituted alkyl groups include $-CH_2CH_2NO_2$, $-CH_2CH_2CO_2H$, $-CH_2CH_2SO_2CH_3$, $-CH_2CH_2COPh$, and the like.

For the purpose of the present disclosure, the term "cycloalkyl" as used by itself or as part of another group refers to saturated and partially unsaturated (e.g. containing one or two double bonds) cyclic aliphatic hydrocarbons containing one to three rings having from three to twelve carbon atoms (*i.e.*, C_{3-12} cycloalkyl) or the number of carbons designated. In one embodiment, the cycloalkyl group has two rings. In one embodiment, the cycloalkyl group has one ring. In another embodiment, the cycloalkyl group is chosen from a C_{3-8} cycloalkyl group. In another embodiment, the cycloalkyl group is chosen from a C_{3-6} cycloalkyl group. Non-limiting exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornyl, decalin, adamantyl, cyclohexenyl, and the like.

For the purpose of the present disclosure, the term "optionally substituted cycloalkyl" as used by itself or as part of another group means that the cycloalkyl as defined above is either unsubstituted or substituted with one, two, or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl. In one embodiment, the optionally substituted cycloalkyl is substituted with two substituents. In another embodiment, the optionally substituted cycloalkyl is substituted with one substituent. Non-limiting exemplary optionally substituted cycloalkyl groups include:



For the purpose of the present disclosure, the term "alkenyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one, two or three carbon-to-carbon double bonds. In one embodiment, the alkenyl group is chosen from a C_{2-6} alkenyl group. In another embodiment, the alkenyl group is chosen from a C_{2-4} alkenyl group. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, *sec*-butenyl, pentenyl, and hexenyl.

For the purpose of the present disclosure, the term "optionally substituted alkenyl" as used herein by itself or as part of another group means the alkenyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

For the purpose of the present disclosure, the term "alkynyl" as used by itself or as part of another group refers to an alkyl group as defined above containing one to three carbon-to-carbon triple bonds. In one embodiment, the alkynyl has one carbon-to-carbon triple bond. In one embodiment, the alkynyl group is chosen from a C_{2-6} alkynyl group. In another embodiment, the alkynyl group is chosen from a C_{2-4} alkynyl group. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

For the purpose of the present disclosure, the term "optionally substituted alkynyl" as used herein by itself or as part of another group means the alkynyl as defined above is either unsubstituted or substituted with one, two or three substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclo.

For the purpose of the present disclosure, the term "haloalkyl" as used by itself or as part of another group refers to an alkyl group as defined above substituted by one or more fluorine, chlorine, bromine and/or iodine atoms. In one embodiment, the alkyl group is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the haloalkyl group is chosen from a C_{1-4} haloalkyl group. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

For the purpose of the present disclosure, the term "hydroxyalkyl" as used by itself or as part of another group refers to an alkyl group as defined above substituted with one or more, *e.g.*, one, two, or three, hydroxy groups. In one embodiment, the hydroxyalkyl is a monohydroxyalkyl, *i.e.*, substituted with exactly one hydroxy group. In another

embodiment, the hydroxyalkyl is a dihydroxyalkyl, *i.e.*, substituted with exactly two hydroxy groups. In another embodiment, the hydroxyalkyl group is chosen from a C_{1-4} hydroxyalkyl group. In another embodiment, the hydroxyalkyl group is chosen from a C_{2-4} hydroxyalkyl group. Non-limiting exemplary hydroxyalkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

For the purpose of the present disclosure, the term "alkoxy" as used by itself or as part of another group refers to an optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl attached to a terminal oxygen atom. In one embodiment, the alkoxy group is chosen from a C_{1-4} alkoxy group. In another embodiment, the alkoxy group is chosen from a C_{1-4} alkyl attached to a terminal oxygen atom, *e.g.*, methoxy, ethoxy, and *tert*-butoxy.

For the purpose of the present disclosure, the term "alkylthio" as used by itself or as part of another group refers to a sulfur atom substituted by an optionally substituted alkyl group. In one embodiment, the alkylthio group is chosen from a C_{1-4} alkylthio group. Non-limiting exemplary alkylthio groups include $-SCH_3$, and $-SCH_2CH_3$.

For the purpose of the present disclosure, the term "alkoxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with any of the above-mentioned alkoxy groups. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

For the purpose of the present disclosure, the term "heteroalkyl" as used by itself or part of another group refers to a stable straight or branched chain hydrocarbon radical containing 1 to 10 carbon atoms and at least two heteroatoms, which can be the same or different, selected from O, N, or S, wherein: 1) the nitrogen atom(s) and sulfur atom(s) can optionally be oxidized; and/or 2) the nitrogen atom(s) can optionally be quaternized. The heteroatoms can be placed at any interior position of the heteroalkyl group or at a position at which the heteroalkyl group is attached to the remainder of the molecule. In one embodiment, the heteroalkyl group contains two oxygen atoms. Non-limiting exemplary heteroalkyl groups

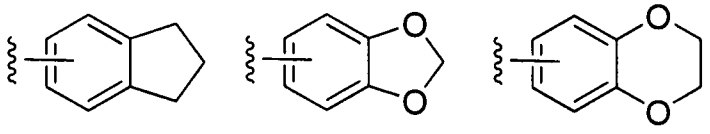
include $-CH_2OCH_2CH_2OCH_3$, $-OCH_2CH_2OCH_2CH_2OCH_3$, $-CH_2NHCH_2CH_2OCH_2$, $-OCH_2CH_2NH_2$, and $-NHCH_2CH_2N(H)CH_3$.

For the purpose of the present disclosure, the term "haloalkoxy" as used by itself or as part of another group refers to a haloalkyl attached to a terminal oxygen atom. Non-limiting exemplary haloalkoxy groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, and 2,2,2-trifluoroethoxy.

For the purpose of the present disclosure, the term "aryl" as used by itself or as part of another group refers to a monocyclic or bicyclic aromatic ring system having from six to fourteen carbon atoms (*i.e.*, C_6-C_{14} aryl). Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph"), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In one embodiment, the aryl group is chosen from phenyl and naphthyl.

For the purpose of the present disclosure, the term "optionally substituted aryl" as used herein by itself or as part of another group means that the aryl as defined above is either unsubstituted or substituted with one to five substituents independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl. In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In one embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. Non-limiting exemplary substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl and 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, and 3-chloro-4-fluorophenyl. The term optionally

substituted aryl is meant to include groups having fused optionally substituted cycloalkyl and fused optionally substituted heterocyclo rings. Examples include



For the purpose of the present disclosure, the term "aryloxy" as used by itself or as part of another group refers to an optionally substituted aryl attached to a terminal oxygen atom. A non-limiting exemplary aryloxy group is PhO-.

For the purpose of the present disclosure, the term "aralkyloxy" as used by itself or as part of another group refers to an aralkyl group attached to a terminal oxygen atom. A non-limiting exemplary aralkyloxy group is $PhCH_2O$-.

For the purpose of the present disclosure, the term "heteroaryl" or "heteroaromatic" refers to monocyclic and bicyclic aromatic ring systems having 5 to 14 ring atoms, wherein at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen, and sulfur. In one embodiment the heteroaryl contains 1, 2, 3, or 4 heteroatoms independently chosen from oxygen, nitrogen and sulfur. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In one embodiment, the heteroaryl is a 5-membered heteroaryl. In another embodiment, the heteroaryl is a 6-membered heteroaryl. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, benzimidazolyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (*e.g.*, thien-2-yl and thien-3-yl), furyl (*e.g.*, 2-furyl and 3-furyl), pyrrolyl (*e.g.*, 1H-pyrrol-2-yl and 1H-pyrrol-3-yl), imidazolyl (*e.g.*, 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (*e.g.*, 1H-pyrazol-3-yl, 1H-pyrazol-4-yl, and 1H-pyrazol-5-yl), pyridyl (*e.g.*, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (*e.g.*, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, and pyrimidin-5-yl), thiazolyl (*e.g.*, thiazol-2-yl, thiazol-4-yl, and thiazol-

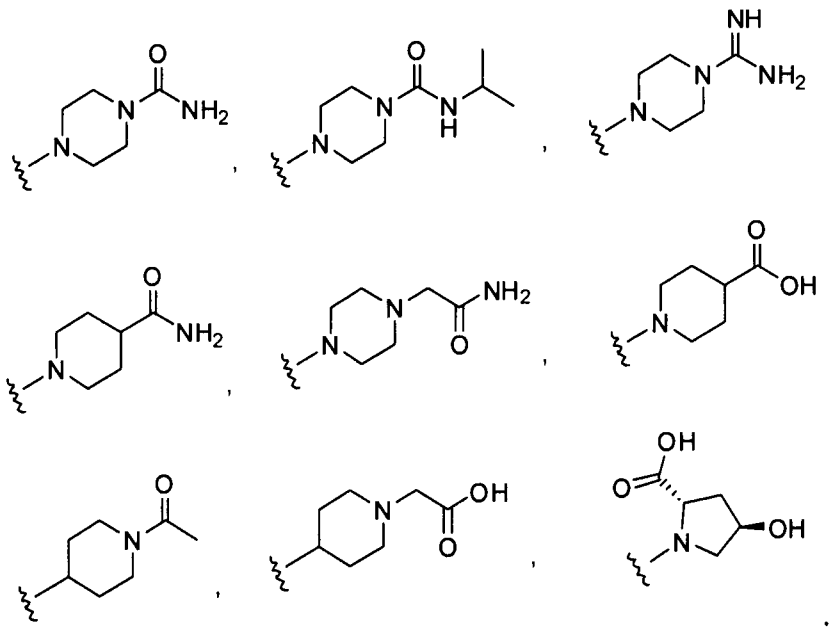
5-yl), isothiazolyl (*e.g.*, isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (*e.g.*, isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term "heteroaryl" is also meant to include possible N-oxides. Exemplary N-oxides include pyridyl N-oxide and the like.

For the purpose of the present disclosure, the term "optionally substituted heteroaryl" as used by itself or as part of another group means that the heteroaryl as defined above is either unsubstituted or substituted with one to four substituents, *e.g.*, one or two substituents, independently chosen from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, and (heteroaryl)alkyl.

In one embodiment, the optionally substituted heteroaryl has one substituent. In one embodiment, the optionally substituted is an optionally substituted pyridyl, *i.e.*, 2-, 3-, or 4-pyridyl. Any available carbon or nitrogen atom can be substituted. In another embodiment, the optionally substituted heteroaryl is an optionally substituted indole.

For the purpose of the present disclosure, the term "heterocyclo" as used by itself or as part of another group refers to saturated and partially unsaturated (e.g. containing one or two double bonds) cyclic groups containing one, two, or three rings having from 3 to 14 ring members. A 3-membered heterocyclo can contain up to 1 heteroatom, a 4-membered heterocyclo can contain up to 2 heteroatoms, a 5-membered heterocyclo can contain up to 4 heteroatoms, and a 6-membered heterocyclo can contain up to 4 heteroatoms, and a 7-membered heterocyclo can contain up to 5 heteroatoms. Each heteroatom is independently selected from oxygen, sulfur, including sulfoxide and sulfone, and/or nitrogen atoms, which can be quaternized. The term "heterocyclo" is meant to include cyclic ureido groups such as 2-imidazolidinone. In one embodiment, the heterocyclo group is chosen from a 5- or 6-membered cyclic group containing one ring and one or two oxygen and/or nitrogen atoms. The heterocyclo can be optionally linked to the rest of the molecule through a carbon or nitrogen atom. Non-limiting exemplary heterocyclo groups include 2-imidazolidinone, piperidinyl, morpholinyl, piperazinyl, and pyrrolidinyl.

For the purpose of the present disclosure, the term "optionally substituted heterocyclo" as used herein by itself or part of another group means the heterocyclo as defined above is either unsubstituted or substituted with one to four substituents independently selected from halo, nitro, cyano, hydroxy, amino, alkylamino, dialkylamino, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, aryloxy, aralkyloxy, alkylthio, carboxamido, sulfonamido, alkylcarbonyl, arylcarbonyl, alkylsulfonyl, arylsulfonyl, ureido, guanidino, carboxy, carboxyalkyl, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, alkoxyalkyl, (amino)alkyl, hydroxyalkylamino, (alkylamino)alkyl, (dialkylamino)alkyl, (cyano)alkyl, (carboxamido)alkyl, mercaptoalkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, and the like. Substitution may occur on any available carbon or nitrogen atom. An optionally substituted heterocyclo can be fused to an aryl group to provide an optionally substituted aryl as described above. Non-limiting exemplary optionally substituted heterocyclo groups include:



For the purpose of the present disclosure, the term "amino" as used by itself or as part of another group refers to $-NH_2$.

For the purpose of the present disclosure, the term "(amino)alkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with an amino group. Non-limiting exemplary amino alkyl groups include $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2CH_2CH_2CH_2NH_2$ and the like.

For the purpose of the present disclosure, the term "diaminoalkyl" as used by itself or as part of another group refers any of the above-mentioned alkyl groups substituted with two amino groups.

For the purpose of the present disclosure, the term "alkylamino" as used by itself or as part of another group refers to -NHR^{13}, wherein R^{13} is any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "dialkylamino" as used by itself or as part of another group refers to -$NR^{14a}R^{14b}$ wherein R^{14a} and R^{14b} are each independently any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "hydroxyalkylamino" as used by itself or as part of another group refers to -NHR^{15}, wherein R^{15} is any hydroxyalkyl group as "hydroxyalkyl" is defined above.

For the purpose of the present disclosure, the term "arylamino" as used by itself or as part of another group refers to -$NR^{16a}R^{16b}$ wherein R^{16a} is any optionally substituted aryl group as "aryl" is defined above and R^{16b} is hydrogen or any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "cycloalkylamino" as used by itself or as part of another group refers to -$NR^{17a}R^{17b}$ wherein R^{17a} is any optionally substituted cycloalkyl group as "cycloalkyl" is defined above and R^{17b} is hydrogen or any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "heteroarylamino" as used by itself or as part of another group refers to -$NR^{18a}R^{18b}$ wherein R^{18a} is any optionally substituted heteroaryl group as "heteroaryl" is defined above and R^{18b} is hydrogen or any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "heterocycloamino" as used by itself or as part of another group refers to -$NR^{19a}R^{19b}$ wherein R^{19a} is any optionally substituted heterocyclo group as "heterocyclo" is defined above and R^{19b} is hydrogen or any alkyl group as "alkyl" is defined above.

For the purpose of the present disclosure, the term "(alkylamino)alkyl" as used by itself or as part of another group refers to any alkyl group as "alkyl" is defined above substituted by any alkylamino group as "alkylamino" is defined above.

For the purpose of the present disclosure, the term "(dialkylamino)alkyl" as used by itself or as part of another group refers to any alkyl group as "alkyl" is defined above substituted by any dialkylamino group as "dialkylamino" is defined above.

For the purpose of the present disclosure, the term "(cyano)alkyl" as used by itself or as part of another group refers to any alkyl group as "alkyl" is defined above substituted with

one or more cyano, *e.g.*, -CN, groups. Non-limiting exemplary (cyano)alkyl groups include $-CH_2CN$, $-CH_2CH_2CN$, $-CH_2CH_2CH_2CN$, and $-CH_2CH_2CH_2CH_2CN$.

For the purpose of the present disclosure, the term "carboxamido" as used by itself or as part of another group refers to a radical of formula $-C(=O)NR^{20a}R^{20b}$, wherein R^{20a} and R^{20b} are each independently hydrogen, optionally substituted alkyl, optionally substituted aryl, or optionally substituted heteroaryl, or R^{20a} and R^{20b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. In one embodiment, R^{20a} and R^{20b} are each independently hydrogen or optionally substituted alkyl. Non-limiting exemplary carboxamido groups include $-CONH_2$, $-CON(H)CH_3$, $CON(CH_3)_2$, and CON(H)Ph.

For the purpose of the present disclosure, the term "(carboxamido)alkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a carboxamido group. Non-limiting exemplary (carboxamido)alkyl groups include $-CH_2CONH_2$, $-C(H)CH_3CONH_2$, and $-CH_2CON(H)CH_3$.

For the purpose of the present disclosure, the term "sulfonamido" as used by itself or as part of another group refers to a radical of the formula $-SO_2NR^{21a}R^{21b}$, wherein R^{21a} and R^{21b} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{21a} and R^{21b} taken together with the nitrogen to which they are attached from a 3- to 8-membered heterocyclo group. Non-limiting exemplary sulfonamido groups include $-SO_2NH_2$, $-SO_2N(H)CH_3$, and $-SO_2N(H)Ph$.

For the purpose of the present disclosure, the term "alkylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by any of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylcarbonyl group is $-COCH_3$.

For the purpose of the present disclosure, the term "arylcarbonyl" as used by itself or as part of another group refers to a carbonyl group, *i.e.*, -C(=O)-, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylcarbonyl group is -COPh.

For the purpose of the present disclosure, the term "alkylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-SO_2-$, substituted by any of the above-mentioned optionally substituted alkyl groups. A non-limiting exemplary alkylsulfonyl group is $-SO_2CH_3$.

For the purpose of the present disclosure, the term "arylsulfonyl" as used by itself or as part of another group refers to a sulfonyl group, *i.e.*, $-SO_2-$, substituted by any of the above-mentioned optionally substituted aryl groups. A non-limiting exemplary arylsulfonyl group is $-SO_2Ph$.

For the purpose of the present disclosure, the term "mercaptoalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted by a –SH group.

For the purpose of the present disclosure, the term "carboxy" as used by itself or as part of another group refers to a radical of the formula -COOH.

For the purpose of the present disclosure, the term "carboxyalkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with a -COOH. A non-limiting exemplary carboxyalkyl group is $-CH_2CO_2H$.

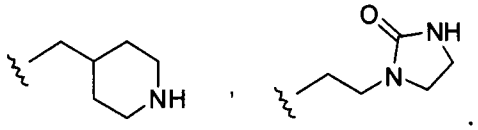
For the purpose of the present disclosure, the term "aralkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the aralkyl group is a C_{1-4} alkyl substituted with one optionally substituted aryl group. Non-limiting exemplary aralkyl groups include benzyl, trityl and phenethyl.

For the purpose of the present disclosure, the term "ureido" as used by itself or as part of another group refers to a radical of the formula $-NR^{22a}-C(=O)-NR^{22b}R^{22c}$, wherein R^{22a} is hydrogen, optionally substituted alkyl, or optionally substituted aryl, and R^{22b} and R^{22c} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, or R^{22b} and R^{22c} taken together with the nitrogen to which they are attached form a 4- to 8-membered heterocyclo group. Non-limiting exemplary ureido groups include $-NH-C(C=O)-NH_2$ and $NH-C(C=O)-NHCH_3$.

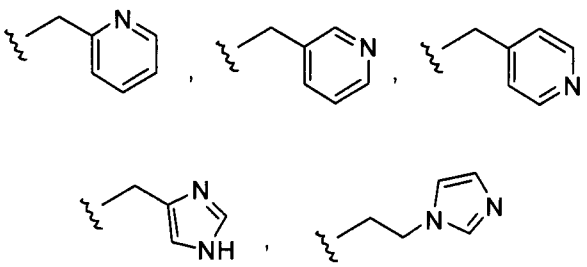
For the purpose of the present disclosure, the term "guanidino" as used by itself or as part of another group refers to a radical of the formula $-NR^{23a}-C(=NR^{24})-NR^{23b}R^{23c}$, wherein R^{23a}, R^{23b}, and R^{23c} are each independently hydrogen, optionally substituted alkyl, or optionally substituted aryl, and R^{24} is hydrogen, alkyl, cyano, alkylsulfonyl, alkylcarbonyl, carboxamido, or sulfonamido. Non-limiting exemplary guanidino groups include $-NH-C(C=NH)-NH_2$, $-NH-C(C=NCN)-NH_2$, $-NH-C(C=NH)-NHCH_3$ and the like.

For the purpose of the present disclosure, the term "azido" as used by itself or as part of another group refers to a radical of the formula $-N_3$.

For the purpose of the present disclosure, the term "(heterocyclo)alkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with one, two, or three optionally substituted heterocyclo groups. In one embodiment, the (heterocyclo)alkyl group is a C_{1-4} alkyl substituted with one optionally substituted heterocyclo group. Non-limiting exemplary (heterocyclo)alkyl groups include:



For the purpose of the present disclosure, the term "(heteroaryl)alkyl" as used by itself or as part of another group refers to any of the above-mentioned alkyl groups substituted with one, two, or three optionally substituted heteroaryl groups. In one embodiment, the (heteroaryl)alkyl group is a C_{1-4} alkyl substituted with one optionally substituted heteroaryl group. Non-limiting exemplary (heteroaryl)alkyl groups include:



For the purpose of the present disclosure, the term "alkylcarbonylamino" as used by itself or as part of another group refers to an alkylcarbonyl group attached to an amino nitrogen. A non-limiting exemplary alkylcarbonylamino group is $-NHCOCH_3$.

The present invention disclosed herein is also meant to encompass prodrugs of any of the disclosed compounds. As used herein, prodrugs are considered to be any covalently bonded carriers that release the active parent drug *in vivo*. In general, such prodrugs will be functional derivatives of compounds of any of Formulae **I-XVI**, which will be readily convertible *in vivo*, *e.g.*, by being metabolized, into the required compound of Formulae **I-XVI**. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, *Design of Prodrugs*, H. Bundgaard ed., Elsevier (1985); "Drug and Enzyme Targeting, Part A," K. Widder *et al.* eds., Vol. 112 in *Methods in Enzymology*, Academic Press (1985); Bundgaard, "Design and Application of Prodrugs," Chapter 5 (pp. 113-191) in *A Textbook of Drug Design and Development*, P. Krogsgaard-Larsen and H. Bundgaard eds., Harwood Academic Publishers (1991); Bundgaard *et al.*, *Adv.*

Drug Delivery Revs. *8*:1-38 (1992); Bundgaard *et al.*, *J. Pharmaceut. Sci.* *77*:285 (1988); and Kakeya *et al.*, *Chem. Pharm. Bull.* *32*:692 (1984). Non-limiting examples of prodrugs include esters or amides of compounds of any of Formulae **I-XVI** having hydroxyalkyl or aminoalkyl as a substituent, and these can be prepared by reacting such parent compounds with anhydrides such as succinic anhydride.

The invention disclosed herein is also intended to encompass any of the disclosed compounds being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively, and preferably ^{3}H, ^{11}C, and ^{14}C. Isotopically-labeled compounds of the present invention can be prepared by methods known in the art.

The present invention is also directed to ^{3}H, ^{11}C, or ^{14}C radiolabeled compounds of any of Formulae **I-XVI**, as well as their pharmaceutically acceptable salts, prodrugs and solvates, and the use of any such compounds as radioligands for their ability to bind to the sodium channel. For example, one use of the labeled compounds of the present invention is the characterization of specific receptor binding. Another use of a labeled Compound of the Invention is an alternative to animal testing for the evaluation of structure-activity relationships. For example, the receptor assay can be performed at a fixed concentration of a labeled Compound of the Invention and at increasing concentrations of a test compound in a competition assay. For example, a tritiated compound of any of Formulae **I-XVI** can be prepared by introducing tritium into the particular compound, for example, by catalytic dehalogenation with tritium. This method may include reacting a suitably halogen-substituted precursor of the compound with tritium gas in the presence of a suitable catalyst, for example, Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)*, Chapter 6 (1987). ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

Some of the compounds disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is meant to encompass the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be

separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

The term "chiral center" refers to a carbon atom to which four different groups are attached.

The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive.

The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

The terms "a" and "an" refer to one or more.

The term "treat," "treating" or "treatment" is meant to encompass administering to a subject a Compound of the Invention for the purposes of amelioration or cure, including preemptive and palliative treatment.

The term "about," as used herein in connection with a measured quantity, refers to the normal variations in that measured quantity, as expected by the skilled artisan making the measurement and exercising a level of care commensurate with the objective of measurement and the precision of the measuring equipment.

The invention disclosed herein also encompasses the use of salts of the disclosed compounds, including all non-toxic pharmaceutically acceptable salts thereof of the disclosed compounds. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts and basic salts. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like;

alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, phosphate, sulphate and the like; organic acid salts such as citrate, lactate, tartrate, maleate, fumarate, mandelate, acetate, dichloroacetate, trifluoroacetate, oxalate, formate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparginate, glutamate and he like.

Acid addition salts can be formed by mixing a solution of the particular Compound of the Invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, oxalic acid, dichloroacetic acid, or the like. Basic salts can be formed by mixing a solution of the Compound of the Invention with a solution of a pharmaceutically acceptable non-toxic base such as sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate and the like.

The invention disclosed herein is also meant to encompass solvates of any of the disclosed compounds. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a Compound of the Invention with a solvent molecule such as, *e.g.*, a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to the Compound of the Invention is 2:1, 1:1 or 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. Compounds of any of Formulae **I-XVI** can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the invention includes both solvated and unsolvated forms of compounds of any of Formulae **I-XVI**. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et a.l*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation

of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.*: 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a compound of any of Formulae **I-XVI** in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.*, filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

Since compounds of Formulae **I-XVI** are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated by employing these compounds. The present invention is thus directed generally to a method for treating a disorder responsive to the blockade of sodium channels in an animal suffering from, or at risk of suffering from, said disorder, said method comprising administering to the animal an effective amount of a compound represented by any of defined Formulae **I-XVI**, or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

The present invention is further directed to a method of modulating sodium channels in an animal in need thereof, said method comprising administering to the animal a modulating-effective amount of at least one compound represented by any of defined Formulae **I-XVI**, or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

More specifically, the present invention provides a method of treating stroke, neuronal damage resulting from head trauma, epilepsy, neuronal loss following global and focal ischemia, pain (*e.g.*, acute pain, chronic pain, which includes but is not limited to neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain), a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), migraine, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia. In one embodiment, the invention provides a method of treating pain. In another embodiment, the type of pain is chronic pain. In another embodiment, the type of pain is neuropathic pain. In another embodiment, the type of pain is postoperative pain. In another embodiment, the type of pain is inflammatory pain. In another embodiment, the type of pain is surgical pain. In another embodiment, the type of pain is acute pain. In another embodiment, the treatment of pain (*e.g.*, chronic pain, such as

neuropathic pain, postoperative pain, or inflammatory pain, acute pain or surgical pain) is preemptive. In another embodiment, the treatment of pain is palliative. In each instance, such method of treatment requires administering to an animal in need of such treatment an amount of a Compound of the Invention that is therapeutically effective in achieving said treatment. In one embodiment, the amount of such compound is the amount that is effective to block sodium channels *in vivo*.

Chronic pain includes, but is not limited to, inflammatory pain, postoperative pain, cancer pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, burn pain, and other forms of neuralgia, neuropathic, and idiopathic pain syndromes.
Chronic somatic pain generally results from inflammatory responses to tissue injury such as nerve entrapment, surgical procedures, cancer or arthritis (Brower, *Nature Biotechnology* 2000; 18: 387-391).

The inflammatory process is a complex series of biochemical and cellular events activated in response to tissue injury or the presence of foreign substances (Levine, *Inflammatory Pain, In: Textbook of Pain,* Wall and Melzack eds., 3rd ed., 1994). Inflammation often occurs at the site of injured tissue, or foreign material, and contributes to the process of tissue repair and healing. The cardinal signs of inflammation include erythema (redness), heat, edema (swelling), pain and loss of function (ibid.). The majority of patients with inflammatory pain do not experience pain continually, but rather experience enhanced pain when the inflamed site is moved or touched. Inflammatory pain includes, but is not limited to, that associated with osteoarthritis and rheumatoid arthritis.

Chronic neuropathic pain is a heterogenous disease state with an unclear etiology. In chronic neuropathic pain, the pain can be mediated by multiple mechanisms. This type of pain generally arises from injury to the peripheral or central nervous tissue. The syndromes include pain associated with spinal cord injury, multiple sclerosis, post-herpetic neuralgia, trigeminal neuralgia, phantom pain, causalgia, and reflex sympathetic dystrophy and lower back pain. Chronic pain is different from acute pain in that patients suffer the abnormal pain sensations that can be described as spontaneous pain, continuous superficial burning and/or deep aching pain. The pain can be evoked by heat-, cold-, and mechano-hyperalgesia or by heat-, cold-, or mechano-allodynia.

Neuropathic pain can be caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to, pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Stroke (spinal or brain) and spinal cord injury can also induce neuropathic pain. Cancer-related neuropathic pain results from tumor growth compression of adjacent nerves, brain, or spinal cord. In addition, cancer treatments, including chemotherapy and radiation therapy, can also cause nerve injury. Neuropathic pain includes but is not limited to pain caused by nerve injury such as, for example, the pain from which diabetics suffer.

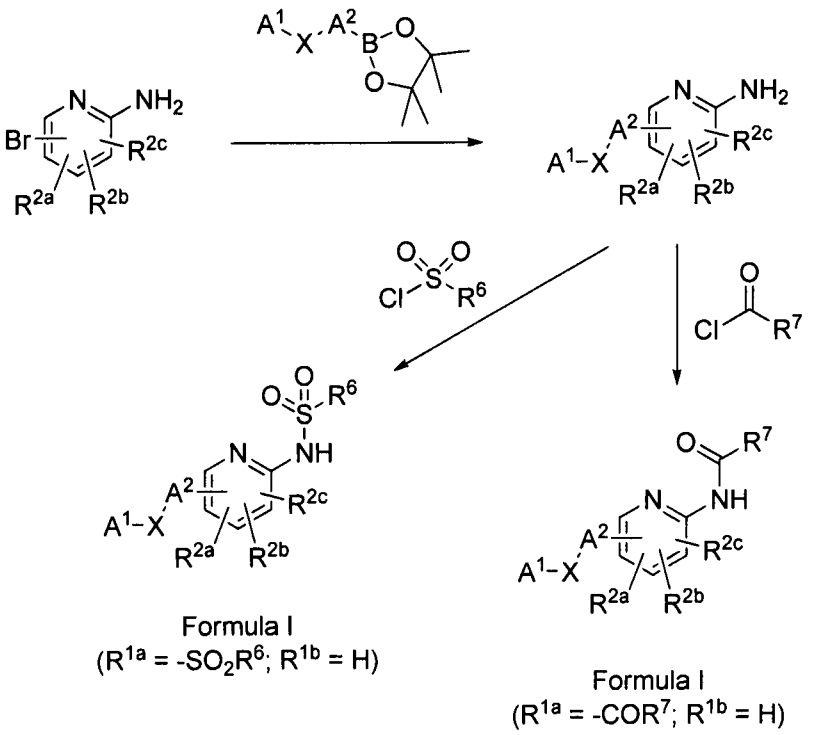
The present invention is also directed to the use of a compound represented by any of defined Formulae **I-XVI**, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in the manufacture of a medicament for treating a disorder responsive to the blockade of sodium channels (*e.g.*, any of the disorders listed above) in an animal suffering from said disorder.

The present invention is also directed to the use of a compound represented by any of defined Formulae **I-XVI**, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, in the manufacture of a medicament, in particular a medicament for modulating sodium channels, in an animal in need thereof.

General Synthesis of Compounds

Compounds of the Invention are prepared using methods known to those skilled in the art in view of this disclosure. For example, compounds of Formula **I** wherein R^{1a} is $-SO_2R^6$ or $-COR^7$ and R^{1b} is hydrogen can be prepared according to General Scheme 1.

General Scheme 1

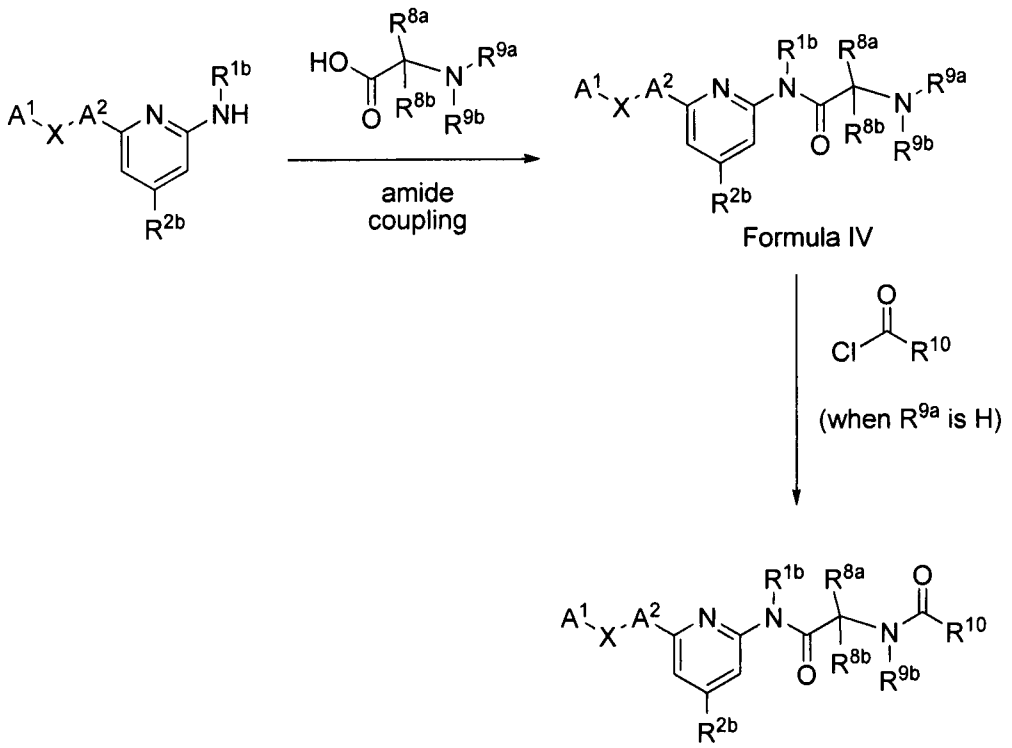


Formula I
(R^{1a} = $-SO_2R^6$; R^{1b} = H)

Formula I
(R^{1a} = $-COR^7$; R^{1b} = H)

Compounds of Formula **IV** can be prepared according to General Scheme 2. When R^{9a} of Formula **IV** is hydrogen, the compound can be further reacted, *e.g.*, with $R^{10}COCl$, to give additional Compounds of the Invention.

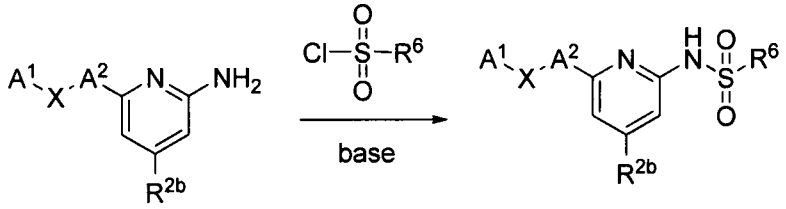
General Scheme 2



Formula IV

Compounds of Formula **VIII** can be prepared according to General Scheme 3.

General Scheme 3



Formula VIII

Testing of Compounds

Representative Compounds of the present invention were assessed by sodium mobilization and/or electrophysiological assays for sodium channel blocker activity. One aspect of the present invention is based on the use of the compounds herein described as sodium channel blockers. Based upon this property, compounds of the invention are considered useful in treating a condition or disorder responsive to the blockade of sodium ion channels, *e.g.*, stroke, neuronal damage resulting from head trauma, epilepsy, seizures, general epilepsy with febrile seizures, severe myoclonic epilepsy in infancy, neuronal loss following global and focal ischemia, migraine, familial primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, dystonia, tremor, mental retardation, autism, a neurodegenerative disorder (*e.g.*, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), or Parkinson's disease), manic depression, tinnitus, myotonia, a movement disorder, cardiac arrhythmia, or providing local anesthesia. Compounds of the Invention are also expected to be effective in treating pain, *e.g.*, acute pain, chronic pain, which includes but is not limited to, neuropathic pain, postoperative pain, and inflammatory pain, or surgical pain.

More specifically, the present invention is directed to compounds of Formulae **I-XVI** that are blockers of sodium channels. According to the present invention, those compounds having useful sodium channel blocking properties exhibit an IC_{50} for $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, $Na_v1.4$, $Na_v1.5$, $Na_v1.6$, $Na_v1.7$, $Na_v1.8$, and/or $Na_v1.9$ of about 100 μM or less, *e.g.*, about 50 μM or less, about 10 μM or less, about 5 μM or less, or about 1 μM or less, in sodium mobilization and/or electrophysiological assays. In certain embodiments, Compounds of the Invention exhibit an IC_{50} for $Na_v1.7$ of 100 μM or less, about 50 μM or less, about 10 μM or less, about 5 μM or less, about 1 μM or less, about 0.5 μM or less, or about 0.1 μM or less. Compounds of the Invention can be tested for their Na^+ channel blocking activity using

methods known in the art and by the following fluorescence imaging and electrophysiological *in vitro* assays and/or *in vivo* assays.

In one embodiment, Compounds of the Invention demonstrate substantially no penetration across the CNS blood-brain barrier in a mammal. Such compounds are referred to as "peripherally restricted" as a means to designate their PNS versus CNS tissue selectivity.

In one embodiment, the PNS:CNS concentration ratio of a peripherally restricted Compound of the Invention is about 5:1, about 10:1, about 20:1, about 30:1; about 50:1; about 100:1, about 250:1, about 500:1, about 1000:1, about 5,000:1, about 10,000:1, or more. Compounds of the Invention can be tested for their ability to penetrate the central nervous system using *in vitro* and *in vivo* methods known in the art.

***In Vitro* Assay Protocols**

FLIPR® Assays

Recombinant $Na_v1.7$ Cell Line: *In vitro* assays were performed in a recombinant cell line expressing cDNA encoding the alpha subunit ($Na_v1.7$, SCN9a, PN1, NE) of human $Na_v1.7$ (Accession No. NM_002977). The cell line was provided by investigators at Yale University (Cummins *et al, J. Neurosci. 18(23)*: 9607-9619 (1998)). For dominant selection of the $Na_v1.7$-expressing clones, the expression plasmid co-expressed the neomycin resistance gene. The cell line was constructed in the human embryonic kidney cell line, HEK293, under the influence of the CMV major late promoter, and stable clones were selected using limiting dilution cloning and antibiotic selection using the neomycin analogue, G418. Recombinant beta and gamma subunits were not introduced into this cell line. Additional cell lines expressing recombinant $Na_v1.7$ cloned from other species can also be used, alone or in combination with various beta subunits, gamma subunits or chaperones.

Non-recombinant Cell Lines Expressing Native $Na_v1.7$: Alternatively, *in vitro* assays can be performed in a cell line expressing native, non-recombinant $Na_v1.7$, such as the ND7 mouse neuroblastoma X rat dorsal root ganglion (DRG) hybrid cell line ND7/23, available from the European Cell Culture Collection (Cat. No. 92090903, Salisbury, Wiltshire, United Kingdom). The assays can also be performed in other cell lines expressing native, non-recombinant $Na_v1.7$, from various species, or in cultures of fresh or preserved sensory

neurons, such as dorsal root ganglion (DRG) cells, isolated from various species. Primary screens or counter-screens of other voltage-gated sodium channels can also be performed, and the cell lines can be constructed using methods known in the art, purchased from collaborators or commercial establishments, and they can express either recombinant or native channels. The primary counter-screen is for one of the central neuronal sodium channels, $Na_V1.2$ (rBIIa), expressed in HEK293 host cells (Ilyin *et al.*, *Br. J. Pharmacol. 144*:801-812 (2005)). Pharmacological profiling for these counter-screens is carried out under conditions similar to the primary or alternative $Na_v1.7$ assays described below.

Cell maintenance: Unless otherwise noted, cell culture reagents were purchased from Mediatech of Herndon, VA. The recombinant $Na_v1.7$/HEK293 cells were routinely cultured in growth medium consisting of Dulbecco's minimum essential medium containing 10% fetal bovine serum (FBS, Hyclone, Thermo Fisher Scientific, Logan, UT), 100 U/mL penicillin, 100 μg/mL streptomycin, 2-4 mM L-glutamine, and 500 mg/mL G418. For natural, non-recombinant cell lines, the selective antibiotic was omitted, and additional media formulations can be applied as needed.

Assay Buffer: The assay buffer was formulated by removing 120 mL from a 1 L bottle of fresh, sterile dH_2O (Mediatech, Herndon, VA) and adding 100 mL of 10X HBSS that does not contain Ca^{++} or Mg^{++} (Gibco, Invitrogen, Grand Island, NY) followed by 20 mL of 1.0 M Hepes, pH 7.3 (Fisher Scientific, BP299-100). The final buffer consisted of 20 mM Hepes, pH 7.3, 1.261 mM $CaCl_2$, 0.493 mM $MgCl_2$, 0.407 mM $Mg(SO)_4$, 5.33 mM KCl, 0.441 mM KH_2PO_4, 137 mM NaCl, 0.336 mM Na_2HPO_4 and 0.556 mM D-glucose (Hanks *et al., Proc. Soc. Exp. Biol. Med. 71*:196 (1949)), and the simple formulation was typically the basic buffer throughout the assay (*i.e.*, all wash and addition steps).

CoroNa™ Green AM Na^+ Dye for Primary Fluorescence Assay: The fluorescence indicator used in the primary fluorescence assay was the cell permeant version of CoroNa™ Green (Invitrogen, Molecular Probes, Eugene, OR), a dye that emits light in the fluorescence range (Harootunian *et al., J. Biol. Chem. 264(32)*:19458-19467 (1989)). The intensity of this emission, but not the wavelength range, is increased when the dye is exposed to Na^+ ions, which it can bind with partial selectivity. Cells expressing $Na_v1.7$ or other sodium channels were loaded with the CoroNa™ Green dye immediately in advance of the fluorescence assay, and then, after agonist stimulation, the mobilization of Na^+ ions was detected as the Na^+ ions flowed from the extracellular fluid into the cytoplasm through the activated sodium channel

pores. The dye was stored in the dark as a lyophilized powder, and then an aliquot was dissolved immediately before the cell loading procedure, according to the instructions of the manufacturer to a stock concentration of 10 mM in DMSO. It was then diluted in the assay buffer to a 4X concentrated working solution, so that the final concentration of dye in the cell loading buffer was 5 μM.

Membrane Potential Dye for Alternative Fluorescence Assays: A fluorescence indicator that can be used in alternative fluorescence assays is the blue version membrane potential dye (MDS, Molecular Devices, Sunnyvale, CA), a dye that detects changes in molecules following a change in membrane potential. An increase in fluorescence is expected if agonist stimulation provokes a change in membrane potential. Cells expressing $Na_v1.7$ or other sodium channels are incubated with the membrane potential dye 30-60 minutes before the fluorescence assay. In the case of the KCl pre-stimulation version of the assay, the dye and all other components are washed out immediately before the assay, and the dye is then replaced. In the version lacking KCl pre-stimulation, the dye remains on the cells and is not washed out or replaced. The dye is stored in the dark as a lyophilized powder, and then an aliquot dissolved in assay buffer to form a 20X-concentrated stock solution that can be used for several weeks.

Agonists: In the fluorescence assays, two agonists were used in combination, namely 1) veratridine; and 2) the venom from the yellow scorpion, *Leiurus quinquestriatus hebraeus*. Veratridine is an alkaloid small molecule that facilitates the capture of channel openings by inhibiting inactivation, and the scorpion venom is a natural preparation that includes peptide toxins selective for different subsets of voltage-gated sodium channels. These scorpion toxins inhibit the fast inactivation of their cognate target channels. Stock solutions of the agonists were prepared to 40 mM in DMSO (veratridine) and 1 mg/mL in dH_2O (scorpion venom), and then diluted to make a 4X or 2X stock (depending on the particular assay) in assay buffer, the final concentration being 100 μM (veratridine) and 10 μg/mL (scorpion venom). Both of the agonists were purchased from Sigma Aldrich, St. Louis, MO.

Test Compounds: Test compounds were dissolved in DMSO to yield 10 mM stock solutions. The stock solutions were further diluted using DMSO in 1:3 serial dilution steps with 10 points (10,000 μM, 3,333 μM, 1,111 μM, 370 μM, 123 μM, 41μM, 14 μM, 4.6 μM, 1.5 μM and 0.5 μM). The stock solutions were further diluted in assay buffer (1:125) as 4X stock serial dilutions with a DMSO concentration of 0.8% (final [DMSO], in the assay, from

the compounds component = 0.2%), so that the compounds' final concentrations in the assay were 20 μM, 6.7 μM, 2.2 μM, 0.74 μM, 0.25 μM and 0.08 μM, 0.03 μM, 0.01μM, 0.003 μM and 0.001 μM. If a particular test article appeared to be especially potent, then the concentration curve was adjusted, *e.g.*, to 10-fold lower concentrations, in order to perform the dose-response in a more relevant concentration range. Compound dilutions were added during the dye-loading and pre-stimulation step, and then again during the fluorescence assay, early in the kinetic read. Compound dilutions were added in duplicate rows across the middle 80 wells of the 96-well plate, whereas the fully stimulated and the fully inhibited controls (positive and negative) were located in the top 4 side wells and the bottom 4 side wells, respectively, on the left and right sides of the assay plate.

Data Analysis: The data were analyzed according to methods known to those skilled in the art or using the GraphPad® Prism 4.0 Program (available from GraphPad Software, San Diego, CA) to determine the IC_{50} value for the test article. At least one standard reference compound was evaluated during each experiment.

FLIPR® or FLIPR^{TETRA}® sodium dye assay with KCl and test article pre-incubation: Cells were prepared by plating the recombinant HEK293 cells or other host cells expressing either recombinant or non-recombinant, native, $Na_V1.7$ alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a 96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately fewercells and less media. The plate was then incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO_2, 95% humidity, in preparation for the assay. For counter-screens of other voltage-gated sodium channels, the procedure was very similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or isoform.

The next day, at the start of the assay, the media was flicked from the cells and the wells were washed once with 50 μl/well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3) and then pre-incubated with the test articles, CoroNa™ Green AM sodium dye (for cell loading) and KCl for re-polarization and synchronization of the channels in the entire population of cells. For this dye-loading and pre-stimulation step, the components were added as follows, immediately after the wash step: 1) first, the compound dilutions and controls were added as 4X concentrates in assay buffer at 50 μL/well; 2) CoroNa™ Green AM dye was diluted from the stock solution to 20

μM in assay buffer (4X concentrate) and added to the plate at 50 μL/well; and 3) finally, a solution of 180 mM KCl (2X) was prepared by diluting a 2M stock solution into assay buffer and the solution was added to the cells at 100 μl/well. The cells were incubated at 25°C in the dark for 30 min. before their fluorescence was measured.

The plates containing dye-loaded cells were then flicked to remove the pre-incubation components and washed once with 100 μL/well assay buffer. A 100 μL/well aliquot of assay buffer was added back to the plate, and the real-time assay was commenced. The fluorescence of cells was measured using a fluorescence plate reader (FLIPR$^{TETRA®}$ or FLIPR384®, MDS, Molecular Devices, Sunnyvale, CA). Samples were excited by either a laser or a PMT light source (Excitation wavelength = 470-495 nM) and the emissions were filtered (Emission wavelength = 515-575 nM). The additions of compound and the channel activators in this cell-based, medium-to-high throughput assay were performed on the fluorescence plate reader and the results (expressed as relative fluorescence units) were captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there was a 15 sec. base line, with camera shots taken every 1.5 sec., then the test compounds were added, then another 120 sec. baseline was conducted, with camera shots taken every 3 sec.; and finally, the agonist solution (containing veratridine and scorpion venom) was added. The amplitude of fluorescence increase, resulting from the binding of Na^+ ions to the CoroNa™ Green dye, was captured for ~180 sec. thereafter. Results were expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole agonist stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well with the test articles present in standard amounts (*e.g.*, 10 μM) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen will typically be profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gate sodium channels or other biologically relevant target molecules.

FLIPR® or FLIPR$^{TETRA®}$ membrane potential assay with KCl and test article pre-incubation: Cells are prepared by plating the recombinant HEK293 cells or other host cells expressing either recombinant or non-recombinant, native, $Na_V1.7$ alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a

96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately fewer cells and less media. The plate is then incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO_2, 95% humidity, in preparation for the assay (see, *e.g.*, Benjamin *et. al., J. Biomol. Screen 10(4)*:365-373 (2005)). For screens and counter-screens of other voltage-gated sodium channels, the assay protocol is similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or sodium channel isoform being tested.

The next day, at the start of the assay, the media is flicked from the cells and the wells are washed once with 50 µL/well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3) and then pre-incubated with the test articles, the membrane potential dye (for cell loading), and the KCl for re-polarization and synchronization of the channels in the entire population of cells. For this dye-loading and pre-stimulation step, the components are added as follows, immediately after the wash step: 1) first, the compound dilutions and controls are added as 4X concentrates in assay buffer at 50 µL/well; 2) membrane potential dye is diluted from the stock solution in assay buffer (4X concentrate) and added to the plate at 50 µL/well; and 3) finally, a solution of 180 mM KCl (2X) is prepared by diluting a 2M stock solution into assay buffer and the solution added to the cells at 100 µL/well. The cells are incubated at 37°C in the dark for 30-60 min. before their fluorescence is measured.

The plates containing dye-loaded cells are then flicked to remove the pre-incubation components and washed once with 50 µL/well assay buffer. A 50 µL/well aliquot of membrane potential dye is added back to the plate, and the real-time assay is commenced. The fluorescence of cells is measured using a fluorescence plate reader (FLIPR$^{TETRA®}$ or FLIPR384®, MDS, Molecular Devices, Sunnyvale, CA). Samples are excited by either a laser or a PMT light source (Excitation wavelength = 510-545 nM) and the emissions are filtered (Emission wavelength = 565-625 nM). The additions of the compounds (first) and then the channel activators (later) in this are performed on the fluorescence plate reader and the results, expressed as relative fluorescence units (RFU), are captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there is a 15 sec. base line, with camera shots taken every 1.5 sec., then the test compounds are added, then another 120 sec. baseline is conducted, with camera shots taken every 3 sec.; and finally, the agonist

solution (containing veratridine and scorpion venom) is added. The amplitude of fluorescence increase, resulting from the detection of membrane potential change, is captured for ~120 sec. thereafter. Results are expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well with the test articles present in standard amounts (*e.g.*, 10 μM) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen are typically profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gate sodium channels or other biologically relevant target molecules.

FLIPR® or FLIPR^{TETRA}® sodium dye assay without KCl and test article pre-incubation: Cells are prepared by plating the recombinant HEK293 cells or other host cells expressing either recombinant or non-recombinant, native, $Na_V1.7$ alpha subunit, alone or in combination with various beta and gamma subunits at a density of ~40,000 cells/well into a 96-well black, clear-bottom, PDL-coated plate. The assay can be adapted to 384-well or 1,536-well format, if desired, using proportionately fewer cells and less media. The plate is then incubated in growth media, with or without selective antibiotic, overnight at 37°C at 5% CO_2, 95% humidity, in preparation for the assay. For counter-screens of other voltage-gated sodium channels, the procedure is very similar, though optimal densities of cells, media and subsequent assay components can be fine-tuned for the particular cell line or isoform.

The next day, at the start of the assay, the media is flicked from the cells and the wells washed once with 50 μL/well assay buffer (1X Hank's balanced salt solution without sodium bicarbonate or phenol red, 20 mM Hepes, pH 7.3). Membrane potential dye is then added to each well of the 96-well plate (50 μL/well), from a freshly diluted sample of the stock (now at 4X concentration) in the assay buffer. The cells are incubated at 37°C in the dark for 30-60 min. before their fluorescence is measured.

In this standard membrane potential assay, the 96-well plate containing dye-loaded cells is then loaded directly onto the plate reader without aspirating the dye solution and without any further washing of the cells. The fluorescence of cells is measured using a fluorescence plate reader (FLIPR^{TETRA}® or FLIPR384®, MDS, Molecular Devices, Sunnyvale, CA). Samples are excited by either a laser or a PMT light source (Excitation wavelength = 510-

545 nM) and the emissions are filtered (Emission wavelength = 565-625 nM). The additions of the compounds (first, 50 μL/well from a 4X stock plate) and then the channel activators (later, 100 μL/well from a 2X stock solution) in this kinetic assay are performed on the fluorescence plate reader and the results, expressed as relative fluorescence units (RFU), are captured by means of camera shots every 1-3 sec., then displayed in real-time and stored. Generally, there is a 15 sec. base line, with camera shots taken every 1.5 sec., then the test compounds are added, then another 120 sec. baseline is conducted, with camera shots taken every 3 sec.; and finally, the agonist solution (containing veratridine and scorpion venom) is added. The amplitude of fluorescence increase, resulting from the detection of membrane potential change, is captured for ~120 sec. thereafter. Results are expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the latter part of the stimulation; or the maximum minus the minimum during the whole stimulation period; or by taking the area under the curve for the whole stimulation period.

The assay can be performed as a screening assay as well, with the test articles present in standard amounts (*e.g.*, 10 μM) in only one or two wells of a multi-well plate during the primary screen. Hits in this screen are typically profiled more exhaustively (multiple times), subjected to dose-response or competition assays and tested in counter screens against other voltage-gate sodium channels or other biologically relevant target molecules.

Electrophysiology Assay

Cells: The $hNa_v1.7$ expressing HEK-293 cells were plated on 35 mm culture dishes pre-coated with poly-D-lysine in standard DMEM culture media (Mediatech, Inc., Herndon, VA) and incubated in a 5% CO_2 incubator at 37°C. Cultured cells were used approximately 12 - 48 hours after plating.

Electrophysiology: On the day of experimentation, the 35 mm dish was placed on the stage of an inverted microscope equipped with a perfusion system that continuously perfuses the culture dish with fresh recording media. A gravity driven superfusion system was used to apply test solutions directly to the cell under evaluation. This system consists of an array of glass pipette connected to a motorized horizontal translator. The outlet of the shooter was positioned approximately 100 μm from the cell of interest.

Whole cell currents were recorded using the whole-cell patch clamp configuration using an Axopatch 200B amplifier (Axon Instruments, Foster City CA), 1322A A/D converter

(Axon Instruments) and pClamp software (v. 8; Axon Instruments) and stored on a personal computer. Gigaseals were formed and the whole-cell configuration was established in voltage clamp mode, and membrane currents generated by $hNa_v1.7$ were recorded in gap-free mode. Borosilicate glass pipettes have resistance values between 1.5 and 2.0 MΩ when filled with pipette solution and series resistance (< 5 MΩ) was compensated 75 – 80%. Signals were sampled at 50 kHz and low pass filtered at 3 kHz.

Voltage protocols: After establishing the whole-cell configuration in voltage clamp mode, voltage protocols were run to establish the 1) test potential, 2) holding potential, and 3) the conditioning potential for each cell.

After establishing the whole-cell configuration in voltage clamp mode, a standard I-V protocol was run to determine the potential at which the maximal current (I_{max}) is elicited. This potential was the test potential (V_t). To determine a conditioning potential at which 100% of channels were in the inactivated state, a standard steady-state inactivation (SSIN) protocol was run using a series of fifteen 100 ms-long depolarizing prepulses, incrementing in 10 mV steps, immediately followed by a 5 ms testing pulse, V_t, to V_{max}. This protocol also permitted determination of the holding potential at which all channels are in the resting state.

For compounds causing significant retardation of recovery from inactivation, an estimate of the affinity for the inactivated state of the channel (K_i) was generated using the following protocol. From the negative, no residual inactivation, holding potential, the cell was depolarized to the conditioning voltage for 2-5 seconds, returned to the negative holding potential for 10 -20 ms to relieve fast inactivation and then depolarized to the test potential for ~15 ms. This voltage protocol was repeated every 10-15 seconds, first to establish a baseline in the absence of the test compound, then in the presence of the test compound.

After a stable baseline was established, the test compound was applied and block of the current elicited by the test pulse assessed. In some cases, multiple cumulative concentrations were applied to identify a concentration that blocked between 40- 60 % of this current. Washout of the compound was attempted by superfusing with control solution once steady-state block was observed. An estimate of the K_i was calculated as follows:

$$\boldsymbol{K_i} = [\text{drug}]^*\{\boldsymbol{FR}/(1-\boldsymbol{FR})\}, \qquad \text{Eq. 1}$$

where [drug] is the concentration of a drug, and

$$\boldsymbol{FR} = \boldsymbol{I}(\text{after drug})/\boldsymbol{I}(\text{control}), \qquad \text{Eq. 2}$$

where *I* is the peak current amplitude. If multiple concentrations were used, K_i was determined from the fit of a logistic equation to FRs plotted against corresponding drug concentrations.

In the alternative, the voltage clamp protocol to examine $hNa_v1.7$ currents was as follows. First, the standard current-voltage relationship was tested by pulsing the cell from the holding voltage (V_h) of -120 mV by a series of 5 msec long square-shaped test pulses incrementing in +10 mV steps over the membrane voltage range of -90 mV to + 60 mV at the pace of stimulation of 0.5 Hz. This procedure determines the voltage that elicits the maximal current (V_{max}). Second, V_h was re-set to -120 mV and a steady-state inactivation (SSIN) curve was taken by the standard double-pulse protocol: 100 ms depolarizing pre-pulse was incremented in steps of +10 mV (voltage range from -90 mV to 0 mV) immediately followed by the 5ms long test pulse to -10 mV at the pace of stimulation of 0.2 Hz. This procedure determines the voltage of full inactivation (V_{full}). Third, the cell was repeatedly stimulated with the following protocol, first in the absence of the test compound then in its presence. The protocol consisted of depolarizing the cell from the holding potential of -120 mV to the V_{full} value for 4.5 seconds then repolarizing the cell to the holding potential for 10 ms before applying the test pulse to the V_{max} for 5 ms. The amount of inhibition produced by the test compound was determined by comparing the current amplitude elicited by the test pulse in the absence and presence of the compound.

In a further alternative, the voltage clamp protocol to examine $hNa_v1.7$ currents was as follows. After establishing the whole-cell configuration in voltage clamp mode, two voltage protocols were run to establish: 1) the holding potential; and 2) the test potential for each cell.

Resting block: To determine a membrane potential at which the majority of channels are in the resting state, a standard steady-state inactivation (SSIN) protocol was run using 100 ms prepulses x 10 mV depolarizing steps. The holding potential for testing resting block (V_{h1}) was 20 mV more hyperpolarized than the first potential where inactivation was observed with the inactivation protocol.

From this holding potential a standard I-V protocol was run to determine the potential at which the maximal current (Imax) is elicited. This potential was the test potential (Vt).

The compound testing protocol was a series of 10 ms depolarizations from the V_{h1} (determined from the SSIN) to the Vt (determined from the I-V protocol) repeated every 10-

15 seconds. After a stable baseline was established, a high concentration of a test compound (highest concentration solubility permits or that which provides ~50% block) was applied and block of the current assessed. Washout of the compound was attempted by superfusing with control solution once steady-state block was observed. The fractional response was calculated as follows:

$$K_r = [\text{drug}]^*\{FR/(1-FR)\}, \qquad \text{Eq. 3}$$

where [drug] is the concentration of a drug, and

$$FR = I(\text{after drug})/I(\text{control}), \qquad \text{Eq. 2}$$

where I is the peak current amplitude and was used for estimating resting block dissociation constant, K_r.

Block of inactivated channels: To assess the block of inactivated channels the holding potential was depolarized such that 20-50% of the current amplitude was reduced when pulsed to the same Vt as above. The magnitude of this depolarization depends upon the initial current amplitude and the rate of current loss due to slow inactivation. This was the second holding potential (Vh2). The current reduction was recorded to determine the fraction of available channels at this potential (h).

$$h = I\ @\ Vh2 / Imax. \qquad \text{Eq. 4}$$

At this membrane voltage a proportion of channels was in the inactivated state, and thus inhibition by a blocker includes interaction with both resting and inactivated channels.

To determine the potency of the test compound on inactivated channels, a series of currents were elicited by 10 ms voltage steps from Vh2 to Vt every 10-15 seconds. After establishing a stable baseline, the low concentration of the compound was applied. In some cases, multiple cumulative concentrations will have to be applied to identify a concentration that blocks between 40-60 % of the current. Washout is attempted to re-establish baseline. Fractional responses were measured with respect to a projected baseline to determine K_{app}.

$$K_{app} = [\text{drug}]^*\{FR/(1-FR)\}, \qquad \text{Eq. 5}$$

where [drug] is the concentration of a drug.

This K_{app} value, along with the calculated K_r and h values, were used to calculate the affinity of the compound for the inactivated channels (K_i) using the following equation:

$$K_i = (1-h) / ((1/K_{app}) - (h/K_r)). \qquad \text{Eq. 6}$$

Solutions and chemicals: For electrophysiological recordings the external solution was either standard, DMEM supplemented with 10 mM HEPES (pH adjusted to 7.34 with NaOH

and the osmolarity adjusted to 320) or Tyrodes salt solution (Sigma, USA) supplemented with 10 mM HEPES (pH adjusted to 7.4 with NaOH; osmolarity = 320). The internal pipette solution contained (in mM): NaCl (10), CsF (140), $CaCl_2$ (1), $MgCl_2$ (5), EGTA (11), HEPES (10: pH 7.4, 305 mOsm). Compounds were prepared first as series of stock solutions in DMSO and then dissolved in external solution; DMSO content in final dilutions did not exceed 0.3%. At this concentration, DMSO did not affect sodium currents. Vehicle solution used to establish base line was also contacting 0.3% DMSO.

Data analysis: Data was analyzed off-line using Clampfit software (pClamp, v.8; Axon Instruments) and graphed using GraphPad Prizm (v. 4.0) software.

***In Vivo* Assay for Pain**

The compounds can be tested for their antinociceptive activity in the formalin model as described in Hunskaar *et al., J. Neurosci. Methods 14*: 69-76 (1985). Male Swiss Webster NIH mice (20-30 g; Harlan, San Diego, CA) can be used in all experiments. Food is withdrawn on the day of experiment. Mice are placed in Plexiglass jars for at least 1 hour to acclimate to the environment. Following the acclimation period, mice are weighed and given either the compound of interest administered i.p. or p.o., or the appropriate volume of vehicle (for example, 10 % Tween-80 or 0.9 % saline, and other pharmaceutically acceptable vehicles) as control. Fifteen minutes after the i.p. dosing, and 30 minutes after the p.o. dosing mice are injected with formalin (20 μL of 5% formaldehyde solution in saline) into the dorsal surface of the right hind paw. Mice are transferred to the Plexiglass jars and monitored for the amount of time spent licking or biting the injected paw. Periods of licking and biting are recorded in 5-minute intervals for 1 hour after the formalin injection. All experiments are done in a blinded manner during the light cycle. The early phase of the formalin response is measured as licking / biting between 0-5 minutes, and the late phase is measured from 15-50 minutes. Differences between vehicle and drug treated groups can be analyzed by one-way analysis of variance (ANOVA). A P value <0.05 is considered significant. Compounds are considered to be efficacious for treating acute and chronic pain if they have activity in blocking both the early and second phase of formalin-induced paw-licking activity.

***In Vivo* Assays for Inflammatory or Neuropathic Pain**

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a test compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a compound of Formulae **I-XVI**. The control group is administered the carrier as used for the test compound. The volume of carrier administered to the control group is the same as the volume of carrier and test compound administered to the test group.

Inflammatory Pain: To assess the actions of the compounds of Formulae **I-XVI** on the treatment of inflammatory pain the Freund's complete adjuvant ("FCA") model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical and thermal hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (Bartho *et al.*, *Naunyn-Schmiedeberg's Archives of Pharmacol. 342*:666-670 (1990)). The left hind paw of each animal is administered a 50 µL intraplantar injection of 50% FCA. 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the paw withdrawal threshold (PWT), or to noxious thermal stimuli by determining the paw withdrawal latency (PWL), as described below. Rats are then administered a single injection of either a test compound or 30 mg/Kg of a positive control compound (indomethacin). Responses to noxious mechanical or thermal stimuli are then determined 1, 3, 5 and 24 hours post administration (admin). Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ reversal} = \frac{[(\text{post administration PWT or PWL})-(\text{pre-administration PWT or PWL})]}{[(\text{baseline PWT or PWL}) - (\text{pre-administration PWT or PWL})]} \text{ X } 100$$

Neuropathic Pain: To assess the actions of the test compounds for the treatment of neuropathic pain the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Seltzer *et al.*, *Pain 43*:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O_2 inhalation anesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve

exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to ½ of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and vetbond tissue glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{baseline PWT}) - (\text{pre-administration PWT})]} \text{ X } 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anesthesia. Following induction of anesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4 - S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4 - L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is (are) isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is (are) not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT,

as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a compound of Formulae **I-XVI** for the left rear paw of the animal. The animals can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in Kim *et al.*, *Pain 50*(3):355-363 (1992).

Tactile Allodynia: Sensitivity to non-noxious mechanical stimuli can be measured in animals to assess tactile allodynia. Rats are transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A series of von Frey monofilaments are applied to the plantar surface of the hindpaw to determine the animal's withdrawal threshold. The first filament used possesses a buckling weight of 9.1 gms (.96 log value) and is applied up to five times to see if it elicits a withdrawal response. If the animal has a withdrawal response, then the next lightest filament in the series would be applied up to five times to determine if it also could elicit a response. This procedure is repeated with subsequent lesser filaments until there is no response and the identity of the lightest filament that elicits a response is recorded. If the animal does not have a withdrawal response from the initial 9.1 gms filament, then subsequent filaments of increased weight are applied until a filament elicits a response and the identity of this filament is recorded. For each animal, three measurements are made at every time point to produce an average withdrawal threshold determination. Tests can be performed prior to, and at 1, 2, 4 and 24 hours post drug administration.

Mechanical Hyperalgesia: Sensitivity to noxious mechanical stimuli can be measured in animals using the paw pressure test to assess mechanical hyperalgesia. In rats, hind paw withdrawal thresholds ("PWT"), measured in grams, in response to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy), as described in Stein (*Biochemistry & Behavior 31*: 451-455 (1988)). The rat's paw is placed on a small platform, and weight is applied in a graded manner up to a maximum of 250 grams. The endpoint is taken as the weight at which the paw is completely withdrawn. PWT is determined once for each rat at each time point. PWT can be measured only in the injured paw, or in both the injured and non-injured paw. In one non-limiting embodiment, mechanical hyperalgesia associated with nerve injury induced pain (neuropathic pain) can be assessed in rats. Rats are tested prior to surgery to determine a baseline, or normal, PWT. Rats are tested again 2 to 3 weeks post-surgery, prior to, and at

different times after (*e.g.*, 1, 3, 5 and 24 hr) drug administration. An increase in PWT following drug administration indicates that the test compound reduces mechanical hyperalgesia.

***In Vivo* Assay for Anticonvulsant Activity**

The Compounds of the Invention can be tested for *in vivo* anticonvulsant activity after i.v., p.o., or i.p. injection using any of a number of anticonvulsant tests in mice, including the maximum electroshock seizure test (MES). Maximum electroshock seizures are induced in male NSA mice weighing between 15-20 g and in male Sprague-Dawley rats weighing between 200-225 g by application of current (for mice: 50 mA, 60 pulses/sec, 0.8 msec pulse width, 1 sec duration, D.C.; for rats: 99 mA, 125 pulses/sec, 0.8 msec pulse width, 2 sec duration, D.C.) using a Ugo Basile ECT device (Model 7801). Mice are restrained by gripping the loose skin on their dorsal surface and saline-coated corneal electrodes are held lightly against the two corneae. Rats are allowed free movement on the bench top and ear-clip electrodes are used. Current is applied and animals are observed for a period of up to 30 seconds for the occurrence of a tonic hindlimb extensor response. A tonic seizure is defined as a hindlimb extension in excess of 90 degrees from the plane of the body. Results can be treated in a quantal manner.

Pharmaceutical Compositions

Although a Compound of the Invention can be administered to a mammal in the form of a raw chemical without any other components present, the compound is preferably administered as part of a pharmaceutical composition containing the compound combined with a suitable pharmaceutically acceptable carrier. Such a carrier can be selected from pharmaceutically acceptable excipients and auxiliaries.

Pharmaceutical compositions within the scope of the present invention include all compositions where a Compound of the Invention is combined with a pharmaceutically acceptable carrier. In one embodiment, the compound is present in the composition in an amount that is effective to achieve its intended therapeutic purpose. While individual needs may vary, a determination of optimal ranges of effective amounts of each compound is within the skill of the art. Typically, a compound can be administered to a mammal, *e.g.*, a human, orally at a dose of from about 0.0025 to about 1500 mg per kg body weight of the

mammal, or an equivalent amount of a pharmaceutically acceptable salt, prodrug, or solvate thereof, per day to treat the particular disorder. A useful oral dose of a Compound of the Invention administered to a mammal is from about 0.0025 to about 50 mg per kg body weight of the mammal, or an equivalent amount of the pharmaceutically acceptable salt, prodrug, or solvate thereof. For intramuscular injection, the dose is typically about one-half of the oral dose.

A unit oral dose may comprise from about 0.01 to about 50 mg, and preferably about 0.1 to about 10 mg, of the compound. The unit dose can be administered one or more times daily, *e.g.*, as one or more tablets or capsules, each containing from about 0.01 to about 50 mg of the compound, or an equivalent amount of a pharmaceutically acceptable salt, prodrug or solvate thereof.

A pharmaceutical composition of the present invention can be administered to any animal that may experience the beneficial effects of a Compound of the Invention. Foremost among such animals are mammals, *e.g.*, humans and companion animals, although the invention is not intended to be so limited.

A pharmaceutical composition of the present invention can be administered by any means that achieves its intended purpose. For example, administration can be by the oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, intranasal, transmucosal, rectal, intravaginal or buccal route, or by inhalation. The dosage administered and route of administration will vary, depending upon the circumstances of the particular subject, and taking into account such factors as age, gender, health, and weight of the recipient, condition or disorder to be treated, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In one embodiment, a pharmaceutical composition of the present invention can be administered orally and is formulated into tablets, dragees, capsules or an oral liquid preparation. In one embodiment, the oral formulation comprises extruded multiparticulates comprising the Compound of the Invention.

Alternatively, a pharmaceutical composition of the present invention can be administered rectally, and is formulated in suppositories.

Alternatively, a pharmaceutical composition of the present invention can be administered by injection.

Alternatively, a pharmaceutical composition of the present invention can be administered transdermally.

Alternatively, a pharmaceutical composition of the present invention can be administered by inhalation or by intranasal or transmucosal administration.

Alternatively, a pharmaceutical composition of the present invention can be administered by the intravaginal route.

A pharmaceutical composition of the present invention can contain from about 0.01 to 99 percent by weight, and preferably from about 0.25 to 75 percent by weight, of active compound(s).

A method of the present invention, such as a method for treating a disorder responsive to the blockade of sodium channels in an animal in need thereof, can further comprise administering a second therapeutic agent to the animal in combination with a Compound of the Invention. In one embodiment, the other therapeutic agent is administered in an effective amount.

Effective amounts of the other therapeutic agents are known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range.

A Compound of the Invention (*i.e.*, the first therapeutic agent) and the second therapeutic agent can act additively or, in one embodiment, synergistically. Alternatively, the second therapeutic agent can be used to treat a disorder or condition that is different from the disorder or condition for which the first therapeutic agent is being administered, and which disorder or condition may or may not be a condition or disorder as defined herein. In one embodiment, a Compound of the Invention is administered concurrently with a second therapeutic agent; for example, a single composition comprising both an effective amount of a compound of any of Formulae **I-XVI**, and an effective amount of the second therapeutic agent can be administered. Accordingly, the present invention further provides a pharmaceutical composition comprising a combination of a Compound of the Invention, the second therapeutic agent, and a pharmaceutically acceptable carrier. Alternatively, a first pharmaceutical composition comprising an effective amount of a compound of any of Formulae **I-XVI** and a second pharmaceutical composition comprising an effective amount of the second therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Compound of the Invention is administered prior or subsequent to

administration of an effective amount of the second therapeutic agent. In this embodiment, the Compound of the Invention is administered while the second therapeutic agent exerts its therapeutic effect, or the second therapeutic agent is administered while the Compound of the Invention exerts its therapeutic effect for treating a disorder or condition.

The second therapeutic agent can be an opioid agonist, a non-opioid analgesic, a non-steroidal anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, a β-adrenergic blocker, an anticonvulsant, an antidepressant, an anticancer agent, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a seizure, an agent for treating a stroke, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, or a mixture thereof.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen,

muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Examples of other suitable non-opioid analgesics include the following, non limiting, chemical classes of analgesic, antipyretic, nonsteroidal antiinflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, see Paul A. Insel, *Analgesic Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout*, in Goodman & Gilman's *The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti Inflammatory Drugs* in Remington: *The Science and Practice of Pharmacy* Vol. II 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties. Suitable Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, bromocriptine, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergonovine, ergot, ergotamine, flumedroxone acetate, fonazine, ketanserin, lisuride, lomerizine, methylergonovine, methysergide, metoprolol, naratriptan, oxetorone, pizotyline, propranolol, risperidone, rizatriptan, sumatriptan, timolol, trazodone, zolmitriptan, and mixtures thereof.

Examples of useful β-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine hydrochloride,

butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, (S)-citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol,

ritanserin, roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

Examples of useful anticancer agents include, but are not limited to, acivicin, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, and cisplatin.

Therapeutic agents useful for treating an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, or a serotonin antagonist.

Examples of useful therapeutic agents for treating Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide, bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsapirone, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meprobamate and tybamate.

Examples of useful therapeutic agents for treating epilepsy or seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, benzodiazepines, gamma-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue

plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating a pruritic condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below; menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating psychosis include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, mesoridazine besylate, and thoridazine hydrochloride; thioxanthenes such as chloroprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine; quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

Examples of useful therapeutic agents for treating ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepan and dantrolene.

Examples of useful therapeutic agents for treating cognitive disorders include, but are not limited to, agents for treating dementia such as tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

Examples of useful therapeutic agents for treating a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and divalproex.

Examples of useful therapeutic agents for treating vomiting include, but are not limited to, 5-HT3 receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazine, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

Examples of useful therapeutic agents for treating dyskinesia include, but are not limited to, reserpine and tetrabenazine.

Examples of useful therapeutic agents for treating depression include, but are not limited to, tricyclic antidepressants such as amitryptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotiline, nefazadone, nortriptyline, protriptyline,

trazodone, trimipramine, and venlafaxine; selective serotonin reuptake inhibitors such as citalopram, (S)-citalopram, fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and psychostimulants such as dextroamphetamine and methylphenidate.

A pharmaceutical composition of the present invention is preferably manufactured in a manner which itself will be known in view of the instant disclosure, for example, by means of conventional mixing, granulating, dragee-making, dissolving, extrusion, or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active compound with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients include fillers such as saccharides (for example, lactose, sucrose, mannitol or sorbitol), cellulose preparations, calcium phosphates (for example, tricalcium phosphate or calcium hydrogen phosphate), as well as binders such as starch paste (using, for example, maize starch, wheat starch, rice starch, or potato starch), gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, one or more disintegrating agents can be added, such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate.

Auxiliaries are typically flow-regulating agents and lubricants such as, for example, silica, talc, stearic acid or salts thereof (*e.g.*, magnesium stearate or calcium stearate), and polyethylene glycol. Dragee cores are provided with suitable coatings that are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropymethyl-cellulose phthalate can be used. Dye agents or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Examples of other pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, or soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain a compound in the form of granules,

which can be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers, or in the form of extruded multiparticulates. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils or liquid paraffin. In addition, stabilizers can be added.

Possible pharmaceutical preparations for rectal administration include, for example, suppositories, which consist of a combination of one or more active compounds with a suppository base. Suitable suppository bases include natural and synthetic triglycerides, and paraffin hydrocarbons, among others. It is also possible to use gelatin rectal capsules consisting of a combination of active compound with a base material such as, for example, a liquid triglyceride, polyethylene glycol, or paraffin hydrocarbon.

Suitable formulations for parenteral administration include aqueous solutions of the active compound in a water-soluble form such as, for example, a water-soluble salt, alkaline solution, or acidic solution. Alternatively, a suspension of the active compound can be prepared as an oily suspension. Suitable lipophilic solvents or vehicles for such as suspension may include fatty oils (for example, sesame oil), synthetic fatty acid esters (for example, ethyl oleate), triglycerides, or a polyethylene glycol such as polyethylene glycol-400 (PEG-400). An aqueous suspension may contain one or more substances to increase the viscosity of the suspension, including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. The suspension may optionally contain stabilizers.

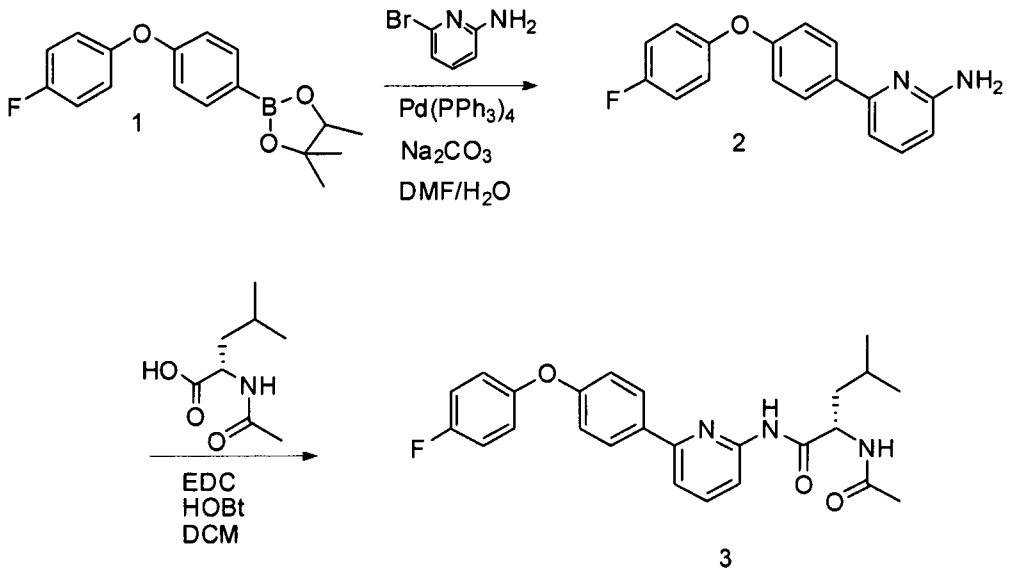
The following examples are illustrative, but not limiting, of the compounds, compositions and methods of the present invention. Suitable modifications and adaptations of the variety of conditions and parameters normally encountered in clinical therapy and which are obvious to those skilled in the art in view of this disclosure are within the spirit and scope of the invention.

EXAMPLES

EXAMPLE 1

Synthesis of (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide

Scheme 1



Compound **2**: 2-(4-(4-Fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (compound **1**; 368 mg, 1.4 mmol), 6-bromopyridin-2-amine (250 mg, 1.4 mmol) and sodium carbonate (1.2 g, 11.2 mmol) were dissolved in DMF/H_2O (15 mL). Tetrakis(triphenylphosphine) palladium (81 mg, 0.07 mmol) was added thereto and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature and partitioned between EtOAc and water. The organic layer was separated and then dried over anhydrous Na_2SO_4. The solvent was evaporated and the oily residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to give 6-(4-(4-fluorophenoxy)phenyl)pyridin-2-amine as pale yellow oil (372 mg, 92%). R_f = 0.6, eluent (1:1 EtOAc:hexanes), LC/MS: m/z = 281 $[M+H]^+$.

In an alternative procedure, to a solution of 6-bromopyridin-2-amine (4.329 g, 25.02 mmol, Aldrich) in dioxane (150 mL) was added compound **1** (7.88 g, 25.08 mmol), 2M aqueous Na_2CO_3 solution (25 mL, 50 mmol) and $PdCl_2$(dppf) (1.027 g, 1.26 mmol). The reaction vessel was heated at reflux under nitrogen overnight. After cooling, the reaction was partitioned between 100 mL EtOAc and 50 mL water. The organic layer was washed once with 25 mL brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with 20-50% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give 6-(4-(4-fluorophenoxy)phenyl)pyridin-2-amine as a thick pale yellow oil (5.994 g, 21.38 mmol, 85% yield, LC/MS: m/z = 281.2 $[M+H]^+$).

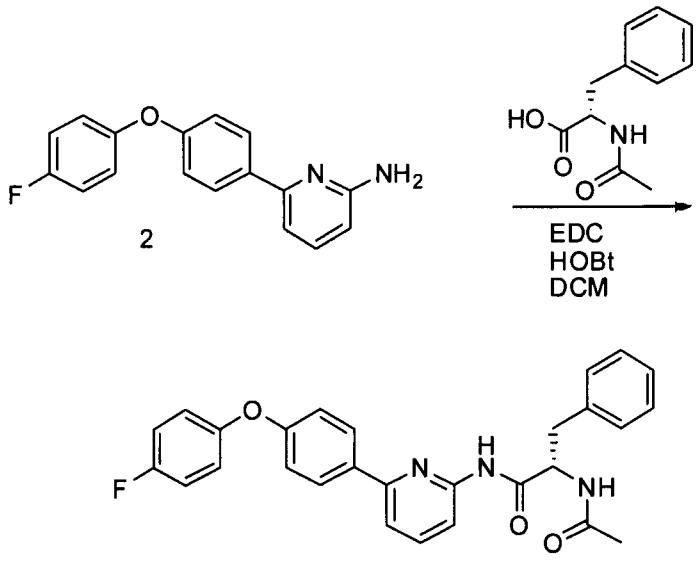
Compound **3**: A mixture of AcN-(L)-Leu-OH (Sigma-Aldrich, 61.9 mg, 0.36 mmol), EDC (82 mg, 0.43 mmol), HOBt (58.0 mg, 0.43 mmol) in dry DCM was stirred for 1h and

compound **2** (100 mg, 0.36 mmol) was added thereto. The reaction mixture was allowed to stir overnight at room temperature. After the reaction was complete, it was quenched with saturated NH_4Cl. The aqueous layer was extracted with EtOAc and $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give oily residue. The residue was purified by preparative TLC (10% MeOH in DCM with 1% NH_4OH) to give (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide (compound **3**) as a white solid (61 mg, 39 %). LC/MS: m/z = 436 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): 8.52 (s, br, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.68 (t, J = 8.1 Hz, 2H), 7.37 (d, J = 7.7 Hz, 2H), 6.93-7.02 (m, 6H), 5.90 (br, s, 1H), 4.53-4.66 (m, 1H), 2.0 (s, 3H), 1.60-1.78 (m, 2H), 1.49-1.60 (m, 1H), 0.91 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.2 Hz, 3H). Unless otherwise indicated all ^1H NMR chemical shifts reported herein are denoted by the delta (δ) scale.

EXAMPLE 2

Synthesis of (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-phenylpropanamide

Scheme 2

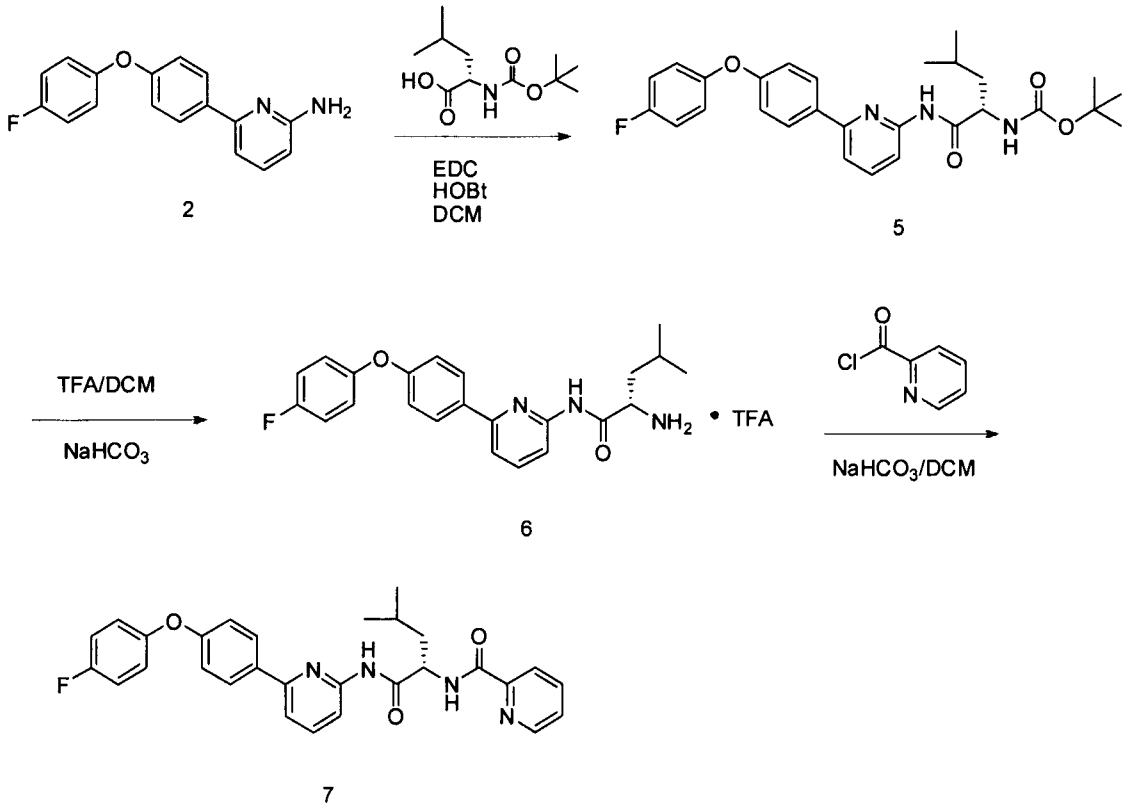


Compound **4**: A mixture of AcN-(L)-Phe-OH (purchased from Sigma-Aldrich, 74.5 mg, 0.36 mmol), EDC (82 mg, 0.43 mmol), HOBt (58.0 mg, 0.43 mmol) in dry DCM was stirred for 1h and compound **2** (100 mg, 0.36 mmol) was added thereto. The reaction mixture was stirred for 2 days at room temperature (67% conversion by LC/MS analysis) and it was quenched with saturated. NH_4Cl. The aqueous layer was extracted with EtOAC and $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give solid residue. The crude residue was purified by preparative TLC (1st purification: 50% EtOAc in hexanes; 2nd purification: 10% MeOH in DCM with 1% NH_4OH) to give (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-phenylpropanamide (compound **4**) as a white solid (26 mg, 15%). LC/MS: m/z = 470 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): 8.46-8.45 (br, s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.70 (dd, J = 7.4 Hz, 8.0 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.24-7.37 (m, 6H), 7.02-7.12 (m, 6H), 6.13 (s, br, 1H), 4.88 (m, 1H), 3.22 (d, J = 7.1 Hz, 2H), 2.05 (s, 3H).

EXAMPLE 3

Synthesis of (S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide

Scheme 3

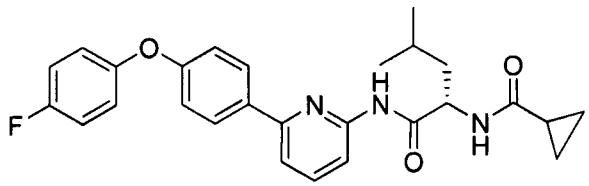


Compound **5**: A mixture of Boc-Leu-OH (purchased from Sigma-Aldrich, 4.17 g, 18.0 mmol), EDC (4.1 g, 21.5 mmol), HOBt (2.9 g, 21.5 mmol) in dry DCM (300 mL) was stirred for 1h at room temperature and compound **2** (5.0 g, 18.0 mmol) was added thereto. The reaction mixture was stirred for 12 h at room temperature. After the reaction was complete, it was quenched with saturated NH_4Cl. The aqueous layer was extracted with EtOAc and $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give oily residue which was then purified by column chromatography (silica gel, 30% EtOAc in hexane) to give compound **5** as pale yellow oil (4.0 g, 75% yield based on the recovered starting material (2.0g)). LC/MS: m/z = 496 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): 8.67 (br, s, 1H), 8.12 (d, J = 8.33 Hz, 2H), 7.90 (d, J = 8.99 Hz, 2H),), 7.76 (t, J = 7.89 Hz, 1H), 7.42 (d, J = 7.67 Hz, 1H), 7.00-7.09 (m, 5H), 4.86 (br, s, 1H), 4.31 (br, s, 1H), 1.48-1.87 (m, 3H), 1.45 (s, 9H), 0.95 (d, J = 6.36 Hz, 6H).

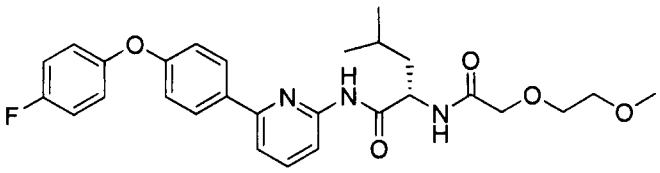
Compound **6**: Compound **5** (1.0 g, 2.0 mmol) was dissolved in dry DCM (15 mL) and treated with TFA (15 mL). The mixture was stirred for 1h at room temperature and solvent was evaporated. The resulting residue was dissolved in a 5:1 mixture of THF:MeOH (10 mL) and $NaHCO_3$ (253 mg) was added thereto. The suspension was stirred for 10 min, diluted with DCM, and filtered. The solvent was evaporated and the compound **6** was

obtained quantitatively as TFA salt which was used for the next step without further purification.

Compound **7**: Compound **6** (50.0 mg, 0.10 mmol) was treated with picolinoyl chloride hydrochloride (14.2 mg, 0.10 mmol) in a 1:1 mixture of DCM/saturated $NaHCO_3$. After the reaction was complete, the organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC (10:1 DCM:MeOH) to give (S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide (compound **7**) (25mg, 51%). LC/MS: m/z = 499 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.63 (s, 1H), 8.59 (d, J = 4.4 Hz, 1H), 8.43 (d, J = 7.9Hz, 1H), 8.21 (d, J = 7.9 Hz, 1H), 8.12 (d, J = 7.9Hz, 1H), 7.83-7.95 (m, 3H), 7.74 (t, J = 7.9 Hz, 1H), 7.41-7.48 (m, 1H), 7.42 (d, J = 7.0 Hz, 1H), 6.99-7.08 (m, 6H), 4.78-4.88 (m, 1H), 1.93-2.03 (m, 1H), 1.74-1.90 (m, 1H), 1.0 (t, J = 6.1 Hz , 6H).

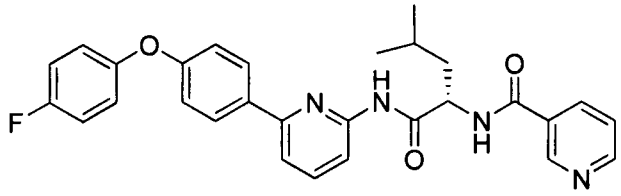


Compound **8**: In a similar fashion, compound **6** (58.0 mg, 0.11 mmol) was treated with cyclopropanecarbonyl chloride (12.0 mg, 0.11 mmol) to give (S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide (32 mg, 62%). LC/MS: m/z = 463 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.52 (s, 1H), 8.08 (d, J = 7.89 Hz, 1H), 7.92 (d, J = 8.77Hz, 1H), 7.74 (t, J = 7.89 Hz, 1H), 7.43 (d, J = 7.89 Hz, 1H), 6.99-7.11 (m, 6H), 6.04-6.15 (m, 1H), 4.63-4.73 (m, 1H), 1.56-1.88 (m, 2H), 1.37-1.49 (m, 1H), 0.94-1.06 (m, 8H), 0.79 (d, J = 7.89 Hz, 2H).

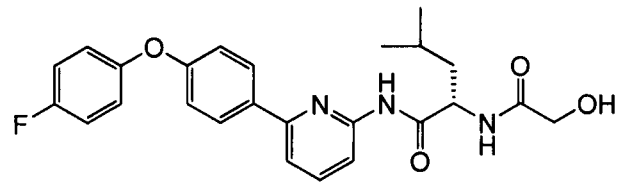


Compound **9**: In a similar fashion, compound **6** (100.0 mg, 0.2 mmol) was treated with 2-(2-methoxyethoxy)acetyl chloride (30.5 mg, 0.2 mmol) to give S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-(2-methoxyethoxy)acetamido)-4-methylpentanamide (65 mg, 65%). LC/MS: m/z = 510 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.65 (s, 1H), 8.03 (d, J = 7.90 Hz, 1H), 7.86 (d, J = 8.77 Hz, 2H), 7.67 (t, J = 7.89 Hz, 1H), 7.47 (d, J = 7.89 Hz, 1H), 7.36 (d, J = 7.02 Hz, 1H), 6.91-7.03 (m, 6H), 4.52-4.63

(m, 1H), 4.01 (d, J = 3.50 Hz, 2H), 3.63-3.70 (m, 2H), 3.48-3.57 (m, 2H), 3.37 (s, 3H), 1.43-2.02 (m, 3H), 0.92 (t, J = 6.14 Hz, 6H).



Compound **10**: In a similar fashion, compound **6** (53.3 mg, 0.1 mmol) was treated with nicotinyl chloride hydrochloride (14.1 mg, 0.1 mmol) to give S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl) nicotinamide (2.7 mg, 5.0 %). LC/MS: m/z = 499 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 9.03 (s, 1H), 8.70 (dd, J = 1.54, 5.26 Hz, 1H), 8.42-8.47 (m, 1H), 7.95 (d, J = 8.77 Hz, 2H), 7.89-7.93 (m, 1H), 7.73 (t, J = 8.11 Hz, 1H), 7.64 (m, 1H), 7.50 (d, J = 7.24 Hz, 1H), 6.91-7.10 (m, 6H), 4.82 (br, s, 1H), 1.65-1.85 (m, 3H), 0.94 (dd, J = 4.17 Hz, 6.14 Hz , 6H).

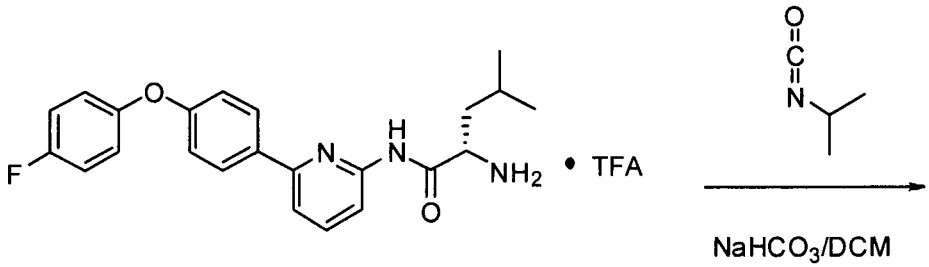


Compound **90**: In similar fashion, compound **6** (as the HCl salt) (300 mg, 0.70 mmol) was treated with glycolic acid (53.2 mg, 0.7 mmol) in the presence of EDC (160 mg, 0.84 mmol), HOBt (113.4 mg, 0.84 mmol), DIEA (0.13 mL, 0.7 mmol) in dry DCM. The reaction mixture was stirred overnight at room temperature. After the reaction was complete, it was quenched with saturated NH_4Cl. The aqueous layer was extracted with EtOAc and $CHCl_3$. The organic phase was dried over anhydrous Na_2CO_3 and concentrated. The oily residue was purified by preparative TLC to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-4-methylpentanamide (201 mg, 64%). ^1H NMR (400 MHz, CD_3OD): 8.07 (1H, d, J = 9.0 Hz), 8.02-8.07 (2H, m), 7.82 (1H, t, J = 8.1Hz), 7.60 (1H, d, J = 7.7 Hz), 7.03-7.19 (6H, m), 4.72-4.73 (1H, m), 4.07 (12H, s), 1.72-1.80 (3H, m), 0.97-1.03 (6H, m); LC/MS: *m/z* = 452.1 $[M+H]^+$.

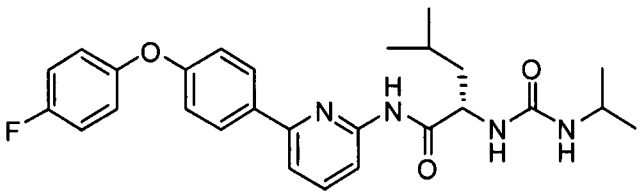
EXAMPLE 4

Synthesis of (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(3-isopropylureido)-4-methylpentanamide

Scheme 4

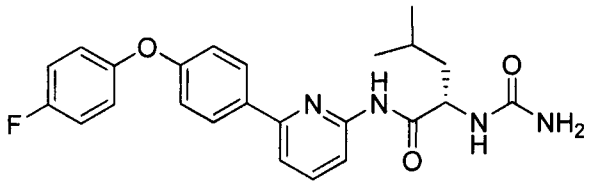


6

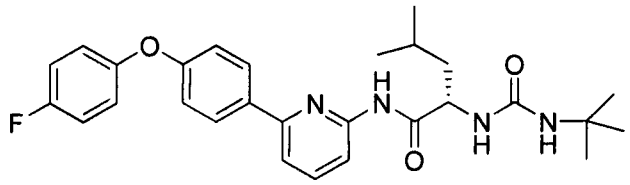


11

Compound **11**: Compound **6** (100.0 mg, 0.2 mmol) in a mixture of DCM/saturated $NaHCO_3$ (1:1, 10 mL) was treated with isopropyl isocyanate (0.05 mL, 0.47 mmol) and stirred for 2 h at room temperature. After the reaction was complete, the mixture was diluted with DCM and dried over anhydrous Na_2CO_3. The solvent was evaporated and the residue was purified by preparative TLC (EtOAc:hexane= 1:1) to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(3-isopropylureido)-4-methylpentanamide as a white solid (4.8 mg, 21%). LC/MS: m/z = 479 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.05 (d, J = 8.99 Hz, 3H), 7.81 (t, J = 8.33 Hz, 1H), 7.59 (d, J = 7.67 Hz, 1H), 7.01-7.19 (m, 6H), 4.41-4.48 (m, 1H), 3.79-3.85 (m, 1H), 1.56-1.82 (m, 3H), 1.15 (dd, J = 1.54 Hz, 6.58 Hz, 6H), 1.00 (dd, J = 2.41 Hz, 6.58 Hz, 6H).



Compound **12**: In a similar fashion, compound **6** (50.0 mg, 0.1 mmol) was treated with potassium cyanate (31.6 mg, 0.39 mmol) in water and stirred for 3 days at room temperature. After the reaction was complete, the reaction mixture was extracted with EtOAc. The organic phase was dried with anhydrous Na_2CO_3 and the solvent was evaporated. The residue was purified by preparative TLC (1:9 MeOH:DCM) to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methyl-2-ureidopentanamide as a white solid (17 mg, 33%). LC/MS: m/z = 437 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.07 (d, J = 8.99 Hz, 3H), 7.81 (t, J = 8.11 Hz, 1H), 7.59 (d, J = 7.89 Hz, 1H), 7.06-7.19 (m, 3H), 7.05 (d, J = 8.77 Hz, 2H), 4.41-4.48 (m, 1H), 1.56-1.87 (m, 3H), 1.01 (dd, J = 2.86 Hz, 6.58 Hz, 6H).

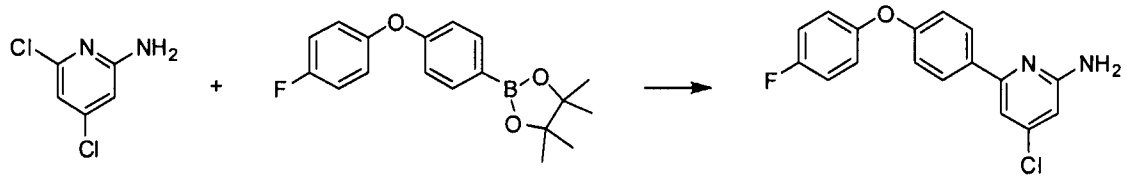


Compound **13**: In a similar fashion, compound **6** (439.0 mg, 0.87 mmol) in a mixture of DCM/saturated $NaHCO_3$ (1:1, 30 mL) was treated with t-butyl isocyanate (86 mg, 0.87 mmol) and stirred for 1 h at room temperature. After the reaction was complete, the mixture was diluted with DCM and dried over anhydrous Na_2CO_3. The solvent was evaporated and the residue was then purified by column chromatography (silica gel, 50% EtOAc in hexane) to give (S)-2-(3-(tert-butyl)ureido)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide as a white solid (268 mg, 62%). LC/MS: m/z = 493 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.78 (br, s, 1H), 8.10 (d, J = 8.11 Hz, 1H), 7.92 (d, J = 8.99 Hz, 2H), 7.71 (t, J = 7.89 Hz, 1H), 7.41 (d, J = 7.67 Hz, 1H), 6.99-7.10 (m, 6H), 4.75 (br, s, 1H), 4.44 (br, s, 2H), 1.71-1.82 (m, 2H), 1.52-1.60 (m, 1H), 1.32 (s, 9H), 0.97 (d, J = 6.14 Hz, 6H).

EXAMPLE 5

Synthesis of (S)-N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-N-(2,3-dihydroxypropyl) methanesulfonamide

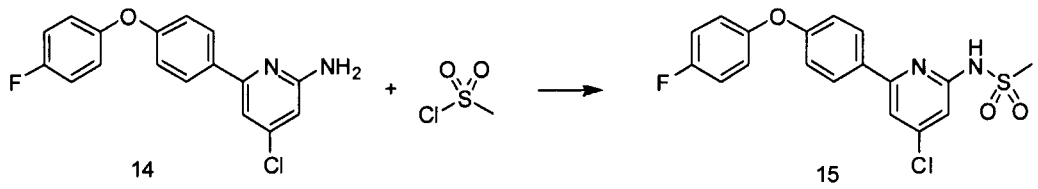
Scheme 5



1 14

Compound **14**: To a solution of the 4,6-dichloropyridin-2-amine (1.636 g, 10.04 mmol, Small Molecules, Inc.) in dioxane (100 mL) was added 2-(4-(4-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (compound **1**, 3.157 g, 10.05 mmol), 2M aqueous Na_2CO_3 solution (10.0 mL, 20.0 mmol) and $PdCl_2(dppf)$ (0.413 g, 0.51 mmol). The vessel was heated at reflux under nitrogen overnight. After cooling, the reaction was partitioned between 100 mL EtOAc and 50 mL water. The organics were isolated and the aqueous extracted once more with 25 mL EtOAc. The combined organic layers were washed once with 25 mL brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with 10-40% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to yield 4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-amine (compound **14**) as a thick yellow oil (2.215 g, 7.04 mmol, 70% yield, LC/MS: m/z = 315.1 $[M+H]^+$).

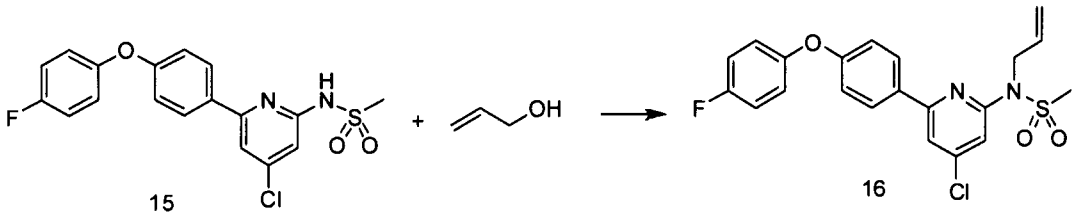
Scheme 6



Compound **15**: To a solution of compound **14** (0.496 g, 1.58 mmol) in DCM (5 mL) was added iPr_2NEt (0.42 mL, 2.41 mmol) and methanesulfonyl chloride (0.14 mL, 1.80 mmol, Aldrich). After 3 days additional methanesulfonyl chloride (0.14 mL, 1.80 mmol) was added. After one additional day more iPr_2NEt (0.42 mL, 2.41 mmol) and methanesulfonyl chloride (0.10 mL, 1.29 mmol) were successively added. After 2 days the reaction was quenched with 5 mL 1N aqueous NaOH. Acetonitrile (10 mL) was added to the reaction mixture and then heated at 50°C for 3 days. The reaction was cooled and partitioned between 50 mL EtOAc and 25 mL water. The organic layer was washed once with 25 mL brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 10-40% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo*. The residue was triturated with 5 mL 10% EtOAc / hexanes, filtered, and rinsed once with 2 mL 10% EtOAc / Hexanes. The solid was dried under vacuum at 50°C to yield N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide (compound **15**) as a tan powder (0.345 g, 0.878 mmol, 56% yield, LC/MS: m/z = 393.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.88 (s, 1H), 8.11 (d, J =

9.2 Hz, 2H), 7.72 (s, 1H), 7.32-7.24 (m, 2H), 7.20-7.13 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.89 (s, 1H), 3.42 (s, 3H).

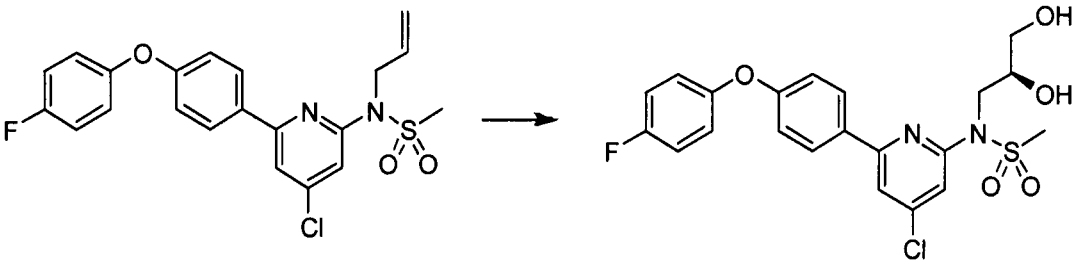
Scheme 7



15 16

Compound **16**: To a solution of triphenyl phosphine (0.215 g, 0.82 mmol, Aldrich) in THF (5 mL) was added a 40% DEAD solution in toluene (0.37 mL, 0.81 mmol, Aldrich). This reaction mixture was stirred for 3 minutes then added to a solution of compound **15** (0.290 g, 0.74 mmol) in THF (5 mL). The reaction mixture was stirred for another 2 minutes then allyl alcohol (0.07 mL, 1.0 mmol, Aldrich) was added. After 3 h to an additional amount of triphenyl phosphine (0.215 g, 0.82 mmol) in THF (5 mL) was added a 40% DEAD solution in toluene (0.37 mL, 0.81 mmol). This reaction mixture was stirred for 2 minutes then added to the sulfonamide reaction mixture. After 1 minute more allyl alcohol (0.07 mL, 1.0 mmol) was added. The reaction mixture was stirred for 3 days then evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 0-30% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give N-allyl-N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide (compound **16**) as a colorless oil (0.311 g, 0.72 mmol, 97% yield, LC/MS: m/z = 433.0 $[M+H]^+$).

Scheme 8



16 17

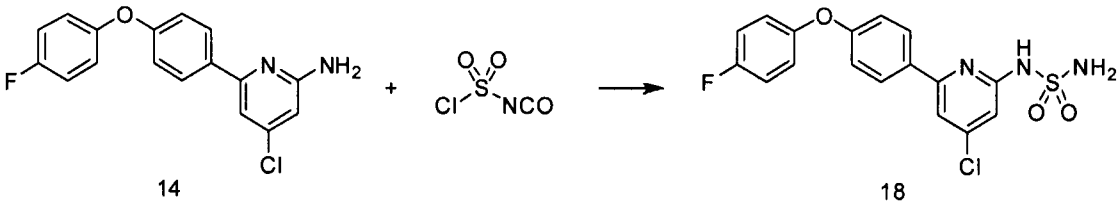
Compound **17**: To a milky suspension of compound **16** (0.311 g, 0.72 mmol) in iPrOH (10 mL) and water (10 mL) was added AD-Mix α (0.978 g, Aldrich). The reaction mixture was stirred overnight then additional water (10 mL) and AD-Mix α (0.981 g) were added.

After stirring overnight more iPrOH (10 mL), water (10 mL), and AD-Mix α (0.978 g) were added. After stirring overnight the reaction was partitioned between 200 mL EtOAc and 50 mL water. The organic layer was washed with 50 mL brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 40-80% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo*. The solid material was triturated with hexanes, filtered and dried under vacuum at 50°C to give (S)-N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-N-(2,3-dihydroxypropyl) methanesulfonamide (compound **17**) as a white powder (0.090 g, 0.19 mmol, 26% yield, LC/MS: m/z = 467.0 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 8.13 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 1.2 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.31-7.25 (m, 2H), 7.20-7.15 (m, 2H), 7.08 (d, J = 8.8Hz, 2H), 5.00 (d, J = 5.2 Hz, 1H), 4.68 (t, J = 6.0 Hz, 1H), 4.10 (dd, J = 14.8 Hz and 3.6 Hz, 1H), 3.86 (dd, J = 14.8 Hz and 8.4 Hz, 1H), 3.67-3.58 (m, 1H), 3.41 (s, 3H), 3.34 (t, J = 5.6 Hz, 2H).

EXAMPLE 6

Synthesis of N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)sulfamide

Scheme 9



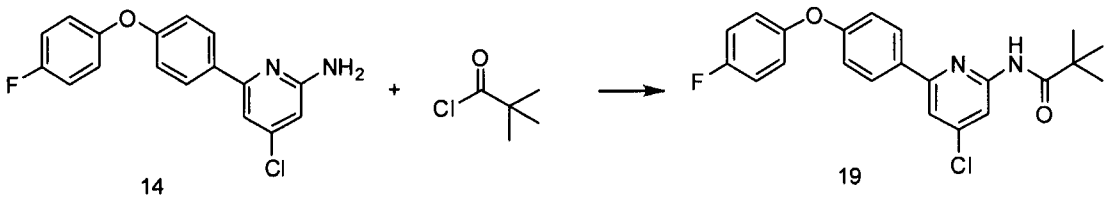
Compound **18**: DCM (5 mL) was cooled with an ice bath in a sealed tube then charged with chlorosulfonyl isocyanate (0.25 mL, 2.87 mmol, Aldrich). A solution of t-butanol (0.39 mL, 4.08 mmol, Aldrich) was added to the reaction dropwise over ~3.5 minutes. The ice bath was removed and the reaction stirred for 10 minutes. This mixture was added to an ice-cooled solution of 4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-amine (compound **14**, 0.630 g, 2.00 mmol) in DCM (5 mL) containing iPr_2NEt (0.52 mL, 2.99 mmol). After 10 minutes the ice bath was removed and the reaction stirred at ambient temperature for 3 days. The reaction was evaporated *in vacuo* and the residue was chromatographed over silica gel eluting with 10-50% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo*. The solid residue was triturated with 5 mL 10% EtOAc/hexanes, filtered and washed once with 1 mL 10% EtOAc/hexanes. The solid was dried under vacuum at 50°C to

give N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)sulfamide (compound **18**) as an off-white powder. (0.125 g, 0.32 mmol, 16% yield, LC/MS: m/z = 394.0 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.61 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.33-7.24 (m, 4H), 7.19-7.13 (m, 2H), 7.05 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 1.6 Hz, 1H).

EXAMPLE 7

Synthesis of (S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide

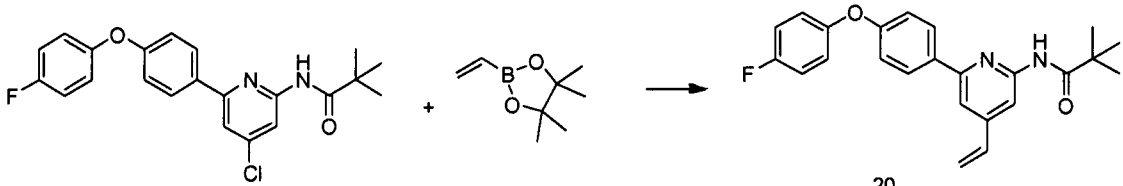
Scheme 10



14 19

Compound **19**: To a solution of compound **14** (10.02 mmol) in DCM was added iPr_2NEt (2.60 mL, 14.93 mmol) and pivaloyl chloride (1.35 mL, 10.96 mmol, Aldrich). The reaction was stirred overnight then washed successively with 50 mL saturated $NaHCO_3$ and 50 mL brine. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 0-20% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)pivalamide as a thick near-colorless oil (2.89 g, 7.25 mmol, 72% yield, LC/MS: m/z = 399.0 $[M+H]^+$).

Scheme 11

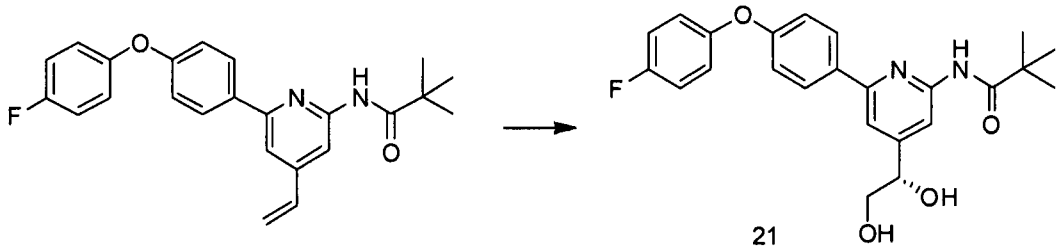


19 20

Compound **20**: To compound **19** (2.89 g, 7.25 mmol) in a screw-cap pressure vessel was added a 1M TBAF solution (22 mL, 22 mmol, Aldrich), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.85 mL, 10.91 mmol, Aldrich) and $PdCl_2$(dppf) (0.475 g, 0.58 mmol). The vessel was flushed with argon, capped and heated at 80°C for 3 days. After cooling, the reaction was partitioned between 200 mL EtOAc and 100 mL water. The organic layer was

washed once with 50 mL brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 0-20% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give N-(6-(4-(4-fluorophenoxy)phenyl)-4-vinylpyridin-2-yl)pivalamide as a thick yellow oil (1.541 g, 3.95 mmol, 54% yield, LC/MS: m/z = 391.2 $[M+H]^+$).

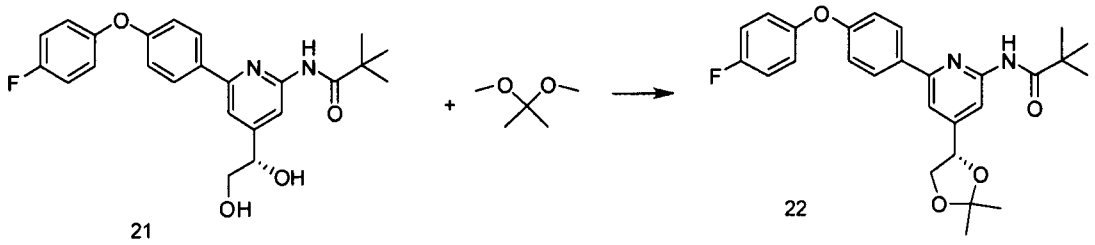
Scheme 12



20 21

Compound **21**: To a solution of compound **20** (1.451 g, 3.95 mmol) in iPrOH (15 mL) was added water (15 mL) and AD-Mix α (5.372 g). The reaction was stirred overnight then partitioned between 100 mL EtOAc and 50 mL water and the mixture filtered over a pad of celite. The organic layer was isolated and washed once more with 50 mL brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 0-100% Acetone in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)pivalamide as a cream-colored solid (1.184 g, 2.79 mmol, 71% yield, LC/MS: m/z = 425.2 $[M+H]^+$).

Scheme 13

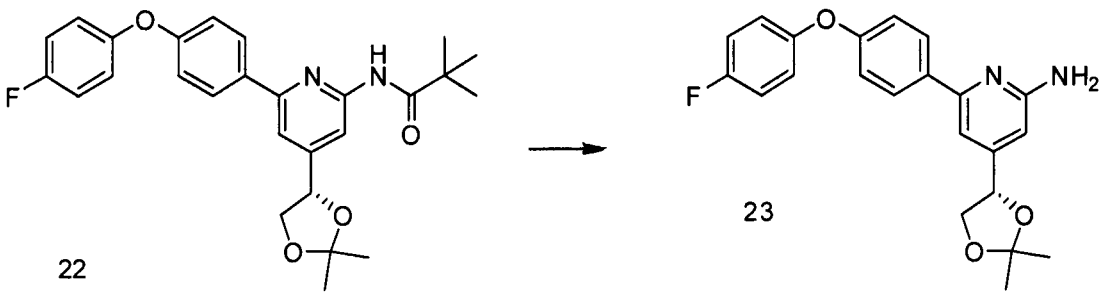


21 22

Compound **22**: To compound **21** (1.179 g, 2.78 mmol) was added 2,2-dimethoxypropane (10 mL, 81.33 mmol, Aldrich) and $TsOH•H_2O$ (0.055 g, 0.29 mmol, Aldrich). The reaction was stirred at ambient temperature for 4 days then 60°C for 1 day. The reaction was evaporated *in vacuo* and the residue was chromatographed over silica gel eluting with 5-30%

EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-N-(4-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)pivalamide as a thick colorless oil (0.959 g, 2.06 mmol, 74% yield, LC/MS: m/z = 465.2 $[M+H]^+$).

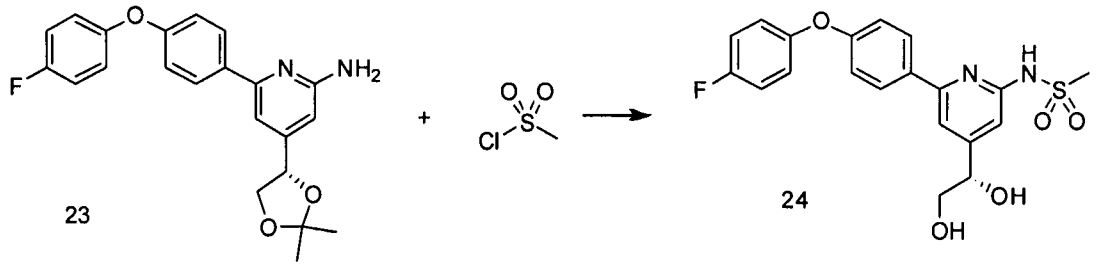
Scheme 14



22 23

Compound **23**: To compound **22** (0.959 g, 2.06 mmol) was added MeOH (12.5 mL), water (12.5 mL), and 85% KOH pellets (0.148 g, 2.24 mmol). The reaction was heated at 60°C overnight, diluted with additional MeOH (50 mL) and the heating was increased to a reflux. After 3 days additional 85% KOH pellets (0.084 g, 1.27 mmol) were added and the refluxing continued for 3 more days. The reaction was then cooled and evaporated *in vacuo* until it appeared that most of the MeOH had been removed. The reaction mixture was partitioned between 50 mL EtOAc and 25 mL brine. The organic layer was washed again with 25 mL brine, dried with $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 10-70% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-amine as a thick near-colorless oil (0.695 g, 1.83 mmol, 89% yield, LC/MS: m/z = 381.2 $[M+H]^+$).

Scheme 15

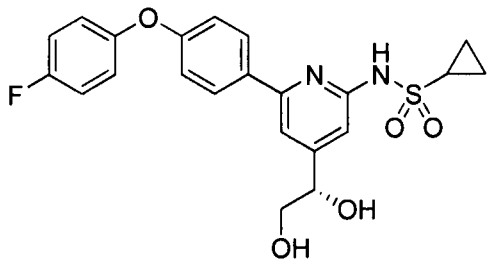


23 24

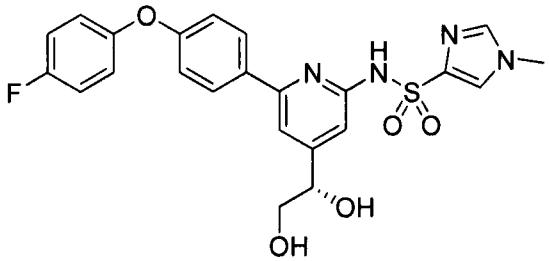
Compound **24**: To a solution of compound **23** (0.097 g, 0.25 mmol) in 1:1 DCM/ pyridine (2.5 mL) was added methanesulfonyl chloride (0.049 mL, 0.63 mmol). After 4 days the reaction was partitioned between 10 mL EtOAc and 10 mL saturated $NaHCO_3$. The organic layer was washed once with 10 mL brine. The organic layer was evaporated *in*

vacuo and MeOH (5 mL) and 4N HCl in dioxane (2.0 mL) were added. After 1 hour the reaction was evaporated *in vacuo*. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled and treated with Amberlite IRA-400(OH) resin to remove the TFA. The solution was frozen and lyophilized to give (S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)methanesulfonamide (0.037 g, 0.088 mmol, 35% yield, LC/MS: m/z = 419.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.53 (s, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.23-7.16 (m, 2H), 7.11-7.05 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.80 (s, 1H), 4.50 (t, J = 5.6 Hz, 1H), 3.42 (d, J = 6.0, 2H), 3.34 (s, 3H).

Using the chemistry described above, the following compounds were prepared:



Compound **25**: (S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)cyclopropanesulfonamide: LC/MS: m/z = 445.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.48 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.24-7.16 (m, 2H), 7.11-7.05 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.84 (s, 1H), 4.50 (t, J = 5.6 Hz, 1H), 3.43 (d, J = 6.0 Hz, 2H), 3.16-3.08 (m, 1H), 1.05-0.99 (m, 2H), 0.99-0.93 (m, 2H).

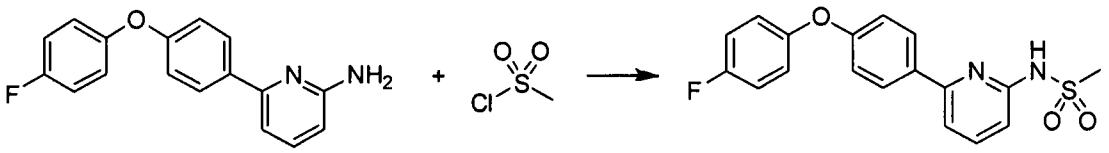


Compound **26**: (S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide: LC/MS: m/z = 485.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.82 (s, 1H), 7.92 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 1.2 Hz, 1H), 7.35 (s, 1H), 7.24-7.16 (m, 2H), 7.10-7.04 (m, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 4.45 (t, J = 6.0 Hz, 1H), 3.57 (s, 3H), 3.38 (d, J = 6.0 Hz, 2H).

EXAMPLE 8

Synthesis of N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide

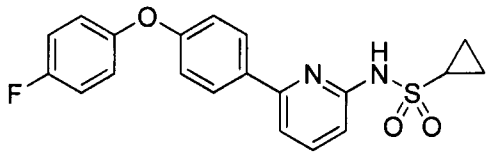
Scheme 16



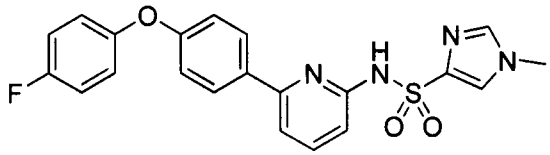
2 27

Compound **27**: To a solution of compound **2** (0.071 g, 0.25 mmol) in 1:1 DCM/pyridine (2.5 mL) was added methanesulfonyl chloride (0.049 mL, 0.63 mmol). After 4 days the reaction was partitioned between 10 mL EtOAc and 10 mL saturated $NaHCO_3$. The organic layer was washed once with 10 mL brine, evaporated *in vacuo*, and MeOH (5 mL) and 4N HCl in dioxane (2.0 mL) were added. After 1 h the reaction mixture was evaporated *in vacuo*. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled and treated with Amberlite IRA-400(OH) resin to remove the TFA. The solution was frozen and lyophilized to yield the product N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide (0.039 g, 0.109 mmol, 43% yield, LC/MS: m/z = 359.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.71 (s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.86 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.37-7.29 (m, 2H), 7.25-7.19 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 3.48 (s, 3H).

Using the chemistry described above, the following compounds were prepared:



Compound **28**: N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)cyclopropane sulfonamide: LC/MS: m/z = 385.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.60 (s, 1H), 8.08 (d, J = 8.8 Hz, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.31-7.24 (m, 2H), 7.18-7.12 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 3.22-3.14 (m, 1H), 1.13-1.07 (m, 2H), 1.07-1.00 (m, 2H).

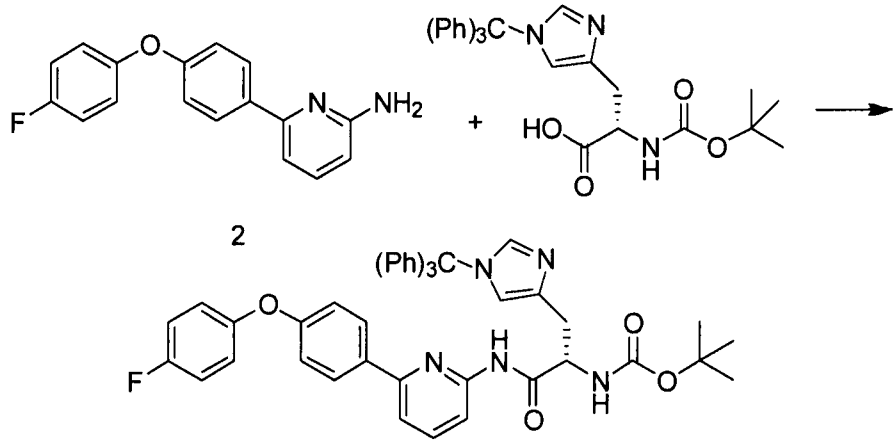


Compound **29**: N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide: LC/MS: m/z = 425.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 11.01 (s, 1H), 8.12-8.01 (m, 3H), 7.83-7.75 (m, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.38-7.29 (m, 2H), 7.24-7.18 (m, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.0 Hz, 1H), 3.71 (s, 3H).

EXAMPLE 9

Synthesis of (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide

Scheme 17



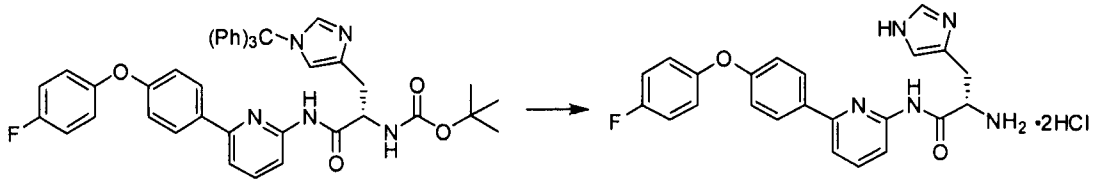
2

30

Compound **30**: To a solution of (S)-2-((tert-butoxycarbonyl)amino)-3-(1-trityl-1H-imidazol-4-yl)propanoic acid (1.990 g, 4.00 mmol, Aldrich) in DCM (20 mL) was added HOBT (0.680 g, 5.03 mmol, Aldrich), EDC•HCl (0.961 g, 5.01 mmol, Aldrich) and iPr_2NEt (0.87 mL, 4.99 mmol). After 5 minutes a solution of compound **2** (1.118 g, 3.99 mmol) in DCM (25 mL) was added. After 4 days more iPr_2NEt (1.05 mL, 6.03 mmol) and HATU (1.667 g, 4.38 mmol, GenScript Corporation) were added. After 3 days the reaction mixture was washed successively with 25 mL water and 25 mL brine. The organic layer was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed over silica gel eluting with 10-90% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-tert-butyl (1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-

yl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl)propan-2-yl)carbamate as a cream-colored foam (1.809 g, 2.38 mmol, 60% yield, LC/MS: m/z = 760.2 $[M+H]^+$).

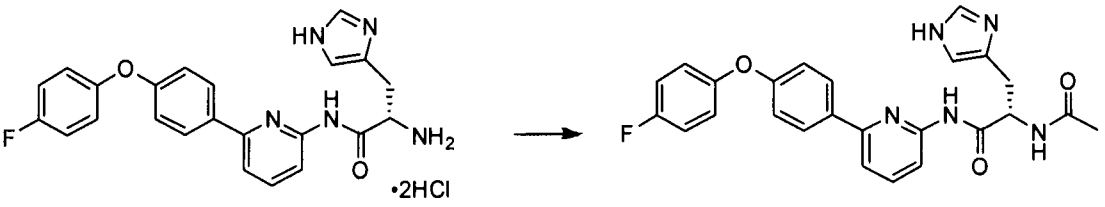
Scheme 18



30 31

Compound **31**: To compound **30** (1.809 g, 2.38 mmol) in dioxane (10 mL) was added 4M HCl in dioxane (2.5 mL, 10.0 mmol). After stirring overnight additional 4M HCl in dioxane (2.5 mL, 10.0 mmol) was added and the reaction was transferred to a sealed tube and heated at 60°C for 3 days. After cooling, the reaction was diluted with 100 mL Et_2O and the solids filtered off and rinsed several times with Et_2O. The material was dried under a stream of nitrogen then under vacuum at 50°C to give (S)-2-amino-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide as the bis-hydrochloride salt as a cream-colored powder (1.145 g, 2.34 mmol, 98% yield, LC/MS: m/z = 418.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.62 (br s, 1H), 14.42 (br s, 1H), 11.13 (s, 1H), 9.09 (s, 1H), 8.72 (br s, 3H), 8.09 (d, J = 8.8 Hz, 2H), 7.98-7.90 (m, 2H), 7.73 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H), 7.31-7.26 (m, 2H), 7.18-7.14 (m, 2H), 7.10 (d, J = 8.8 Hz, 2H), 4.59-4.50 (m, 1H), 3.47-3.40 (m, 1H), 3.36-3.28 (m, 1H).

Scheme 19

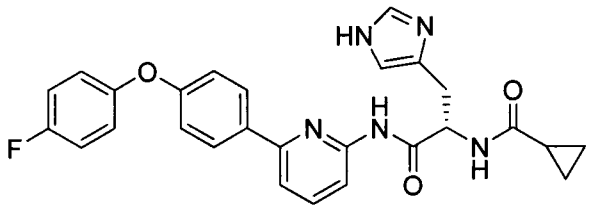


31 32

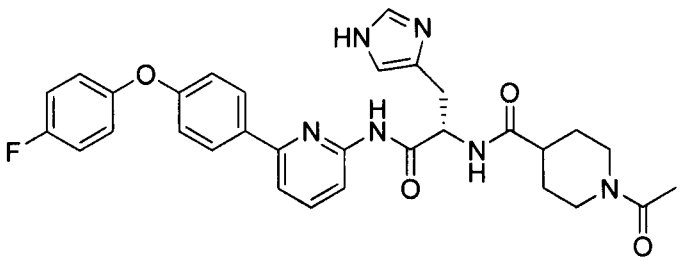
Compound **32**: To a suspension of compound **31** (0.10 mmol) in DCM (1 mL) and acetonitrile (1 mL) with iPr_2NEt (0.058 mL, 0.33 mmol) was added acetyl chloride (0.009 mL, 0.13 mmol, Aldrich). After 2 hours more acetyl chloride (0.007 mL, 0.10 mmol) was added. After stirring overnight the reaction was quenched with MeOH and evaporated *in*

vacuo. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled and treated with Amberlite IRA-400(OH) resin to remove the TFA. The solution was frozen and lyophilized to give (S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide (0.028 g, 0.061 mmol, 61% yield, LC/MS: m/z = 460.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 13.77 (br s, 1H), 10.44 (s, 1H), 8.60 (s, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.25-7.16 (m, 3 H), 7.12-7.06 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.84-4.76 (m, 1H), 3.11-3.04 (m, 1H), 2.98-2.88 (m, 1H), 1.81 (s, 3H).

Using the chemistry described above, the following compounds were prepared:

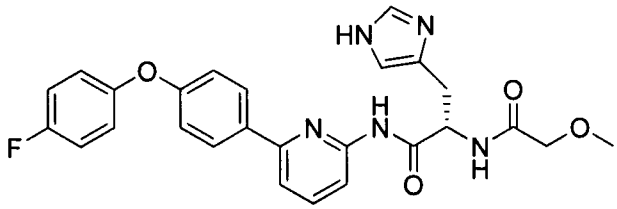


Compound **33**: (S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide: LC/MS: m/z = 486.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.04 (br s, 1H), 10.46 (s, 1H), 8.91 (s, 1H), 8.56 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.4 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.33 (s, 1H), 7.25-7.17 (m, 2H), 7.12-7.06 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.91-4.82 (m, 1H), 3.16-3.09 (m, 1H), 3.01-2.93 (m, 1H), 1.66-1.58 (m, 1H), 0.67-0.55 (m, 4H).



Compound **34**: (S)-1-acetyl-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)piperidine-4-carboxamide: LC/MS: m/z = 571.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.02 (br s, 1H), 10.43 (d, J = 4.4 Hz, 1H), 8.91 (s, 1H), 8.30-8.24 (m, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.86-7.77 (m, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.25-7.17 (m, 2H), 7.12-7.06 (m, 2H), 7.02 (d, J =

8.8 Hz, 2H), 4.87-4.78 (m, 1H), 4.28-4.18 (m, 1H), 3.76-3.66 (m, 1H), 3.18-3.10 (m, 1H), 3.00-2.90 (m, 2H), 2.54-2.35 (m, 2H), 1.91 (s, 3H), 1.67-1.51 (m, 2H), 1.46-1.12 (m, 2H).

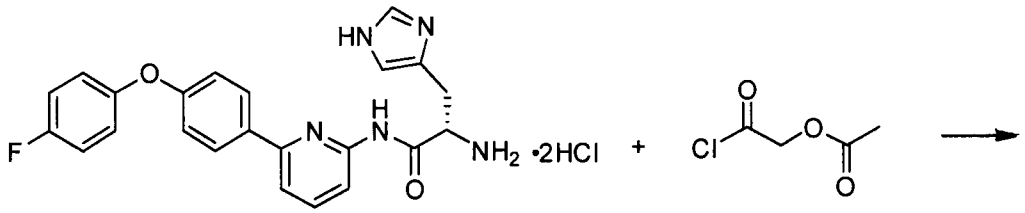


Compound **35**: (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(2-methoxyacetamido): LC/MS: m/z = 490.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.15 (br s, 1H), 10.51 (s, 1H), 8.92 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.84-7.78 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.26-7.17 (m, 2H), 7.13-7.05 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.92-4.83 (m, 1H), 3.80 (s, 2H), 3.23 (s, 3H), 3.22-3.15 (m, 1H), 3.13-3.05 (m, 1H).

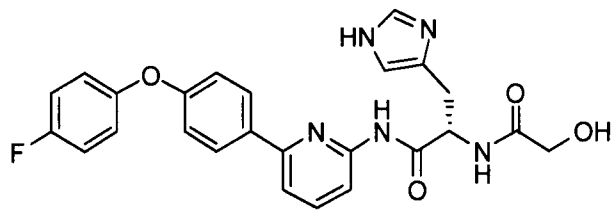
EXAMPLE 10

Synthesis of (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy acetamido)-3-(1H-imidazol-4-yl)propanamide

Scheme 20



31

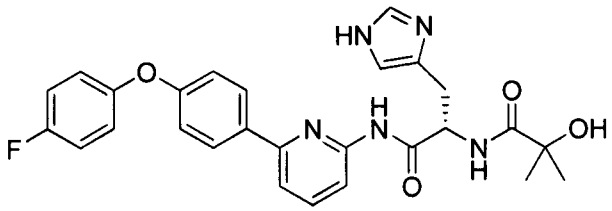


36

Compound **36**: To a suspension of compound **31** (0.10 mmol) in DCM (1 mL) and acetonitrile (1 mL) with iPr_2NEt (0.058 mL, 0.33 mmol) was added 2-chloro-2-oxoethyl acetate (0.011 mL, 0.12 mmol, Aldrich). After stirring overnight the reaction was quenched

with MeOH and evaporated *in vacuo*. The residue was dissolved in 5:1 THF/water (2 mL) and LiOH•H_2O (0.008 g, 0.19 mmol, Aldrich) was added. After 2 hours 1N NaOH (1.0 mL, 1.0 mmol) was added. After 1 hour the reaction was partitioned between DCM and water. The organic layer was separated and evaporated *in vacuo*. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled and treated with Amberlite IRA-400(OH) resin to remove the TFA. The solution was frozen and lyophilized to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-3-(1H-imidazol-4-yl)propanamide (0.007 g, 0.015 mmol, 15% yield, LC/MS: m/z = 476.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.10 (br s, 1H), 10.52 (s, 1H), 8.92 (d, J = 1.2 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.33 (s, 1H), 7.25-7.18 (m, 2H), 7.12-7.06 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.57 (br s, 1H), 4.91-4.83 (m, 1H), 3.80 (s, 2H), 3.24-3.15 (m, 1H), 3.14-3.06 (m, 1H).

Using the chemistry described above the following compound was prepared substituting 1-chloro-2-methyl-1-oxopropan-2-yl acetate as the acid chloride component:

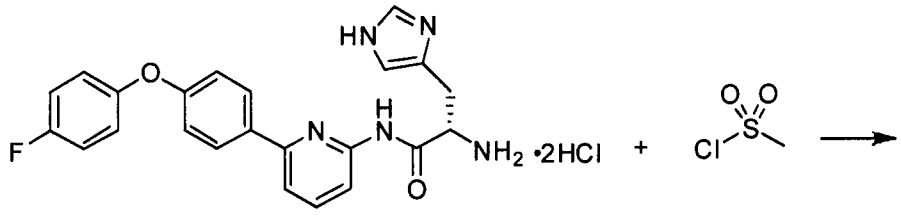


Compound **37**: (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1H-imidazol-4-yl)propanamide: LC/MS: m/z = 504.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.16 (br s, 1H), 10.46 (s, 1H), 8.92 (s, 1H), 8.05-7.99 (m, 3H), 7.91 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.31 (s, 1H), 7.25-7.18 (m, 2H), 7.12-7.06 (m, 2H), 7.03 (d, J = 8.8 Hz, 2H), 5.53 (br s, 1H), 4.84-4.76 (m, 1H), 3.24-3.16 (m, 1H), 3.14-3.05 (m, 1H), 1.17 (s, 3H), 1.11 (s, 3H).

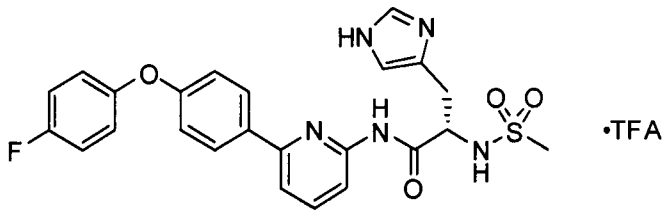
EXAMPLE 11

Synthesis of (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(methylsulfonamido)propanamide

Scheme 21



31



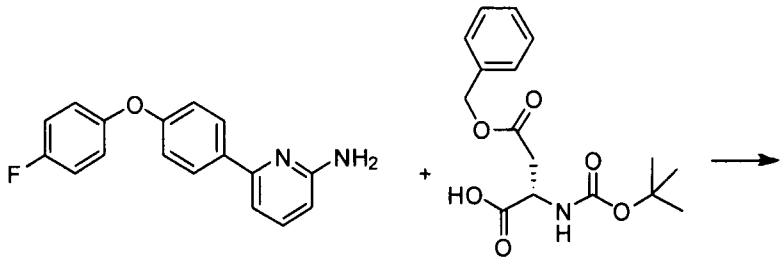
38

Compound **38**: To a solution of compound **31** (0.098 g, 0.20 mmol) in 1:1 DCM/pyridine (2.5 mL) was added the methanesulfonyl chloride (0.016 mL, 0.21 mmol). After 2 hours additional methanesulfonyl chloride (0.007 mL, 0.09 mmol) was added. After 20 minutes the reaction was quenched with MeOH and evaporated *in vacuo*. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled, frozen and lyophilized to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(methylsulfonamido)propanamide as the trifluoroacetate salt as a light tan solid (0.011 g, 0.018 mmol, 9% yield, LC/MS: m/z = 496.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 14.08 (br s, 2H), 10.52 (s, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.86-7.79 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.25-7.18 (m, 2H), 7.12-7.06 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.50-4.41 (m, 1H), 3.18-3.10 (m, 1H), 3.02-2.93 (m, 1H), 2.82 (s, 3H).

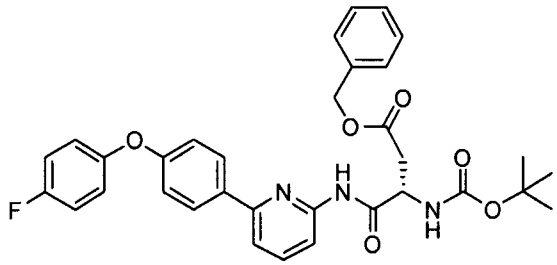
EXAMPLE 12

Synthesis of give (S)-tert-butyl(1-amino-4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate and (S)-tert-butyl(4-amino-1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate

Scheme 22



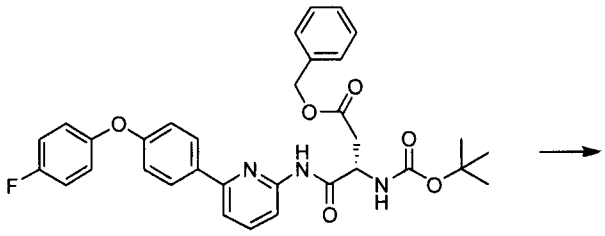
2



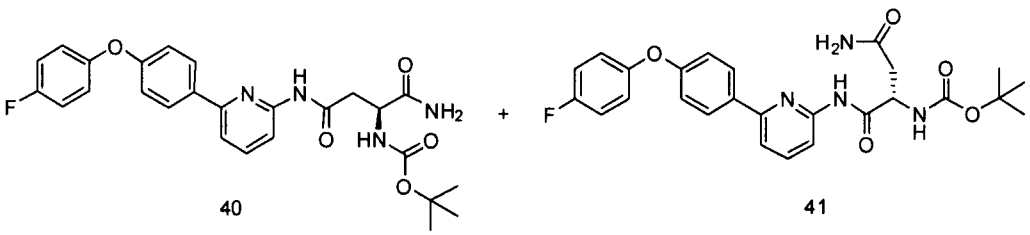
39

Compound **39**: To a solution of (S)-4-(benzyloxy)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoic acid (1.424 g, 4.40 mmol, Advanced ChemTech) in DMF (30 mL) was added iPr_2NEt (0.75 mL, 4.31 mmol) and HATU (1.680 g, 4.42 mmol). The reaction was stirred for 2 minutes then a solution of compound **2** (1.124 g, 4.01 mmol) in DMF (10 mL) with iPr_2NEt (0.75 mL, 4.31 mmol) was added. After stirring overnight the reaction was diluted with 400 mL water. The reaction mixture was extracted three times with 100 mL Et_2O. The combined organic layers were washed once with 50 mL brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with 0-40% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-benzyl 3-((tert-butoxycarbonyl)amino)-4-((6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)amino)-4-oxobutanoate (1.413 g, 2.41 mmol, 60% yield, LC/MS: m/z = 586.2 $[M+H]^+$).

Scheme 23



39



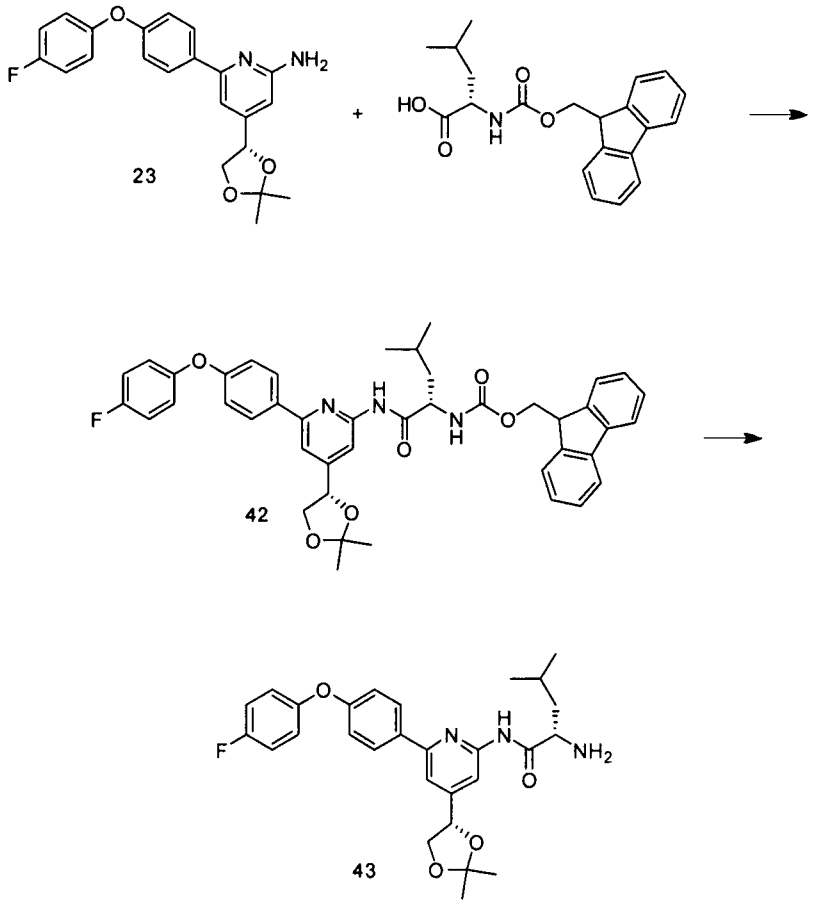
40 41

Compounds **40** and **41**: To compound **39** (1.408 g, 2.40 mmol) was added 7M NH_3 in MeOH (25 mL, Aldrich). After 2 days the reaction mixture was diluted with 100 mL hexanes and 100 mL 1.74 M aqueous HCl was added. The solid that formed was collected and rinsed with water. The solid was repeatedly chromatographed over silica gel eluting with 50-100% EtOAc in hexanes to separate the two close running products. The product fractions were separately collected and concentrated *in vacuo*. The residues were each triturated with 2 mL EtOAc then dried under vacuum at 50°C to give (S)-tert-butyl (1-amino-4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate as a white powder (0.077 g, 0.16 mmol, 6% yield, LC/MS: m/z = 495.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.40 (s, 1H), 8.09 (s, J = 8.8 Hz, 2H), 8.00 (br d, J = 7.6 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.32-7.24 (m, 3H), 7.19-7.13 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.05 (br s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.37-4.29 (m, 1H), 2.84-2.63 (m, 2H), 1.35 (s, 9H); and (S)-tert-butyl (4-amino-1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate as a white powder (0.119 g, 0.24 mmol, 10% yield, LC/MS: m/z = 495.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.26 (s, 1H), 8.09 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.31-7.24 (m, 2H), 7.21-7.13 (m, 3H), 7.08 (d, J = 8.8 Hz, 2H), 6.98 (s, 1H), 4.56-4.48 (m, 1H), 2.62-2.54 (m, 1H), 2.49-2.43 (m, 1H), 1.40 (s, 9H).

EXAMPLE 13

Synthesis of N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide

Scheme 24

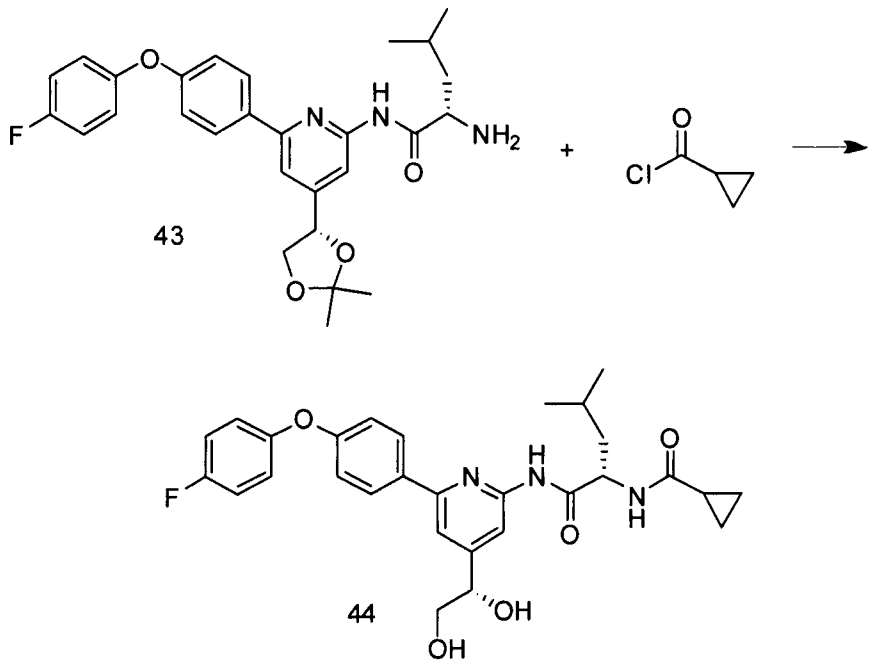


Compound **43**: To a solution of (S)-2-((((9H-fluoren-9-yl)methoxy) carbonyl)amino)-4-methylpentanoic acid (0.407 g, 1.15 mmol, Advanced ChemTech) in DMF (10 mL) was added iPr_2NEt (0.20 mL, 1.15 mmol) and HATU (0.433 g, 1.14 mmol). After stirring for 2 minutes a solution of compound **23** (0.390 g, 1.03 mmol) in DMF (10 mL) with iPr_2NEt (0.20 mL, 1.15 mmol) was added. After stirring for 2 days, a solution of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methylpentanoic acid (0.401 g, 1.13 mmol) in DMF (5 mL) with iPr_2NEt (0.20 mL, 1.15 mmol) and HATU (0.433 g, 1.14 mmol) was prepared and added to the main reaction. After 4 days the reaction was diluted with 250 mL water and solid precipitate (compound **42**) was collected.

Compound **42** was dissolved in DCM (50 mL) and tris-aminoethyl amine (1.54 mL, 10.28 mmol, Aldrich) and DMF (10 mL) were added. After stirring overnight more DMF (10 mL) was added. After stirring overnight the reaction was diluted with 50 mL DCM,

washed successively with 50 mL water/brine, 50 mL pH 5.5 phosphate buffer/brine, and 50 mL brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel eluting with 20-80% EtOAc in hexanes. The product fractions were isolated and evaporated *in vacuo* to give (S)-2-amino-N-(4-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide as a thick yellow oil (0.209 g, 0.42 mmol, 41% yield, LC/MS: m/z = 494.2 $[M+H]^+$).

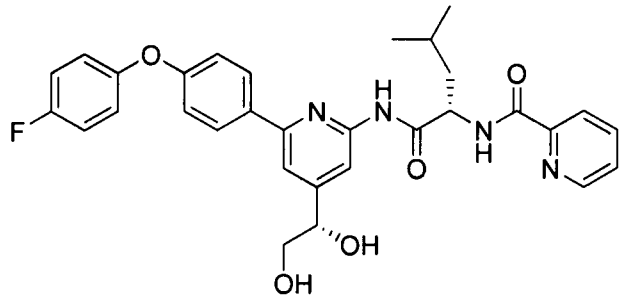
Scheme 25



Compound **44**: To a solution of compound **43** (0.104 g, 0.21 mmol) in DCM (5 mL) was added iPr_2NEt (0.044 mL, 0.25 mmol) and cyclopropanecarbonyl chloride (0.021 mL, 0.23 mmol). After stirring overnight the reaction was concentrated *in vacuo* then dissolved in MeOH (5 mL) and 4N HCl in dioxane (0.5 mL, 2.0 mmol) was added. After stirring overnight the reaction was concentrated *in vacuo*. The residue was chromatographed using reverse-phase HPLC eluting with 20-90% acetonitrile in water, each containing 0.1% TFA. The product fractions were pooled and treated with Amberlite IRA-400(OH) resin to remove the TFA. The solution was frozen and lyophilized to give N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy) phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropane carboxamide (0.033 g, 0.063 mmol, 30% yield, LC/MS: m/z = 522.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.43 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.8 Hz, 2H), 7.97 (s, 1H), 7.50 (s, 1H), 7.24-7.17 (m, 2H), 7.11-7.05 (m, 2H), 7.01 (d, J =

8.8 Hz, 2H), 4.58-4.50 (m, 2H), 3.44 (d, J = 6.0 Hz, 2H), 1.69-1.57 (m, 2H), 1.57-1.40 (m, 2H), 0.86 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.64-0.54 (m, 4H).

Using the chemistry described above the following compound was prepared:

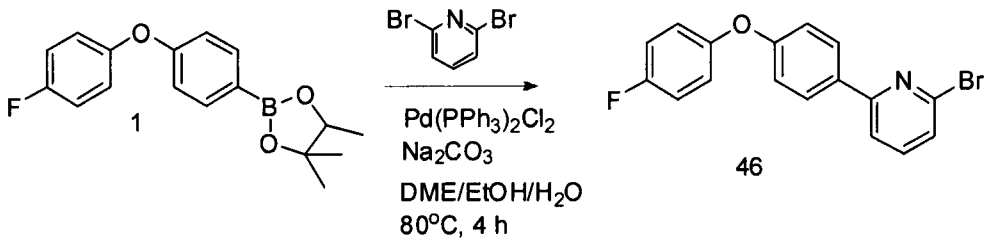


Compound **45**: N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy) phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide: LC/MS: m/z = 559.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 10.64 (s, 1H), 8.78 (d, J = 8.8 Hz, 1H), 8.64 (dt, J = 4.8, 1.2 Hz, 1H), 8.04-7.92 (m, 5H), 7.60-7.56 (m, 1H), 7.51 (s, 1H), 7.25-7.16 (m, 2H), 7.12-7.05 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.87-4.79 (m, 1H), 4.52 (t, J = 5.6 Hz, 1H), 3.44 (d, J = 6.0 Hz, 2H), 1.82-1.71 (m, 1H), 1.67-1.55 (m, 2H), 0.90-0.85 (m, 6H).

EXAMPLE 14

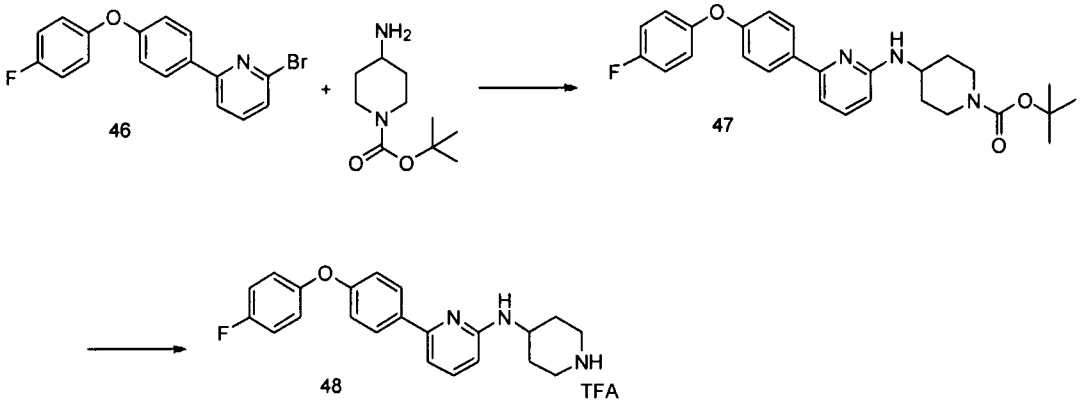
Synthesis of 2-(4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)piperidin-1-yl)acetic acid

Scheme 26



Compound **46**: A 50 mL round bottom flask was charged with compound **1** (1.88 g, 6.0 mmol), 2,6-Dibromopyridine (1.42 g, 6.0 mmol), $Pd(PPh_3)_2Cl_2$ (210 mg, 0.3 mmol), Na_2CO_3 (0.95 g, 9.0 mmol) and DME/EtOH/H_2O (4mL/2mL/4mL). The reaction mixture was purged with argon and then stirred at 80°C under argon for 4 h. The reaction mixture was cooled to room temperature and extracted with EtOAc. The EtOAc was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel using hexanes/EtOAc as the eluent to give compound **46** as white solid (1.55 g, yield 75%) (m/z + H) 345.

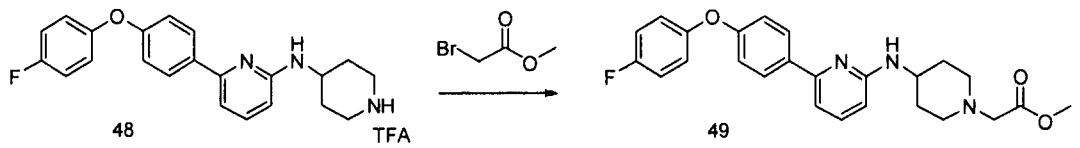
Scheme 27



Compound **48**: A 10 mL reaction flask was charged with compound **2** (100 mg, 0.3 mmol), 4-amino-1-Boc-piperidine (Aldrich, 200 mg, 0.6 mmol), $Pd_2(dba)_3$ (21 mg, 0.036 mmol), NaOBu-t (87 mg, 0.88 mmol), BINAP (29 mg, 0.14 mmol) and dioxane (3 mL). The reaction mixture was purged with argon and stirred at 100°C for 2 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The EtOAc was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel using hexanes/EtOAc as the eluent to give compound **47** as white solid (92 mg, yield 75%) (m/z + H) 407.

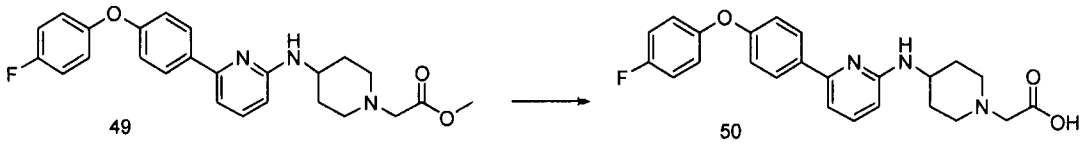
Compound **47** was dissolved in a mixture of DCM/TFA (2mL/2mL) and stirred at room temperature for 1 h. The solvent was removed and the residue was re-dissolved in DCM and concentrated to compound **48** as a TFA salt which was used for next step without further purification.

Scheme 28



Compound **49**: A 50 mL round bottom flask was charged with compound **48** (238 mg, 0.50 mmol), methyl bromoacetate (153 mg g, 1.0 mmol), K_2CO_3 (138 mg, 1 mmol) and DMF (2 mL). The mixture was stirred at 70°C for 2 h. The reaction mixture was cooled to room temperature and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel using hexanes/EtOAc as the eluent to give compound **49** as white solid (206 mg, yield 95%) (m/z + H) 436.

Scheme 29

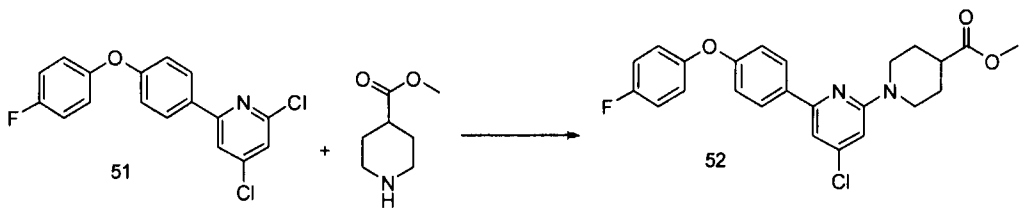


Compound **50**: A 25 mL round bottom flask was charged with compound **49** (100 mg, 0.23 mmol), MeOH (2 mL) and NaOH (6N, 0.038 mL). The reaction mixture was stirred at 50°C for 1 hr and then cooled to 0°C using an ice bath. The pH of the mixture was adjusted to pH 1 using 6M HCl. The precipitate was collected and dried to give 2-(4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)piperidin-1-yl)acetic acid as a white solid (80 mg, yield 95%). LC/MS: m/z = 422 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 7.9 (d, 2H), 7.4 (m, 1H), 6.8 -7.1 (m, 7H), 6.4 (d, 1H), 4.2 (br, 1H), 2.8-3.6 (m, 6H), 1.4-2.3 (m, 4H).

EXAMPLE 15

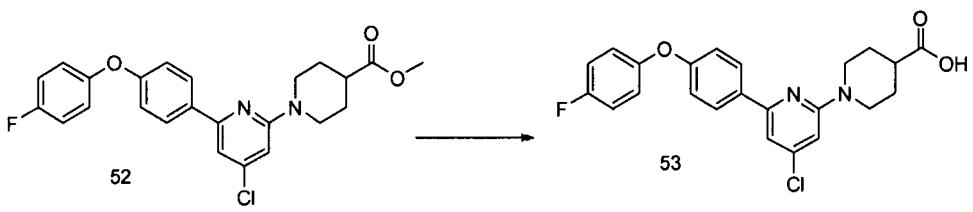
Synthesis of 1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)piperidine-4-carboxylic acid

Scheme 30



Compound **52**: A 5 mL microwavable vial was charged with compound **51** (100 mg, 0.3 mmol), methyl piperidine-4-carboxylate (Aldrich, 43 mg, 0.3 mmol), DIEA (0.1 mL) and DMSO (1.0 mL). The reaction mixture was purged with argon and then stirred at 160°C in the microwave for 20 minutes. The reaction mixture was cooled to room temperature and diluted with EtOAc. The EtOAc was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to flash column chromatography on silica gel using hexanes/EtOAc as the eluent to give compound **52** as white solid (80 mg, yield 61%) (m/z + H) 441.

Scheme 31

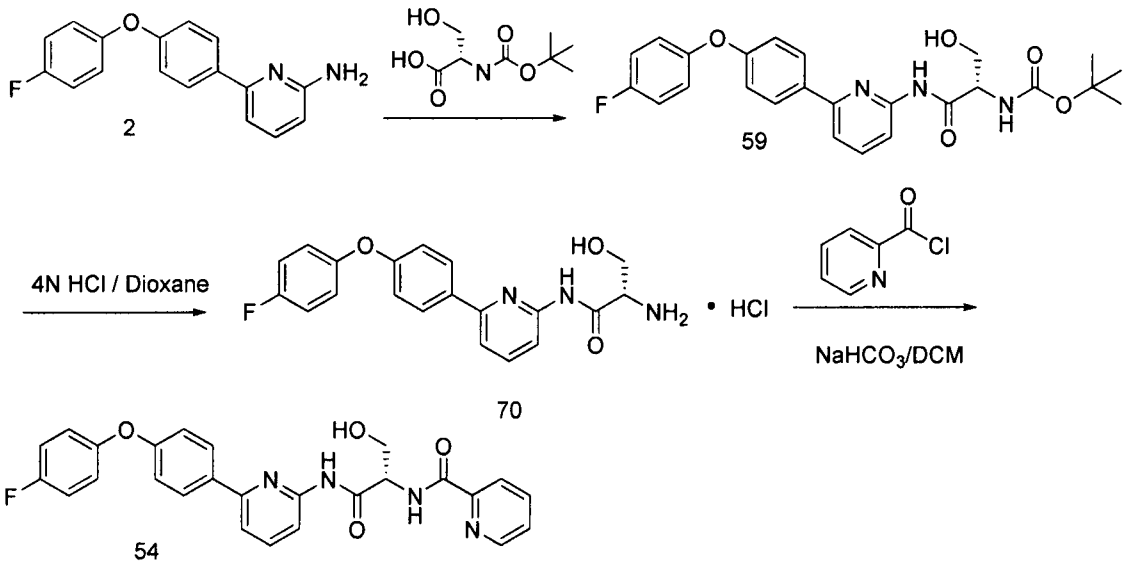


Compound **53**: A 25 mL round bottom flask was charged with compound **52** (80 mg, 0.18 mmol), MeOH (2 mL) and NaOH (6N, 0.050 mL). The reaction mixture was stirred at 50°C for 1 h and then cooled to 0°C using an ice bath. The pH of the mixture was adjusted to pH 1 using 6M HCl. The precipitate was collected and dried to give 1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)piperidine-4-carboxylic acid as a white solid (75 mg, yield 98%). LC/MS: m/z = 427 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 7.9 (d, 2H), 6.8 -7.1 (m, 7H), 6.7 (m, 1H), 3.8 (m, 2H); 3.1 (m, 2H); 2.5 (m, 1H); 1.6-2.1 (m, 4H).

EXAMPLE 16

Synthesis of (S)-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-ureido-propionamide

Scheme 32

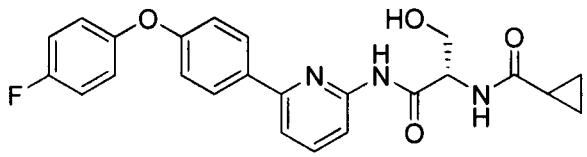


Compound **59**: A mixture of Boc-Ser-OH (purchased from Sigma-Aldrich, 2.7 g, 9.6 mmol) and HATU (purchased from GenScript Corporation, 5.6 g, 14.9 mmol) in a mixture of THF/DCM (160 mL) was stirred for 1 h and compound **2** (2.7 g, 9.6 mmol) was added thereto. The reaction mixture was stirred overnight at room temperature and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with water. The organic phase

was dried over anhydrous Na_2SO_4 and concentrated to give a semi-solid residue. The crude product was purified by column chromatography (silica gel, 30% EtOAc in hexane) to give ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-carbamic acid tert-butyl ester as a white solid (3.3 g, 73% yield). LC/MS: *m/z* = 468 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.10-8.03 (m, 3H), 7.82 (t, J = 8.1 Hz, 1H), 7.59 (d, J = 7.89 Hz, 1H), 7.04-7.17 (m, 6H), 7.58-7.64 (m, 1H), 7.37-7.44 (s, 1H), 7.03-7.21 (m, 6H), 4.37 (br, s, 1H). 3.83-3.93 (m, 2H), 2.94-3.03 (dd, J = 9.87, 14.03 Hz, 1H), 1.49 (s, 9H).

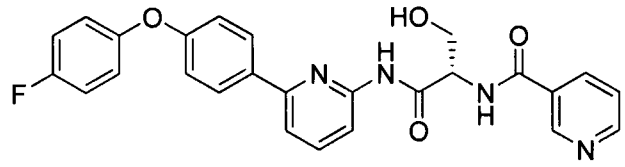
Compound **70**: To compound **59** (2.5 g, 5.3 mmol) in dry dioxane (5 mL) was added 4.0N HCl in dioxane (14 mL, 53 mmol) at 0°C. The reaction mixture was stirred for 2 h at room temperature. After the reaction was complete, the solvent was evaporated. The crude residue was suspended in diethyl ether and filtered (this process repeated for 3 times) to give (S)-2-amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pridin-2-yl}-3-hydroxy-propionamide as the HCl salt (1.9 g, 88% yield). LC/MS: *m/z* = 368 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.17 (d, J = 8.11 Hz, 1H), 8.05 (t, J = 8.77 Hz, 1H), 7.83 (t, J = 7.89 Hz, 1H), 7.59 (d, J = 8.33 Hz, 1H), 7.04-7.18 (m, 6H), 3.84 (m, 2H), 3.65 (t, J = 5.04 Hz, 1H).

Compound **54**: To a suspension of compound **70** (as the HCl salt) (1.0 eq.) in 1:1 mixture of saturated $NaHCO_3$ and dichloromethane was added 2-pyridinecarboxylicacid chloride (93.0 mg, 0.52 mmol) at 0°C. The suspension was stirred at room temperature overnight. After the reaction was complete, the organic layer was separated and aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated to give oily residue which was purified by preparative TLC to give pyridine-2-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide. (119 mg, 53% yield). LC/MS: *m/z* = 473 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.71 (s, 1H), 8.88 (d, J = 7.67 Hz, 1H), 8.72 (d, J = 4.82 Hz, 1H), 8.01-8.17 (m, 6H), 7.87 (t, J = 8.10 Hz, 1H), 7.63-7.68 (m, 2H), 7.04-7.34 (m, 6H), 5.29 (t, J = 5.7 Hz, 1H), 4.86 (br, s, 1H), 3.93-3.99 (m, 1H), 3.80-3.87 (m, 1H).

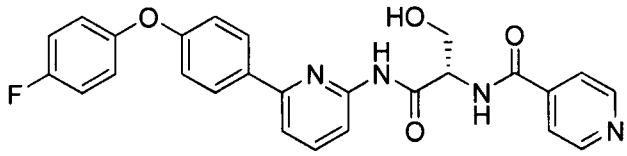


Compound **55**: In similar fashion, compound **70** (as the HCl salt) (32 mg, 0.08 mmol) was treated with cyclopropylcarboxylicacid chloride (93.0 mg, 0.09 mmol) to give cyclopropanecarboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-

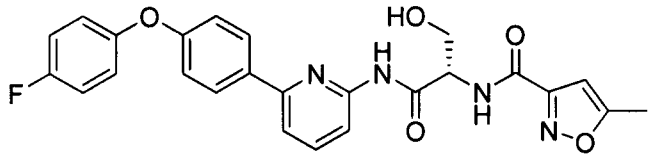
ylcarbamoyl}-2-hydroxy-ethyl)-amide (21 mg, 61% yield). LC/MS: *m/z* = 436 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.04-8.10 (m, 3H), 7.82 (t, J = 8.11 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.0-7.19 (m, 6H), 4.68 (br, s, 1H), 3.86-3.98 (m, 2H), 1.73-1.82 (m, 1H), 0.89-0.94 (m, 2H), 0.80-0.87 (m, 2H).



Compound **56**: In similar fashion, compound **70** (as the HCl salt) (73 mg, 0.18 mmol) was treated with 3-pyridinecarboxylicacid chloride (52.0 mg, 0.29 mmol) to give N-((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-nicotinamide (53.4 mg, 62% yield). LC/MS: *m/z* = 473 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.59 (s, 1H), 9.09 (s, 1H), 8.72-8.82 (m, 2H), 8.27 (d, J = 7.45 Hz, 1H), 8.11 (d, J = 8.55 Hz, 2H), 8.02 (d, J = 7.89 Hz, 1H), 7.86 (t, J = 7.89 Hz, 1H), 7.65 (d, J = 6.80 Hz, 1H), 7.00-7.30 (m, 6H), 5.19 (br, s, 1H), 4.84 (br, s, 1H), 3.87 (s, 2H).

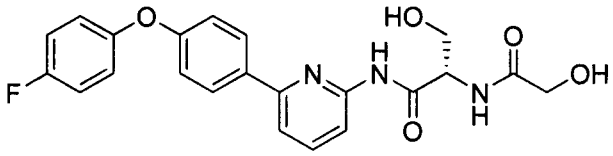


Compound **57**: In similar fashion, compound **70** (as the HCl salt) (30 mg, 0.07 mmol) was treated with 4-pyridinecarboxylicacid chloride (14.5 mg, 0.08 mmol) to give N-((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-isonicotinamide (28 mg, 80% yield). LC/MS: *m/z* = 473 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.62 (s, 1H), 8.82 (d, J = 6.58 Hz, 1H), 8.76 (d, J = 6.14 Hz, 2H), 8.11 (d, J = 8.99 Hz, 2H), 8.01 (d, J = 7.89 Hz, 1H), 7.81-7.89 (m, 3H), 7.65 (d, J = 7.24 Hz, 1H), 7.28 (t, J = 8.55 Hz, 2H), 7.13-7.18 (m, 2H), 7.09 (d, J = 8.99 Hz, 2H), 5.17 (br, s, 1H), 4.83 (br, s, 1H), 3.86 (s, 2H).

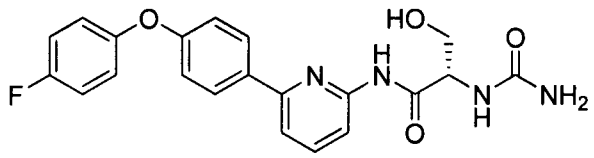


Compound **58**: In similar fashion, compound **70** (as the HCl salt) (90 mg, 0.22 mmol) was treated with 5-methylisoxazole-3-carboxylic acid (35.7 mg, 0.25 mmol) to give 5-methyl-isoxazole-3-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide (68 mg, 64% yield). LC/MS: *m/z* = 477 $[M+H]^+$: ^1H NMR (400 MHz, $CDCl_3$): 9.27 (s, 1H), 8.09 (d, J = 7.23 Hz, 1H), 7.98 (d, J = 7.23 Hz, 1H),

7.91 (d, J = 8.99 Hz, 2H), 7.77 (t, J = 8.11 Hz, 1H), 7.45 (d, J = 7.67 Hz, 1H), 7.01-7.11 (m, 6H), 6.50 (s, 1H), 4.83-4.89 (s, 1H), 4.32 (d, J = 9.41 Hz, 1H), 3.89 (br, s, 1H), 3.28 (br, s, 1H), 2.49 (s, 3H).

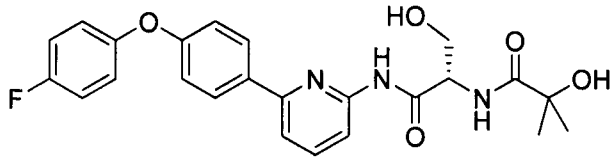


Compound **60**: To a suspension of compound **70** (as the HCl salt) (400 mg, 1.0 mmol) in dry dichloromethane (20 mL) was added HOBt (162 mg, 1.2 mmol) and EDC (229 mg, 1.2 mmol). The reaction mixture was stirred for 30 min at room temperature. Hydroxyacetic acid (76.05 mg, 1.0 mmol) and diisopropylethyl amine (0.2 mL) were added thereto. The reaction mixture was stirred overnight and washed with water. The solvent was evaporated and the residue was purified by preparative TLC (10% MeOH in DCM) to give (S)-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-(2-hydroxy-acetylamino)-propionamide (290 mg, 69% yield). LC/MS: *m/z* = 426 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.55 (s, 1H), 8.10 (d, J = 8.99 Hz, 2H), 8.01 (d, J = 8.33 Hz, 1H), 7.86 (dd, J = 7.89, 16.04 Hz, 2H), 7.65 (d, J = 7.89 Hz, 1H), 7.20-7.31 (m, 2H), 7.13-7.19 (m, 2H), 7.05-7.11 (m, 2H), 5.73 (t, J = 5.38 Hz, 1H), 5.18 (t, J = 5.7 Hz, 1H), 4.62-4.69 (br, s, 1H), 3.89 (d, J = 5.7 Hz, 2H), 3.80-3.86 (m, 1H), 3.67-3.73 (m, 1H).

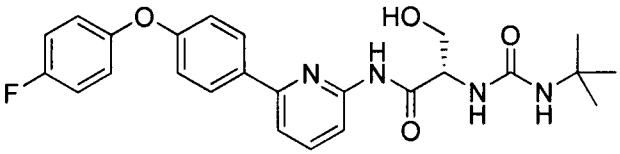


Compound **61**: To a suspension of compound **70** (as the HCl salt) (150 mg, 0.37 mmol) in water (3.7 mL) was added potassium cyanate (90 mg, 1.11 mmol) at 0°C. The reaction mixture was stirred for 3 h at room temperature. Ethyl acetate (10 mL) was added thereto and organic layer was separated. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (silica gel, 7% MeOH in DCM) to give (S)-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-ureido-propionamide (120 mg, 79% yield). LC/MS: *m/z* = 411 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6): 10.24 (s, 1H), 8.10 (d, J = 8.77 Hz, 2H), 8.03 (d, J = 8.11 Hz, 1H), 7.86 (t, J = 7.89 Hz, 1H), 7.64 (d, J = 7.67 Hz, 1H), 7.28 (t, J = 8.55 Hz, 2H), 7.13-7.19 (t, J =

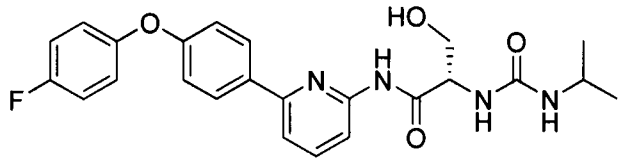
8.55Hz, 2H), 7.09 (d, J = 8.77 Hz, 2H), 6.37 (d, J = 8.11, 1H), 5.80 (s, 2H), 5.07 (t, J = 5.26 Hz, 1H), 4.37-4.44 (br, s, 1H), 3.74-3.80 (m, 1H), 3.57-3.63 (m, 1H).



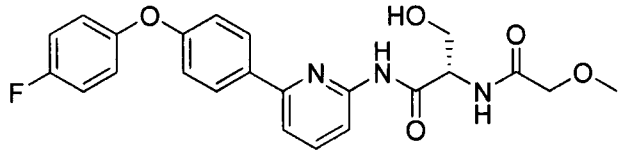
Compound **92**: In a similar fashion, compound **70** (as the HCl salt) (200 mg, 0.50 mmol) was treated with alpha-hydroxyisobutyric acid (52 mg, 0.5 mmol) in the presence of EDC (114 mg, 0.6 mmol), HOBt (81 mg, 0.6 mmol), and DIEA (0.1 mL, 0.5 mmol) in dry DCM. The reaction mixture was stirred for overnight at room temperature. After the work-up, the oily residue was purified by preparative TLC to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxy-2-methylpropanamido)propanamide (125mg, 56%). ^{1}H NMR (400 MHz, CD_3OD): 8.05 (3H, d, J = 8.99 Hz), 8.02-8.07 (2H, m), 7.80 (1H, t, J = 8.10 Hz), 7.57 (6H, d, J = 7.9 Hz), 6.99-7.16 (6H, m), 4.58-4.62 (1H, br), 4.00 (1H, dd, J = 4.6, 11.2 Hz), 3.87 (1H, dd, J = 5.0, 11.2 Hz), 1.41 (6H, d, J = 5.3 Hz). LC/MS: *m/z* = 454.0 $[M+H]^+$.



Compound **89**: In a similar fashion, compound **70** (as the HCl salt) (25 mg, 0.50 mmol) in a mixture of DCM/sat.$NaHCO_3$ (1:1, 3 mL) was treated with t-butyl isocyanate (0.04 mL, 0.19 mmol) and stirred for 2 h at 0°C. After the reaction was complete, the mixture was diluted with DCM and extracted with ethyl acetate. The organic phase was dried with anhydrous Na_2CO_3 and concentrated. The residue was purified by preparative TLC (DCM : MeOH = 1:10) to give (S)-2-(3-(tert-butyl)ureido)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxypropanamide (15 mg, 54%). ^{1}H-NMR (400 MHz, CD_3OD): 7.86 (1H, d, J = 8.30 Hz), 7.82 (2H, d, J = 8.70 Hz), 7.60 (1H, t, J = 8.10 Hz), 7.36 (1H, d, J = 7.6 Hz), 6.79-6.97 (6H, m), 6.07 (1H, br), 4.21 (1H, t, d = 4.6Hz), 3.73 (1H, dd, J = 4.6, 11.0 Hz), 3.57 (1H, dd, J = 5.0, 11.1 Hz), 1.41 (9H, s). LC/MS: *m/z* = 467.1 $[M+H]^+$.



Compound **91**: In a similar fashion, compound **70** (as the HCl salt) (200 mg, 0.5 mmol) in a mixture of DCM/sat. $NaHCO_3$ (1:1, 10 mL) was treated with isopropyl isocyanate (127.5 mg, 1.5 mmol) and stirred for overnight at room temperature. After the work up, the crude residue was purified by preparative TLC (DCM: MeOH = 1:10) to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(3-isopropylureido)propanamide (153 mg, 68%). ^{1}H-NMR (400 MHz, CD_3OD): 8.09 (1H, d, J = 8.30 Hz), 8.05 (2H, d, J = 9.05 Hz), 7.82 (1H, t, J = 7.7 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 7.67Hz), 7.02-7.19 (6H, m), 4.49 (1H, t, J = 4.6Hz), 4.0 (1H, dd, J = 4.6, 11.0 Hz), 3.57-3.88 (2H, m), 3.33 (6H,m). LC/MS: *m/z* = 453.1 $[M+H]^+$.

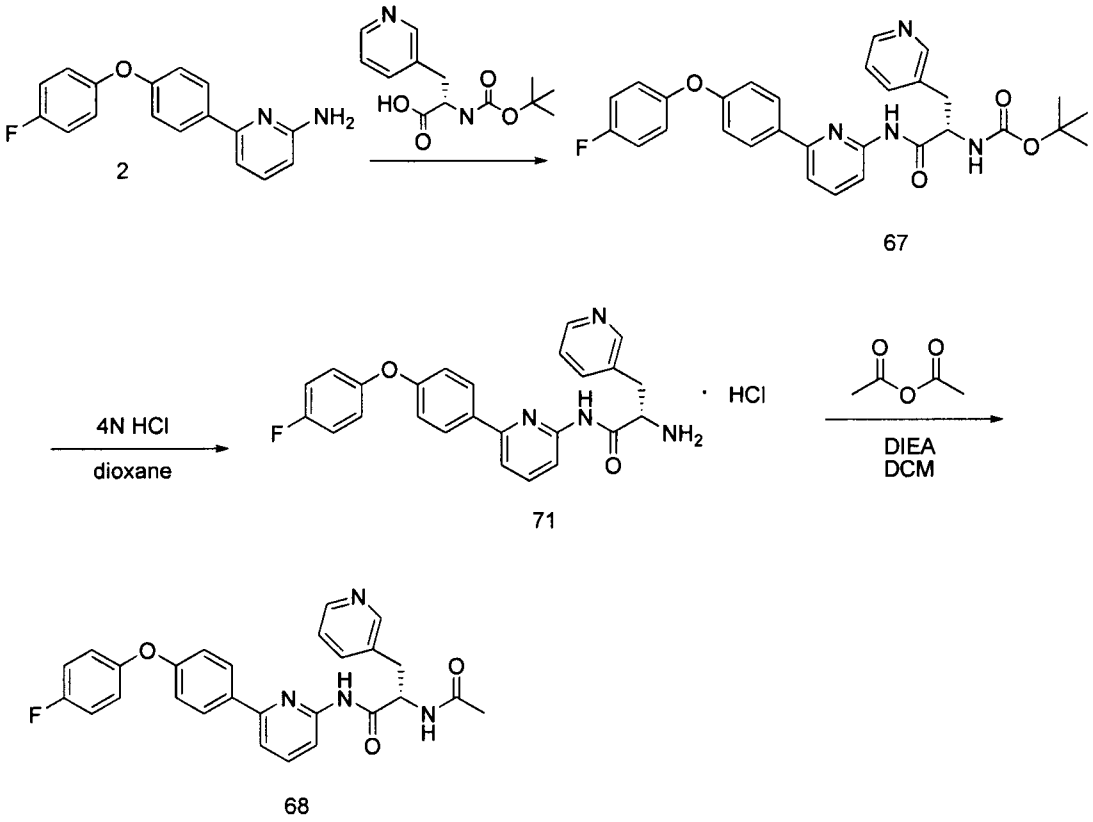


Compound **93**: In a similar fashion, compound **70** (as the HCl salt) (100 mg, 0.25 mmol) was treated with methoxyacetic acid (0.02 mL, 0.25 mmol) in the presence of HATU (94 mg, 0.25 mmol) and DIEA (0.1 mL, 0.5 mmol) in a mixture of DCM/THF (5 mL). The reaction mixture was stirred overnight at room temperature. After the work-up, the oily residue was purified by preparative TLC to give (S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-methoxy-acetamido)propanamide (109 mg, 56%). ^{1}H NMR (400 MHz, CD_3OD): 8.06 (3H, d, J = 9.00 Hz), 7.83 (1H, t, J = 7.60 Hz), 7.60 (1H, d, J = 7.67 Hz), 7.03-7.19 (6H, m), 4.74 (1H, br), 4.01 (2H, s), 3.98 (1H, d, J = 4.60 Hz), 3.91 (1H, dd, J = 5.0, 11.0 Hz), 3.50 (3H, s). LC/MS: *m/z* = 440.1 $[M+H]^+$.

EXAMPLE 17

Synthesis of (S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide

Scheme 33



Compound **67**: A mixture of Boc-3-(3-pyridyl)-Ala-OH (purchased from Sigma-Aldrich, 1.0 g, 3.76 mmol) and EDC (860 mg, 4.5 mmol), HOBt (607.5 mg, 4.5 mmol) in DCM (100 mL) was stirred for 30 min and compound **2** (1.05 g, 3.75 mmol) was added thereto. After the reaction was complete, water was added. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to give pale yellow residue. The crude residue was purified by column chromatography (silica gel, 5% MeOH in DCM) to give ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-pyridin-3-yl-ethyl)-carbamic acid tert-butyl ester (1.0 g, 51% yield). LC/MS: *m/z* = 529 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.51 (s, 1H), 8.42 (s, 1H), 8.06 (d, J = 8.99 Hz, 3H), 7.80-7.90 (m, 2H), 7.58-7.64 (m, 1H), 7.37-7.44 (s, 1H), 7.03-7.21 (m, 6H), 4.56-4.65 (br, s, 1H). 3.24-3.30 (m, 1H), 2.94-3.03 (dd, J = 9.87, 14.03 Hz, 1H), 1.39 (s, 9H).

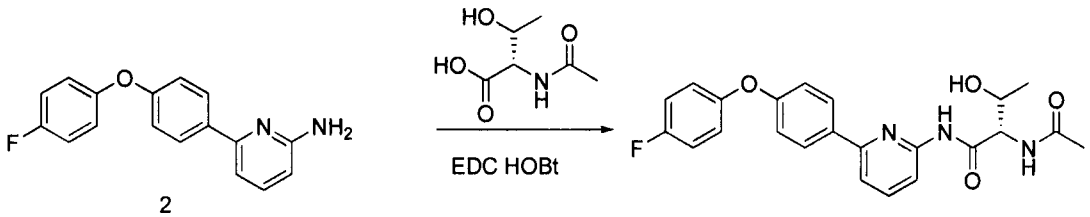
Compound **71**: To compound **67** (250 mg, 0.47 mmol) in dioxane was added 4.0N HCl in dioxane (3 mL). The reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was washed with diethyl ether several times to give (S)-2-amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide as the HCl salt (140 mg, 69% yield) which was used for the next step without further purification. LC/MS: *m/z* = 429 $[M+H]^+$.

Compound **68**: A suspension of compound **71** (as the HCl salt) (200 mg, 0.43 mmol) in dry DCM (8.6 mL) was cooled to 0°C under a N_2 atmosphere and DIEA (0.17 mL, 0.95 mmol) and acetic anhydride (0.09 mL, 0.86 mmol) were added. The reaction mixture was allowed to stir overnight at the room temperature and the solvent was evaporated. The crude product was purified by preparative TLC (10% MeOH in DCM) and then recrystallized (30% EtOAc in hexane) to give (S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide as a white solid (120 mg, 59% yield). LC/MS: *m/z* = 471 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 8.50 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.05 (m, 3H), 7.70-7.86 (m, 2H), 7.58 (d, J = 7.67 Hz, 1H), 7.36-7.41 (m, 1H), 7.01-7.41 (m, 6H), 3.25-3.31 (m, 1H), 3.01-3.08 (m, 1H), 1.96 (s, 3H).

EXAMPLE 18

Synthesis of (S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-butyramide

Scheme 34



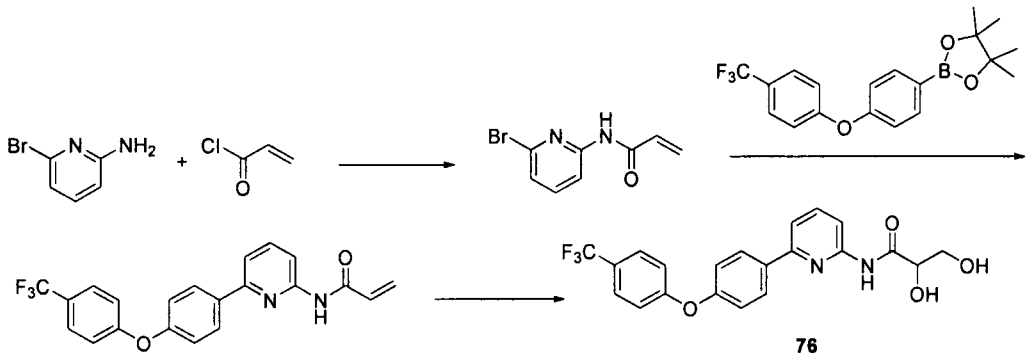
2 69

Compound **69**: A mixture of AcThr-OH (purchased from Sigma-Aldrich, 250 mg, 1.6 mmol) and HATU (purchased from GenScript Corporation, 303 mg, 0.8 mmol) in a mixture of THF/DCM (60 mL) was stirred for 30 min and compound **2** (448 mg, 1.6 mmol) was added thereto. The mixture was stirred overnight at room temperature and then the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give oily residue. The crude residue was purified by preparative TLC (10% MeOH in DCM) to give (S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-butyramide as a white solid (120 mg, 32% yield). LC/MS: *m/z* = 424 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD): 7.99-8.07 (m, 3H), 7.80 (t, J = 8.07 Hz, 1H), 7.56 (d, J = 7.34 Hz, 1H), 7.01-7.16 (m, 6H), 4.57 (s, 1H), 4.25-4.29 (m, 1H). 2.09 (s, 3H), 1.24 (d, J = 6.60 Hz, 3H).

EXAMPLE 19

Synthesis of 2,3-dihydroxy-N-(6-(4-(4-(trifluoromethyl)phenoxy)phenyl) pyridin-2-yl)propanamide

Scheme 35



76

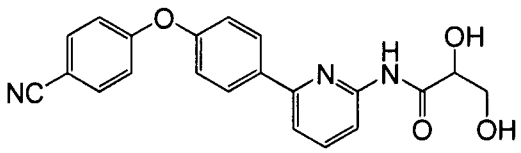
2-Amino-6-bromopyridine (5 g, 0.028 mol) was added to 70 mL of dichloromethane in a 100 mL 3-neck round-bottom flask. Triethylamine (4.0 mL, 0.028 mole) was added and the mixture cooled to 0-5°C with an ice/water bath. At this temperature acryloyl chloride (2.6 g, 0.028 mole) was added drop wise. After complete addition the reaction mixture was allowed to reach room temperature and stirred overnight at room temperature under nitrogen atmosphere. TLC after 16 h indicated that ~10% starting material remained unreacted. Water was added (25mL) and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by 60-120 mesh silica gel column chromatography using 0-10% ethyl acetate heptane as eluent to give 5.1 g (78%) N-(6-bromopyridin-2-yl)acrylamide.

4,4,5,5-tetramethyl-2-(4-(4-(trifluoromethyl)phenoxy)phenyl)-1,3,2-dioxaborolane (1.76 g, 4.8 mmol) and N-(6-bromopyridin-2-yl)acrylamide (1.0 g, 4.4 mmol) were added to 15 mL of THF in a 50 mL 3-neck round bottom flask under nitrogen atmosphere. $Pd(dppf)Cl_2$ (105 mg, 0.14 mmol) and TBAF (9.0 mL, 1M in THF, 9 mmol) were added and the reaction mixture was stirred at 60°C for 16 h. TLC indicated that ~5-10% starting material remained unreacted. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product, which was purified by 230-400 mesh silica gel column chromatography using 0-15% ethyl acetate as eluent to give N-(6-(4-(4-

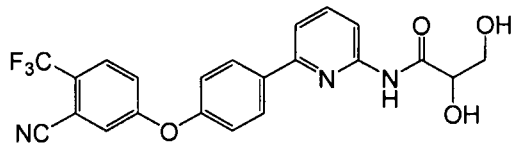
(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)acrylamide as a gummy solid). Trituration with hexane gave a free flowing solid 0.7 g (41%).

N-(6-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)acrylamide (0.39 g, 1 mmol) was suspended in a mixture of 8 mL of acetone and 2 mL of water in a 50 mL 3-neck round bottom flask. The reaction mixture was cooled to 0-10°C with an ice/water bath. At this temperature, NMO (145 mg, 1.24 mmol) and OsO_4 (14 mg, 0.059 mmol) were added and the reaction mixture was stirred at the same temperature for 6 h. TLC indicated that the reaction was complete. The reaction mixture was diluted with ethyl acetate and the resulting solution washed with aqueous sodium bisulfite and brine and dried over sodium sulfate. Evaporation under reduced pressure yielded the crude product, which was purified 60-120 mesh silica gel chromatography using 0-20% ethyl acetate: heptane to yield the desired compound as a thick oily solid which was triturated with hexane to give 180 mg (43%) 2,3-dihydroxy-N-(6-(4-(4-(trifluoromethyl) phenoxy)phenyl)pyridin-2-yl)propanamide (Compound **76**) as a free flowing solid. LC/MS: *m/z* = 419.3 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 9.62 (1 H, s), 8.25-8.00 (3 H, m), 7.95 (1 H, m), 7.80-7.70 (3 H, m), 7.30-7.25 (4 H, m), 6.06 (1 H, s), 4.92 (1 H, m), 4.17-4.12 (1 H, m), 3.69-3.64 (2 H, m).

Using the synthetic methodology described above, the following compounds were prepared:

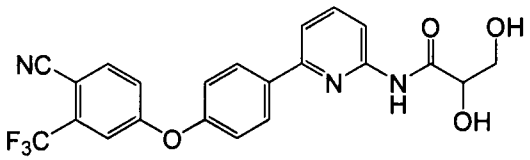


N-(6-(4-(4-cyanophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide (Compound **73**): LC/MS: *m/z* = 376.2 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 9.60 (1 H, s), 8.22-8.12 (2 H, m), 8.12-8.05 (1 H, m), 7.95-7.82 (3 H, m), 7.75-7.70 (1 H, m), 7.30-7.17 (4 H, m), 6.07-6.02 (1 H, m), 4.92-4.87 (1 H, m), 4.17-4.12 (1 H, m), 3.67-3.62 (2 H, m).

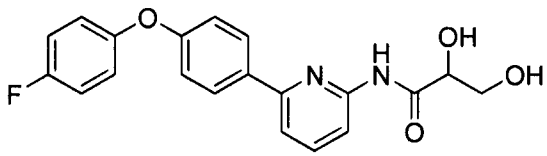


N-(6-(4-(3-cyano-4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide (Compound **74**): LC/MS: *m/z* = 4444.3 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 9.62 (1 H, s), 8.25-8.15 (2 H, m), 8.15-8.05 (1 H, m), 8.05-7.85 (3 H, m),

7.80-7.70 (1 H, m), 7.38-7.22 (2 H, m), 6.07-6.02 (1 H, m), 4.90-4.85 (1 H, m), 4.17-4.12 (1 H, m), 3.67-3.62 (2 H, m).



N-(6-(4-(4-cyano-3-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide (Compound **75**): LC/MS: *m/z* = 4444.3 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 9.62 (1 H, s), 8.27-8.13 (3 H, m), 8.13-8.08 (1 H, m), 7.98-7.90 (1 H, m), 7.76-7.72 (1 H, m), 7.65-7.60 (1 H, m), 7.45-7.38 (1 H, m), 7.38-7.30 (1 H, m), 6.10-6.03 (1 H, m), 4.90-4.85 (1 H, m), 4.17-4.12 (1 H, m), 3.67-3.62 (2 H, m).

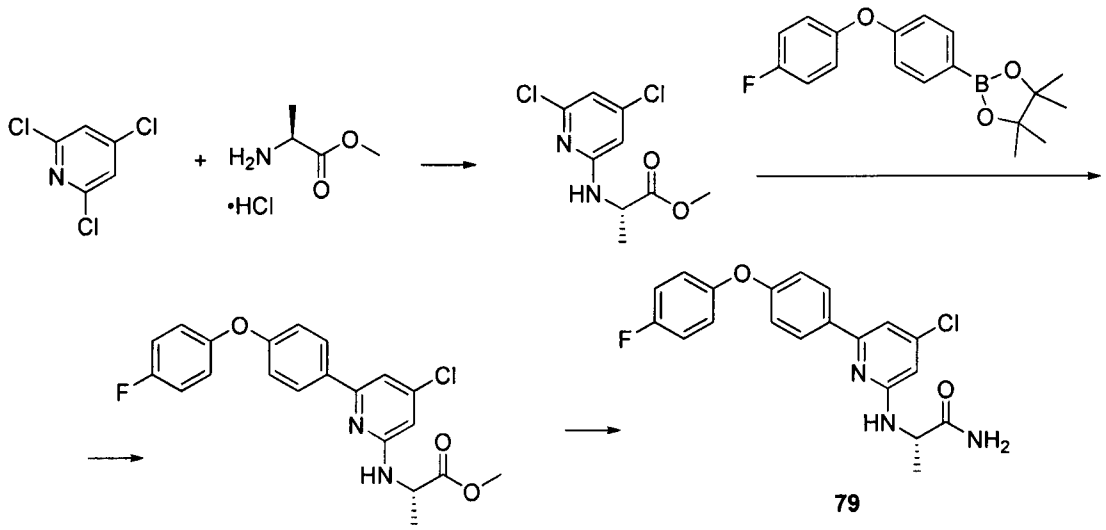


N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide (Compound **72**): LC/MS: *m/z* = 369.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 9.57 (1 H, s), 8.09 (2 H, d, J = 9.0 Hz), 8.05 (1 H, d, J = 8.1 Hz), 7.89 (1 H, t, J = 7.9 Hz), 7.68 (1 H, d, J = 7.9 Hz), 7.31-7.24 (2 H, m), 7.19-7.12 (2 H, m), 7.07 (2 H, d, J = 9.0 Hz), 6.06 (1 H, d, J = 5.7 Hz), 4.92 (1 H, t, J = 5.5 Hz), 4.17-4.12 (1 H, m), 3.69-3.64 (2 H, m).

EXAMPLE 20

Synthesis of (S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino) propanamide

Scheme 36



79

To a solution of the 2,4,6-trichloropyridine (10.694 g, 58.62 mmol) in acetonitrile (100 mL) was added (S)-methyl 2-aminopropanoate hydrochloride (8.198 g, 58.73 mmol) and iPr_2NEt (22.5 mL, 129 mmol). The mixture was heated at reflux for 4 days then additional (S)-methyl 2-aminopropanoate hydrochloride (8.184 g, 58.63 mmol) and iPr_2NEt (10.2 mL, 58.6 mmol) were added. Heating was continued for 5 more days then additional (S)-methyl 2-aminopropanoate hydrochloride (8.191 g, 58.68 mmol) and iPr_2NEt (20 mL, 115 mmol) was added. Heating was continued for 5 more days then the reaction was cooled. The reaction was concentrated *in vacuo* and the residue partitioned between 250 mL EtOAc and 100 mL water to give a gelatinous precipitate. The precipitate was filtered and rinsed with additional EtOAc. The organic filtrate was isolated and washed once with 100 mL brine. The filter cake containing the gelatinous precipitate was washed with MeOH and these washings were combined with the other portion of organic filtrate and evaporated in vacuo. This residue was dissolved in DCM, dried with $MgSO_4$, filtered and evaporated in vacuo. The residue was chromatographed over silica gel with 0-50% EtOAc in hexanes. The isomer fractions were isolated and evaporated *in vacuo* to give (S)-methyl 2-((4,6-dichloropyridin-2-yl)amino)propanoate as a pale tan solid (3.582 g, 14.38 mmol, 25% yield). LC/MS: *m/z* = 249.2 $[M+H]^+$.

To a mixture of (S)-methyl 2-((4,6-dichloropyridin-2-yl)amino)propanoate (1.245 g, 5.00 mmol) in dioxane (25 mL) was added 2-(4-(4-fluorophenoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.571 g, 5.00 mmol), 2M aqueous Na_2CO_3 (5.0 mL, 10 mmol), and $PdCl_2(dppf)$ (0.218 g, 0.267 mmol). The reaction vessel was flushed with argon, sealed, and heated at 80°C overnight. After cooling, the reaction mixture was evaporated *in vacuo* and

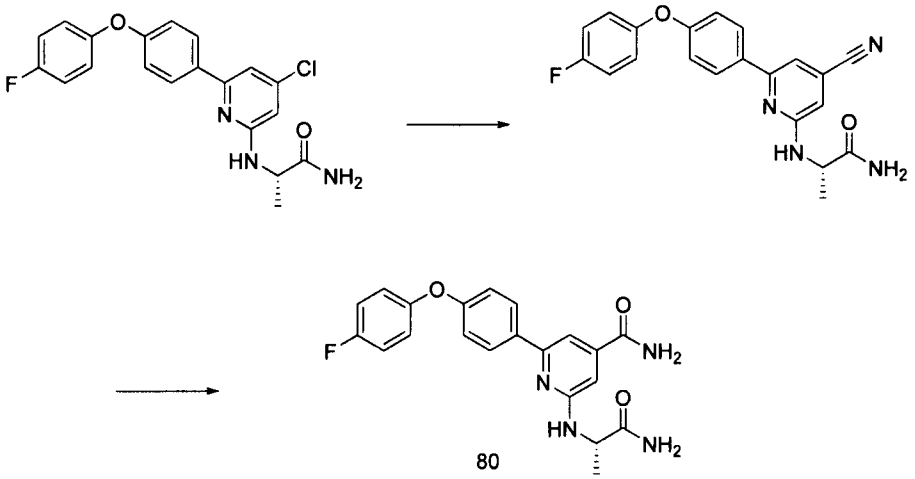
the residue chromatographed over silica gel with 0-30% EtOAc in hexanes. The product fractions were evaporated *in vacuo* to give semi-pure (S)-methyl 2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanoate which was carried on as-is.

To the semi-pure (S)-methyl 2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl) pyridin-2-yl)amino)propanoate (approximately 5.0 mmol) was added 7M NH_3 in MeOH (25 mL, 175 mmol) in a pressure reaction vessel. The vessel was sealed and heated at 50°C for 3 days then at 80°C for 2 additional days. After cooling, the reaction mixture was evaporated *in vacuo* and the residue chromatographed over silica gel with 25-50% acetone in hexanes. The product fractions were evaporated *in vacuo* to give nearly pure (S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide as an oil. 1.126 g of this material was reserved for additional reactions and 0.109 g was further purified via reverse-phase chromatography with a 40-100% acetonitrile in water (+0.1% TFA) gradient. The product fractions were pooled and lyophilized to give pure (S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide (Compound **79**) as the trifluoroacetate salt (0.073 g). LC/MS: *m/z* = 386.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 8.08 (2 H, d, J = 8.8 Hz), 7.43 (1 H, s), 7.31-7.23 (2 H, m), 7.17-7.11 (3 H, m), ~7.0 (1 H, v. broad s), 6.99 (2 H, d, J = 8.6 Hz), 6.94 (1 H, s), 6.58 (1 H, d, J = 1.3 Hz), 4.43-4.35 (1 H, m), 1.33 (3 H, d, J = 7.0 Hz).

EXAMPLE 21

Synthesis of (S)-2-((1-amino-1-oxopropan-2-yl)amino)-6-(4-(4-fluorophenoxy)phenyl) isonicotinamide

Scheme 37



80

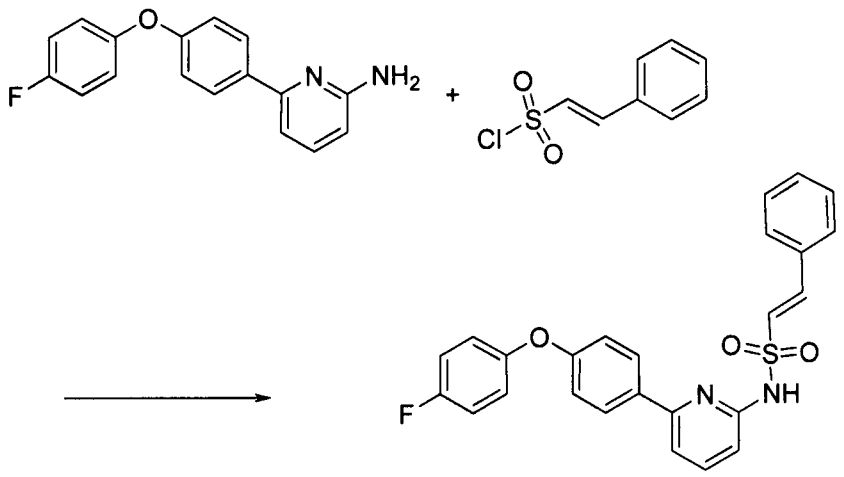
To a solution of (S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide (0.624 g, 1.62 mmol) in DMF (10 mL) was added $Zn(CN)_2$ (0.115 g, 0.98 mmol), Zn powder (0.027 g, 0.41 mmol, <150μm), and $PdCl_2(dppf)$ (0.068 g, 0.083 mmol). The reaction vessel was flushed with argon, sealed, and heated at 120°C overnight. After cooling, the reaction mixture was evaporated *in vacuo* and the residue chromatographed over silica gel with 25-75% acetone in hexanes. The product fractions were evaporated *in vacuo* to give (S)-2-((4-cyano-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide as a tan-orange solid (0.541 g, 1.44 mmol, 89% yield). LC/MS: *m/z* = 377.2 $[M+H]^+$.

To a suspension of (S)-2-((4-cyano-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)propanamide (0.541 g, 1.44 mmol) in EtOH (5 mL) and water (5 mL) was added $PtH(PMe_2O)_2H(PMe_2OH)$ (spatula tip amount). The reaction vessel was flushed with argon, sealed, and heated at 100°C overnight. After cooling, the reaction mixture was evaporated in vacuo. The residue was dissolved in MeOH and filtered over a nylon disk and again evaporated in vacuo. The residue was chromatographed over silica gel with 75-100% acetone in hexanes. The product fractions were isolated and evaporated in vacuo. The resulting oil was triturated with 5 mL 10% EtOAc / hexanes, filtered and dried under vacuum at 40°C to give (S)-2-((1-amino-1-oxopropan-2-yl)amino)-6-(4-(4-fluorophenoxy)phenyl)isonicotinamide (Compound **80**) as a light yellow powder (0.361 g, 0.915 mmol, 64% yield). LC/MS: *m/z* = 395.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6): 8.11 (2 H, d, J = 8.6 Hz), 8.08 (1 H, s), 7.54 (1 H, s), 7.45 (1 H, s), 7.36 (1 H, s), 7.30-7.23 (2 H, m), 7.17-7.10 (2 H, m), 7.03 (2 H, d, J = 8.8 Hz), 6.95 (1 H, br d, J = 6.8 Hz), 6.92-6.88 (2 H, m), 4.43-4.34 (1 H, m), 1.34 (3 H, d, J = 7.0 Hz).

EXAMPLE 22

Synthesis of (E)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-phenylethenesulfonamide

Scheme 38



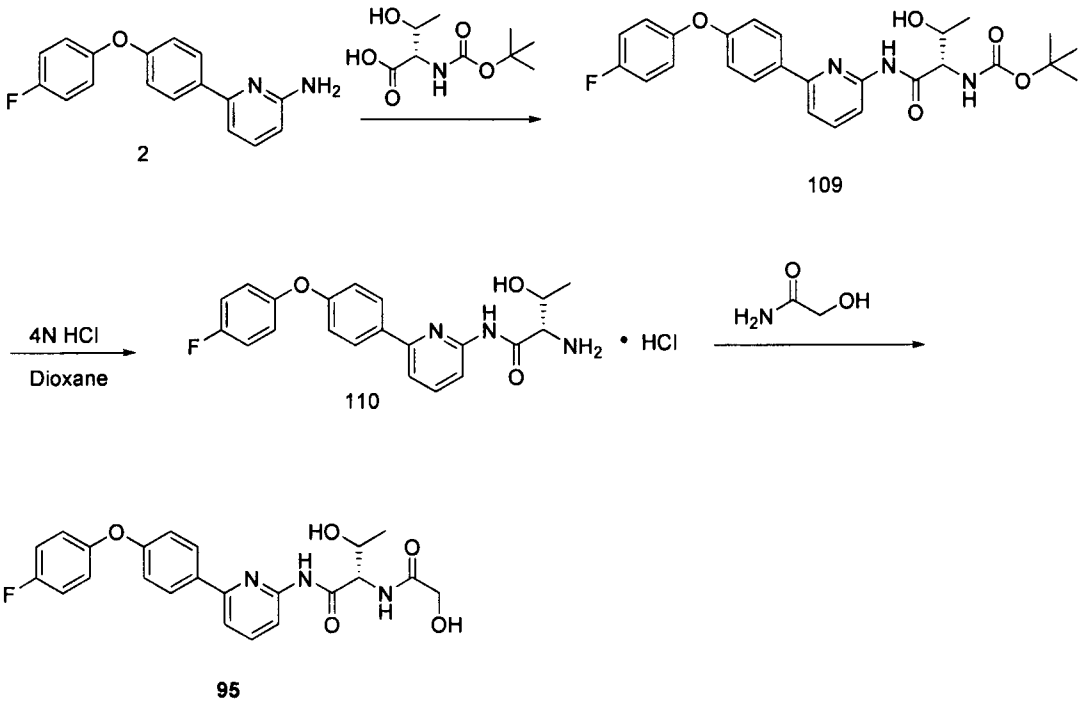
97

In a 50-mL vial with a screw-top septum, 6-(4-(4-fluorophenoxy) phenyl)pyridin-2-amine (1.5 g, 5.36 mmol) was dissolved in pyridine (4 mL) and cooled in an ice bath. To the solution was added 2-phenylethenesulfonyl chloride (Aldrich, 1.6 g, 8 mmol) dissolved in pyridine (3 mL). The reaction mixture was stirred at room temperature for 18 h, the precipitate was collected by vacuum filtration, and the filter cake was washed with 20 mL cold methanol to give (E)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-phenylethenesulfonamide (Compound **97**) (907 mg, white solid). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): 10.94-10.88 (1 H, m), 8.05-7.97 (2 H, m), 7.79-7.66 (4 H, m), 7.56-7.45 (2 H, m), 7.43-7.33 (3 H, m), 7.32-7.24 (2 H, s), 7.16-7.08 (2 H, m), 6.99-6.92 (2 H, m), 6.91-6.84 (1 H, m). LCMS: m/z = 447 $[M+H^+]^+$.

EXAMPLE 23

Synthesis of 2S,3S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxyacetamido)butanamide

Scheme 39



In similar fashion shown in Scheme 32 of EXAMPLE 16, a mixture of Boc-Thr-OH (purchased from Sigma-Aldrich, 219 mg, 1.0 mmol) and HATU (purchased from GenScript Corporation, 606 mg, 1.60 mmol) in a mixture of THF/DCM (10 mL) was stirred for 1 h and compound **2** (280 mg, 1.0 mmol) was added thereto. The reaction mixture was stirred overnight at room temperature. After the work-up, the residue was purified by column chromatography (silica gel, 30% EtOAc in hexane) to give ((S)-1-{6-[4-(4-fluoro- phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-propyl)-carbamic acid tert-butyl ester (Compound **109**) (392 mg, 81.5% yield). Rf = 0.6, LC/MS: m/z = 482.1 $[M+H]^+$.

To compound **109** (392 mg, 0.81 mmol) in dry dioxane (3 mL) was added 4.0N HCl in dioxane (2 mL, 8.1 mmol) at 0°C. The reaction mixture was stirred for 2 h at room temperature to give (S)-2-amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pridin-2-yl}-3-hydroxy-propionamide (Compound **110**) as the HCl salt (312 mg, 92% yield) which was used for the next step without further purification.

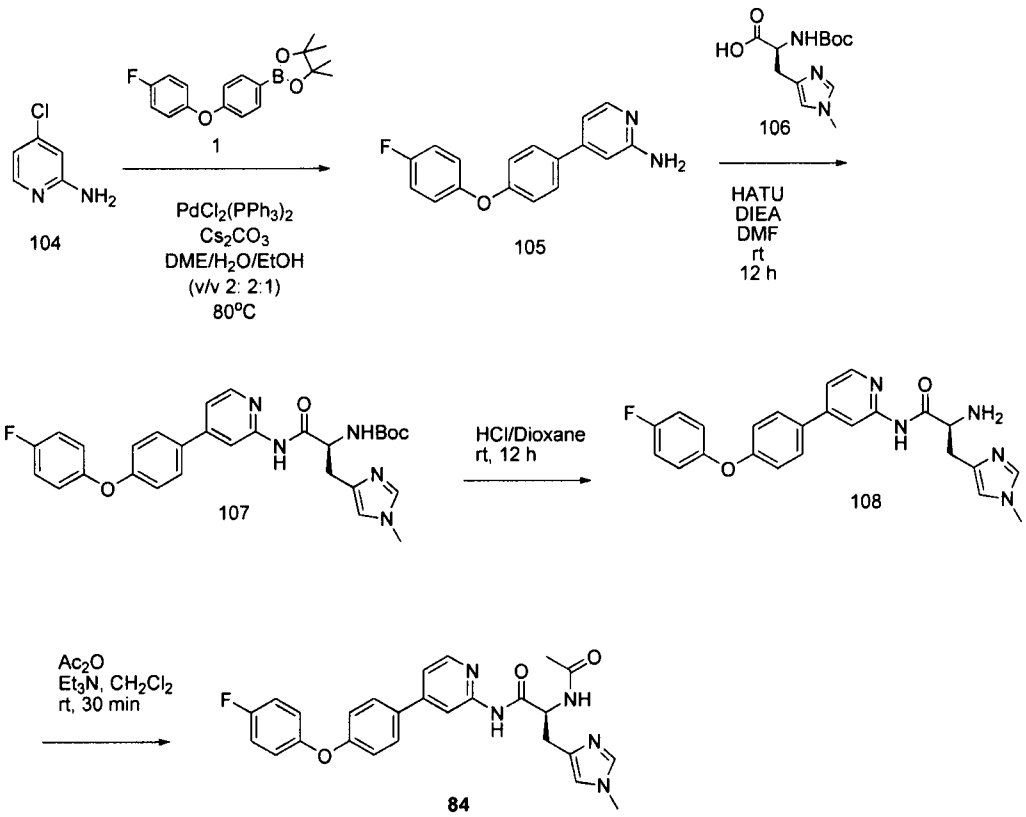
(2S,3S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-amino-butanamide (as the HCl salt) (194 mg, 0.47 mmol) was treated with glycolic acid (35.7 mg, 0.47 mmol) in the presence of HATU (90.7 mg, 0.47 mmol), DIEA (0.17 mL, 0.93 mmol) in a mixture of DCM/THF (5mL). The mixture was stirred overnight at room temperature. After the work-up, the oily residue was purified by preparative TLC to give (2S,3S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxyacetamido)butanamide

(Compound **95**) (98 mg, 48%). ^{1}H NMR (400 MHz, CD_3OD): 8.07 (3H, d, J = 9.00 Hz), 7.85 (1H, t, J = 7.99 Hz), 7.60 (1H, d, J = 7.90 Hz), 7.01-7.19 (6H, m), 4.63 (1H, br), 4.32-4.40 (1H, m), 4.11 (2H, s), 1.27 (3H, d, J = 6.39 Hz). LC/MS: *m/z* = 440.1 $[M+H]^+$.

EXAMPLE 24

Synthesis of (S)-2-acetamido-N-(4-(4-(4-fluorophenoxy)phenyl) pyridine-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide

Scheme 40



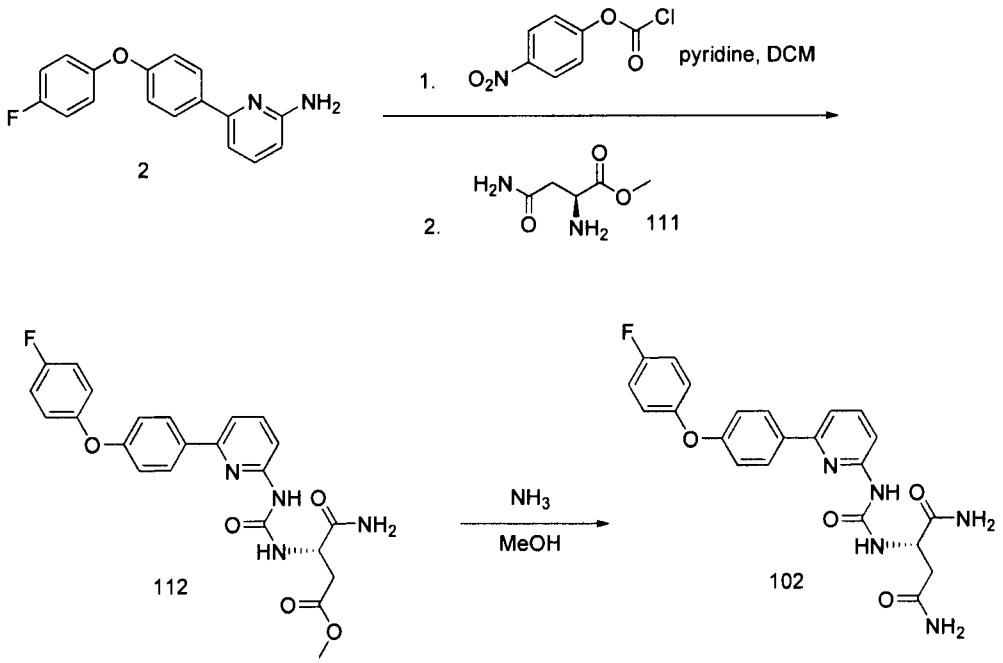
A sealed reaction vessel containing compound **104** (488 g, 3.8 mmol), compound **1** (1 g, 3.18 mmol), $PdCl_2(PPh_3)_2$ (179 mg, 0.25 mmol), Cs_2CO_3 (2 g, 6.4 mmol) in a mixed solvent of DME (6 mL), ethanol (3 mL) and water (6 mL) was heated at 80°C for 2 hours. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and brine (20 mL). After separation of the organic layer, the aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified on Combiflash (40 g silica gel, 0~100% EtOAc/Hexane) to give compound **105** as a brown solid (338 mg, 38%). A mixture of compound **105** (338 mg, 1.2 mmol), compound **106** (260 mg, 1.2 mmol), HATU (454 mg,

1.2 mmol), and DIEA (0.663 mL, 3.6 mmol) in DMF (5 mL) was stirred at room temperature for 12 h. The mixture was loaded on silica gel and purified with Combiflash (5~10% $MeOH/CH_2Cl_2$) to give compound **107** in low yield. A solution of compound **107** in EtOAc was treated with 4 N HCl/dioxane at room temperature for 12 h and compound **108** was obtained by pipetting off the clear solution. Compound **108** was suspended in CH_2Cl_2 (1 mL), and to the suspension was added Ac_2O (0.05 mL) and Et_3N (0.5 mL). The mixture was stirred for 30 min, and then concentrated to dryness. The residue was purified with reverse phase (C-18) column on Combiflash to give (S)-2-acetamido-N-(4-(4-(4-fluorophenoxy)phenyl) pyridine-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide (Compound **84**) as the TFA salt (10 mg). ^1H NMR (400 MHz, CD_3OD): 8.82 (1H, s), 8.36 (1H, dd, J = 2.4, 5.6 Hz), 8.30 (1H, s), 7.78 (2H, m), 7.54 (1H, m), 7.42 (1H, s), 7.21-7.10 (6H, m), 4.93 (1H, m), 3.91 (3H, s), 3.38 (1H, m), 3.15 (1H, m), 2.06 (3H, s). LC/MS: *m/z* = 474 $[M+H]^+$.

EXAMPLE 25

Synthesis of (R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)succinamide

Scheme 41



A solution of compound **2** (100 mg, 0.36 mmol) in DCM (5 mL) was slowly added to a DCM (5 mL) solution containing 4-nitro phenoxy chloroformate (72 mg, 0.36 mmol) and pyridine (57 mg, 0.72 mmol) cooled in an ice bath. After the addition, the ice bath was

removed and the reation mixture was stirred at room temperature for 2 h. A DCM solution (5 mL) containing the amine ester compound **111** (53 mg, 0.36 mmol) and pyridine (29 mg, 0.36 mmol) was added to the reaction mixture dropwise and then stirred at room temperature for 14 h. The reaction mixture was diluted with DCM and 1N HCl and the organic layer was collected, washed with brine, dried over Na_2SO_4 and concentrated under rotary evaporation. The crude product was subjected to flash column chromatography on silica gel (DCM/MeOH) to give compound **112** as white solid (100 mg, yield 62%).

Compound **112** (100 mg, 0.22 mmol) was dissolved in 1 mL of DCM and 5 mL of 7N NH_3 in MeOH was added. The resulting mixture was stirred at room temperature for 14 h. The solvent was removed under rotary evaporation and the residue was subjected to flash column chromatography on silica gel (DCM/MeOH) to give (R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)succinamide (Compound **102**) as white solid (70 mg, yield 73%). ^{1}H NMR (400 MHz, DMSO-d_6): 9.30 (1H, s), 8.55 (1H, br), 8.10 (2H, m), 7.70 (1H, m), 7.10-7.50 (11H, m), 6.85 (1H, s), 4.55 (1H, m), 2.55 (2H, m). LC/MS: *m/z* = 438 $[M+H]^+$.

EXAMPLE 26

The following Compounds of the Invention were prepared using the methodology described in the EXAMPLES above:

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide (Compound **32**): ^{1}H NMR (400 MHz, DMSO-d_6): 11.60 (1H, br), 10.35 (1H, br), 8.20 (1H, br), 8.10 (2H, d, J = 8.2 Hz), 7.90 (1H, d, J = 8.2 Hz), 7.77 (1H, t, J = 8.2 Hz,), 7.57 (1H, d, J = 8.2 Hz), 7.47 (1H, s), 7.20 (2H, t, J = 8.2Hz), 7.09 (2H, m), 7.01 (2H, d, J = 8.2 Hz), 6.78 (1H, br), 4.68 (1H, s), 2.70-3.01 (2H, m), 1.82 (3H, s). LC/MS: *m/z* = 460 $[M+H]^+$.

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide (Compound **77**): ^{1}H NMR (400 MHz, CD_3OD): 7.87-7.99 (3H, m), 7.65 (1H, m), 7.40 (1H, m), 6.85-7.05 (6H, m), 6.80 (1H, s), 4.70 (1H, s), 3.51 (3H, s), 2.80-3.10 (2H, m), 1.82 (3H, s). LC/MS: *m/z* = 474 $[M+H]^+$.

(R)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1-methyl-1H-imidazol-4-yl)propanamide (Compound **78**): ^{1}H NMR

(400 MHz, CD_3OD): δ 8.70 (1H, s), 7.90 (3H, m), 7.71 (1H, m), 7.50 (1H, m), 7.25 (1H, s), 6.90-7.10 (6H, m), 3.80 (3H, s), 2.90-3.20 (3H, m), 1.21 (6H, s). LC/MS: *m/z = 518* $[M+H]^+$

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-propionamidopropanamide (Compound **81**): ^1H NMR (400 MHz, CD_3OD): 7.90 (3H, m), 7.71 (1H, m), 7.50 (1H, m), 7.30-7.55 (2H, m), 6.80-7.10 (6H, m), 6.75 (1H, s), 4.70 (1H, s), 3.55 (3H, s), 2.90-3.20 (2H, m), 1.05 (3H, t, J = 8.2 Hz). LC/MS: *m/z = 488* $[M+H]^+$.

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-isobutyramido-3-(1-methyl-1H-imidazol-4-yl)propanamide (Compound **82**): ^1H NMR (400 MHz, CD_3OD): δ 7.80-8.05 (3H, m), 7.71 (1H, m), 7.50 (1H, m), 7.40 (2H, m), 6.80-7.10 (6H, m), 6.75 (1H, s), 4.70 (1H, s), 3.50 (3H, s), 2.75-3.00 (2H, m), 2.40 (1H, m), 1.01 (6H, m). LC/MS: *m/z = 502* $[M+H]^+$.

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-pivalamidopropanamide (Compound **83**): ^1H NMR (400 MHz, CD_3OD): 7.80-8.05 (3H, m), 7.65 (1H, m), 7.40 (2H, m), 6.80-7.10 (6H, m), 6.75 (1H, s), 4.70 (1H, s), 3.55 (3H, s), 2.75-3.05 (2H, m), 1.11 (9H, s). LC/MS: *m/z = 516* $[M+H]^+$.

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide (Compound **85**): ^1H NMR (400 MHz, CD_3OD): 7.80-8.05 (3H, m), 7.70 (1H, m), 7.40 (2H, m), 6.80-7.10 (6H, m), 6.75 (1H, s), 4.70 (1H, s), 3.50 (3H, s), 2.75-3.00 (2H, m), 1.55 (1H, m), 0.55-0.85 (4H, m). LC/MS: *m/z = 500* $[M+H]^+$.

(S)-3,3,3-trifluoro-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)propanamide (Compound **86**): ^1H NMR (400 MHz, CD_3OD): 7.80-8.05 (3H, m), 7.70 (1H, m), 7.40 (2H, m), 6.80-7.10 (6H, m), 6.75 (1H, s), 4.70 (1H, s), 3.50 (3H, s), 2.75-3.25 (4H, m). LC/MS: *m/z = 542* $[M+H]^+$.

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-5-yl)propanamide (Compound **87**): ^1H NMR (400 MHz, CD_3OD): 8.90 (1H, s), 8.10 (3H, m), 7.80 (1H, m), 7.50 (1H, m), 7.20 (1H, s), 6.95-7.23 (6H, m), 5.05 (1H, m), 4.00 (3H, s), 3.10-3.40 (2H, m), 2.05 (3H, s). LC/MS: *m/z = 474* $[M+H]^+$

(R)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)-4-(trifluoromethyl)benzamide (Compound **88**): ^1H NMR (400 MHz, CD_3OD): 8.65 (1H, s), 7.85-8.05 (5H, m), 7.70 (3H, m), 7.50 (1H, m), 7.30 (1H, s),

6.80-7.10 (6H, m), 5.05 (1H, m), 3.80 (3H, s), 3.20-3.45 (2H, m). LC/MS: *m/z = 604* $[M+H]^+$.

(R)-2-acetamido-3-(1-methyl-1H-imidazol-4-yl)-N-(6-(4-((5-(trifluoromethyl) pyridin-2-yl)oxy)phenyl)pyridin-2-yl)propanamide (Compound **94**): ^1H NMR (400 MHz, CD_3OD): 8.80 (1H, s), 8.40 (1H, s), 7.95-8.15 (4H, m), 7.80 (1H, m)7.60 (1H, m), 7.35 (1H, s), 7.10-7.30 (3H, m), 4.95 (1H, m), 3.90 (3H, s), 3.05-3.30 (2H, m), 2.10 (3H, s). LC/MS: *m/z = 525* $[M+H]^+$.

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide (Compound **98**): ^1H NMR (400 MHz, DMSO-d_6): 10.6 (1H, s), 8.41 (1H, m), 8.28 (1H, m), 8.12 (2H, m), 8.05 (1H, d, J = 8.4 Hz), 7.95 (1H, dd, J = 2, 8.8 Hz), 7.84 (1H, t, J = 8Hz), 7.64 (2H, m), 7.21 (2H, m), 7.10 (2H, m), 7.02 (2H, m), 3.84 (3H, s). LC/MS: *m/z* = 439$[M+H]^+$.

(S)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanamide (Compound **99**): ^1H NMR (400 MHz, CD_3OD): 7.80 (2H, m), 7.55 (1H, m), 7.22 (2H, m), 6.80-7.05 (6H, m), 6.70 (1H, m), 6.52 (1H, s), 4.62 (1H, m), 3.32 (3H, s), 3.15 (3H, s), 2.90 (2H, m). LC/MS: *m/z = 475* $[M+H]^+$.

(S)-methyl 2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanoate (Compound **100**): ^1H NMR (400 MHz, CD_3OD): δ 7.80 (2H, m), 7.60 (1H, m), 7.25 (1H, m), 6.80-7.10 (6H, m), 6.75 (1H, m), 6.52 (1H, s), 4.62 (1H, m), 3.32 (3H, s), 3.15 (3H, s), 2.90 (2H, m). LC/MS: *m/z = 490* $[M+H]^+$.

(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-indol-2-yl)propanamide (Compound **101**): ^1H NMR (400 MHz, DMSO-d_6): 10.65 (1H, s), 9.20 (1H, s), 8.70 (1H, br), 7.80 (2H, m), 7.40-7.70 (3H, m), 7.35 (1H, m), 7.15-7.25 (3H, m), 7.00-7.15 (4H, m), 6.95 (2H, m), 6.70 (3H, m), 4.50 (1H, m), 2.70-2.90 (2H, m). LC/MS: *m/z = 510* $[M+H]^+$.

(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-imidazol-5-yl)propanamide (Compound **103**): ^1H NMR (400 MHz, DMSO-d_6): 11.62 (1H, s), 9.40 (1H, s), 8.70 (1H, br), 8.01 (2H, s), 7.70 (1H, m), 7.50 (3H, m), 6.95-7.25 (8H, m), 6.70 (1H, m), 4.50 (1H, m), 2.60-3.00 (2H, m). LC/MS: *m/z = 461* $[M+H]^+$.

EXAMPLE 27

Representative Compounds of the Invention have been tested in the FLIPR® or FLIPR$^{TETRA®}$ sodium dye assay with KCl assay and/or electrophysiology (EP) assay for sodium channel blocking activity, which is described in detail above. Representative values are presented in TABLE 4.

TABLE 4

Evaluation of compounds as sodium channel (Na_v) blockers

	$Na_v1.7$ Activity (μM)		
Compound Example No.	**FLIPR assay IC_{50} (μM) ± SEM**	**EP assay K_i**	**EP assay K_r**
3	0.042 ± 0.02	0.194 ± 0.070	
4	0.064 ± 0.02	0.130 ± 0.030	
7	0.067 ± 0.007	0.059 ± 0.010	18.000 ± 1.000
8	0.036 ± 0.004		
9	0.091 ± 0.02		
10	0.091 ± 0.03		
11	0.086 ± 0.02		
12	0.096 ± 0.004	0.257 ± 0.060	5.063
13	0.075 ± 0.017	0.075 ± 0.020	10.2000 ± 0.200
15	0.26 ± 0.07		
17	0.094 ± 0.03		
18	1.5 ± 0.3		
24	2.9 ± 0.8		
26	>20		
27	0.34 ± 0.05		
28	0.22 ± 0.07		
29	0.32 ± 0.05		
31	0.18 ± 0.02		
32	0.086 ± 0.02	0.025 ± 0.000	0.580 ± 0.100
33	0.11 ± 0.02	0.206 ± 0.040	5.309 ± 0.560
34	0.58 ± 0.05		
35	0.13 ± 0.02		
36	0.14 ± 0.01		

	$Na_v1.7$ Activity (μM)		
Compound Example No.	**FLIPR assay IC_{50} (μM) ± SEM**	**EP assay K_i**	**EP assay K_r**
37	0.12 ± 0.03		
38	0.14 ± 0.03	0.019 ± 0.010	1.196 ± 0.310
40	0.13 ± 0.03		
41	0.066 ± 0.008		
44	0.059 ± 0.12		
45	0.30 ± 0.07		
50	2.24 ± 0.15		
53	7.34 ± 0.68		
54	0.07 ± 0.02		
55	0.06 ± 0.006		
56	0.14 ± 0.05	0.195 ± 0.070	32.235 ± 8.380
57	0.16 ± 0.03		
58	0.11 ± 0.04		
59	0.31 ± 0.07		
60	0.46 ± 0.08	0.113 ± 0.050	4.944 ± 0.810
61	0.12 ± 0.05		
62	1.34 ± 0.21		
63	1.15 ± 0.07		
64	0.12 ± 0.01		
65	>20		
66	5.0 ± 0.88	1.374 ± 0.170	
70	0.27 ± 0.032	0.046 ± 0.000	0.803 ± 0.200
72	0.074 0.003	0.143 ± 0.030	8.914 ± 1.210
73	0.358 ± 0.020		
74	0.678 ± 0.043		
75	0.609 ± 0.027		
76	>20		
77	0.111 ± 0.007		
78	0.608 ± 0.075		
79	0.276 ± 0.079		
80	1.341 ± 0.277		
81	0.064 ± 0.010		
82	0.046 ± 0.005		
83	0.020 ± 0.002		
84	0.290 ± 0.025		
85	0.111 ± 0.011		

	$Na_v1.7$ Activity (μM)		
Compound Example No.	**FLIPR assay IC_{50} (μM) ± SEM**	**EP assay K_i**	**EP assay K_r**
86	0.084 ± 0.007		
87	0.140 ± 0.002		
88	0.159 ± 0.024		
89	0.134 ± 0.018		
90	0.070 ± 0.012		
91	0.275 ± 0.030		
92	0.198 ± 0.053		
93	0.113 ± 0.027		
94	0.335 ± 0.068		
95	0.172 ± 0.016		
96	>20		
97	1.440 ± 0.194		
98	>20		
99	0.667 ± 0.162		
100	0.226 ± 0.020		
101	4.021 ± 0.366		
102	0.613 ± 0.029		
103	1.619 ± 0.226		

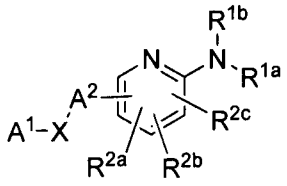
Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof.

Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

All patents and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound having Formula **I**:



I

wherein:

A^1 is selected from the group consisting of:

a) optionally substituted cycloalkyl;

b) optionally substituted heterocyclo;

c) optionally substituted aryl; and

d) optionally substituted heteroaryl;

X is selected from the group consisting of:

a) -O-;

b) -S-;

c) -SO-;

d) $-SO_2-$

e) $-(CR^3R^4)_m-$;

f) $-NR^5-$;

g) $-SO_2NH-$; and

h) $-NHSO_2-$;

wherein:

each R^3 and R^4, which can be identical or different, are selected from the group consisting of:

a) hydrogen;

b) halo; and

c) optionally substituted alkyl; or

each R^3 and R^4 taken together with the carbon atom to which they are attached form a 3- to 8-membered optionally substituted cycloalkyl or optionally substituted heterocyclo;

m is 0, 1, 2, or 3; and

R^5 is selected from the group consisting of hydrogen and optionally substituted alkyl;

A^2 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

R^{1a} is selected from the group consisting of:

a) optionally substituted alkyl;
b) (heterocyclo)alkyl;
c) (heteroaryl)alkyl;
d) (amino)alkyl;
e) (alkylamino)alkyl;
f) (dialkylamino)alkyl;
g) (carboxamido)alkyl;
h) (cyano)alkyl;
i) alkoxyalkyl;
j) hydroxyalkyl;
k) heteroalkyl
l) optionally substituted heterocyclo;
m) $-SO_2R^6$; and
n) $-COR^7$;

wherein:

R^6 is selected from the group consisting of:

a) optionally substituted alkyl;
b) optionally substituted cycloalkyl;
c) optionally substituted aryl;

d) optionally substituted heteroaryl;

e) amino;

f) alkylamino;

g) dialkylamino;

h) cycloalkylamino;

i) heterocycloalkylamino;

j) heteroarylamino;

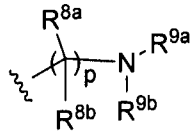
k) arylamino; and

l) optionally substituted alkenyl;

R^7 is selected from the group consisting of:

a) optionally substituted heteroaryl;

b)



; and

c) hydroxyalkyl;

wherein:

p is 0, 1, or 2;

each R^{8a} and R^{8b}, which can be identical or different, are selected from the group consisting of:

a) hydrogen;

b) optionally substituted alkyl;

c) aralkyl;

d) (heterocyclo)alkyl;

e) (heteroaryl)alkyl;

f) (amino)alkyl;

g) (alkylamino)alkyl;

h) (dialkylamino)alkyl;

i) (carboxamido)alkyl;

j) (cyano)alkyl;

k) alkoxyalkyl;

l) hydroxyalkyl;

m) optionally substituted cycloalkyl;

n) optionally substituted aryl;

o) optionally substituted heterocyclo;

p) optionally substituted heteroaryl; and

q) carboxamido;

R^{9a} is selected from the group consisting of:

a) hydrogen;

b) optionally substituted alkyl;

c) $-COR^{10}$;

d) $-SO_2R^{11}$; and

e) $-R^{25}$;

wherein:

R^{10} is selected from the group consisting of:

a) optionally substituted alkyl;

b) aralkyl;

c) (heterocyclo)alkyl;

d) (heteroaryl)alkyl;

e) (amino)alkyl;

f) (alkylamino)alkyl;

g) (dialkylamino)alkyl;

h) (carboxamido)alkyl;

i) (cyano)alkyl;

j) alkoxyalkyl;

k) hydroxyalkyl;

l) heteroalkyl;

m) optionally substituted cycloalkyl;

n) optionally substituted aryl;

o) optionally substituted heterocyclo;

p) optionally substituted heteroaryl;

q) amino;

r) alkylamino;

s) dialkylamino;

t) cycloalkylamino;

u) heterocycloalkylamino;

v) heteroarylamino;

w) arylamino;

x) alkoxy; and

y) haloalkyl

R^{11} is selected from the group consisting of:

a) optionally substituted alkyl;

b) aralkyl;

c) (heterocyclo)alkyl;

d) (heteroaryl)alkyl;

e) (amino)alkyl;

f) (alkylamino)alkyl;

g) (dialkylamino)alkyl;

h) (carboxamido)alkyl;

i) (cyano)alkyl;

j) alkoxyalkyl;

k) hydroxyalkyl;

l) heteroalkyl;

m) optionally substituted cycloalkyl;

n) optionally substituted aryl;

o) optionally substituted heterocyclo;

p) optionally substituted heteroaryl;

q) amino;

r) alkylamino;

s) dialkylamino;

t) cycloalkylamino;

u) heterocycloalkylamino;

v) heteroarylamino; and

w) arylamino;

R^{9b} is selected from the group consisting of hydrogen and optionally substituted alkyl; or

R^{9a} and R^{9b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo;

R^{1b} is selected from the group consisting of:

a) hydrogen;

b) optionally substituted alkyl;

c) (heterocyclo)alkyl;

d) (heteroaryl)alkyl;

e) (amino)alkyl;

f) (alkylamino)alkyl;

g) (dialkylamino)alkyl;

h) (carboxamido)alkyl;

i) (cyano)alkyl;

j) alkoxyalkyl; and

j) hydroxyalkyl; or

R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo;

R^{2a}, R^{2b}, and R^{2c}, which can be identical or different, are selected from the group consisting of:

a) hydrogen;

b) halo;

c) nitro;

d) cyano;

e) hydroxy;

f) amino;

g) alkylamino;

h) dialkylamino;

i) haloalkyl;

j) hydroxyalkyl;

k) alkoxy;

l) haloalkoxy;

m) aryloxy;

n) aralkyloxy;

o) alkylthio;

p) carboxamido;

q) sulfonamido;

r) alkylcarbonyl;

s) arylcarbonyl;

t) alkylsulfonyl;

u) arylsulfonyl;

v) ureido;

w) guanidino;

x) carboxy;

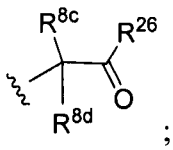
y) carboxyalkyl;

z) optionally substituted alkyl

aa) (amino)alkyl; and

bb) (diamino)alkyl; and

R^{25} is:



;

R^{8c} and R^{8d}, which can be identical or different, are selected from the group consisting of:

a) hydrogen;

b) optionally substituted alkyl;

c) aralkyl;

d) (heterocyclo)alkyl;

e) (heteroaryl)alkyl;

f) (amino)alkyl;

g) (alkylamino)alkyl;

h) (dialkylamino)alkyl;

i) (carboxamido)alkyl;

j) (cyano)alkyl;

k) alkoxyalkyl;

l) hydroxyalkyl;

m) optionally substituted cycloalkyl;

n) optionally substituted aryl;

o) optionally substituted heterocyclo; and

p) optionally substituted heteroaryl; and

R^{26} is selected from the group consisting of:

a) hydroxy;

b) alkoxy;

c) amino;

d) alkylamino;

e) dialkylamino;

f) hydroxyalkylamino;

g) arylamino; and

h) cycloalkylamino,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof,

with the proviso:

when R^7 is optionally substituted heteroaryl, then A^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl.

2. The compound of claim 1, wherein:

X is selected from the group consisting of:

a) -O-;

b) -S-;

c) -SO-;

d) $-SO_2-$

e) $-(CR^3R^4)_m-$;

f) $-NR^5-$; and

g) $-SO_2NH-$;

R^6 is selected from the group consisting of:

a) optionally substituted alkyl;

b) optionally substituted cycloalkyl;

c) optionally substituted aryl;

d) optionally substituted heteroaryl;

e) amino;

f) alkylamino;

g) dialkylamino;

h) cycloalkylamino;

i) heterocycloalkylamino;

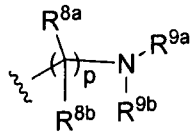
j) heteroarylamino; and

k) arylamino;

R^7 is selected from the group consisting of:

a) optionally substituted heteroaryl; and

b)



;

R^{9a} is selected from the group consisting of:

a) hydrogen;

b) optionally substituted alkyl;

c) -COR^{10}; and

d) -SO_2R^{11}; and

R^{10} is selected from the group consisting of:

a) optionally substituted alkyl;

b) aralkyl;

c) (heterocyclo)alkyl;

d) (heteroaryl)alkyl;

e) (amino)alkyl;

f) (alkylamino)alkyl;

g) (dialkylamino)alkyl;

h) (carboxamido)alkyl;

i) (cyano)alkyl;

j) alkoxyalkyl;

k) hydroxyalkyl;

l) heteroalkyl;

m) optionally substituted cycloalkyl;

n) optionally substituted aryl;

o) optionally substituted heterocyclo;

p) optionally substituted heteroaryl;

q) amino;

r) alkylamino;

s) dialkylamino;

t) cycloalkylamino;

u) heterocycloalkylamino;

v) heteroarylamino;

w) arylamino; and

x) alkoxy;

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

3. The compound of claim 1 or 2, wherein:

X is selected from the group consisting of:

a) -O-;

b) -S-;

c) -SO-;

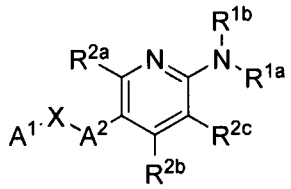
d) $-SO_2-$

e) $-(CR^3R^4)_m-$; and

f) $-SO_2NH-$;

4. The compound of any one of claims 1 to 3, wherein X is -O-;

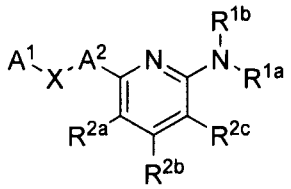
5. The compound of any one of claims 1 to 4 having Formula **II**:



II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

6. The compound of any one of claims 1 to 4 having Formula **III**:



III

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

7. The compound of any one of claims 1 to 6, wherein R^{1b} is hydrogen and R^{1a} is an optionally substituted heterocyclo.

8. The compound of any one of claims 1 to 6, wherein R^{1a} and R^{1b} are taken together with the nitrogen atom to which the are attached form an optionally substituted heterocyclo.

9. The compound of any one of claims 1 to 6, wherein R^{1b} is hydrogen and R^{1a} is (heterocyclo)alkyl.

10. The compound of any one of claims 1 to 6, wherein R^{1b} is hydrogen and R^{1a} is COR^7, wherein R^7 is selected as optionally substituted heteroaryl.

11. The compound of any one of claims 1 to 6, wherein R^{1b} is hydrogen and R^{1a} is (carboxamido)alkyl.

12. The compound of any one of claims 1 to6, wherein R^{1a} is $-SO_2R^6$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

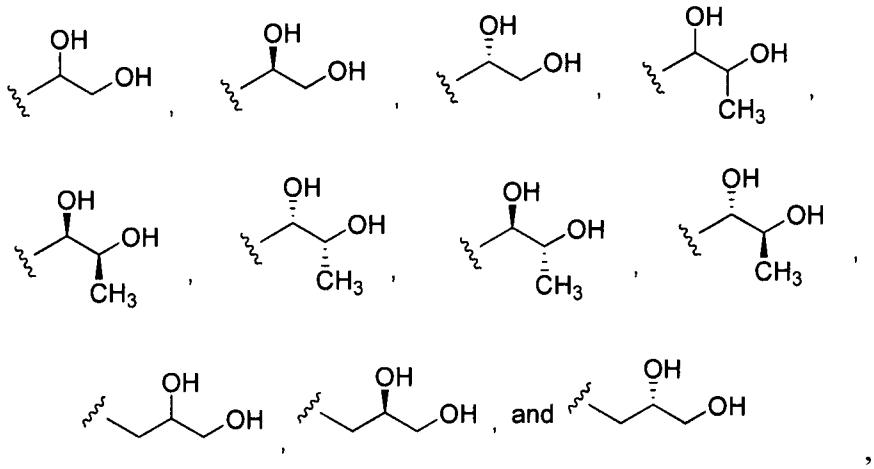
13. The compound of any one of claims 1 to 6, wherein R^{1a} is $-SO_2R^6$ and R^{1b} is selected from the group consisting of hydrogen and hydroxyalkyl.

14. The compound of claims 12 or 13, wherein R^6 is selected from the group consisting of optionally substituted alkyl, amino, optionally substituted heteroaryl, optionally substituted cycloalkyl and optionally substituted alkenyl.

15. The compound of any one of claims 1 to 6, wherein R^{1a} is $-COR^7$ and R^7 is hydroxyalkyl, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

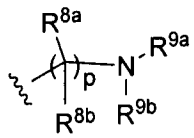
16. The compound claim 15, wherein said hydroxyalkyl is a C_{2-4} dihydroxyalkyl, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

17. The compound of claim 16, wherein said C_{2-4} dihydroxyalkyl is selected from the group consisting of:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

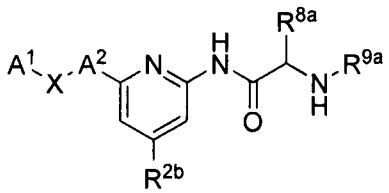
18. The compound of any one of claims 1-6, wherein R^{1a} is $-COR^7$ and R^7 is:



and wherein p is 1 or 2, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

19. The compound of any one of claims 1to 18, wherein R^{2a} and R^{2c} is each hydrogen.

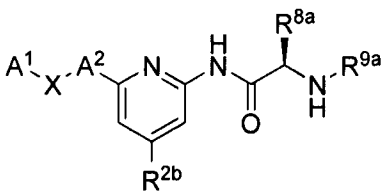
20. The compound of claims 1, 3, and 4 having Formula **V**:



V

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

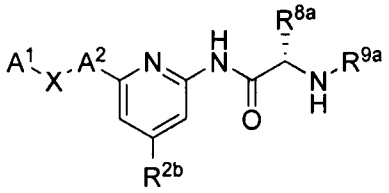
21. The compound of claim 20 having Formula **VI**:



VI

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

22. The compound of claim 20 having Formula **VII**:



VII

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

23. The compound of any one of claims 20-22 wherein R^{9a} is hydrogen.

24. The compound of any one of claims 20 to 22,wherein R^{9a} is $-COR^{10}$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

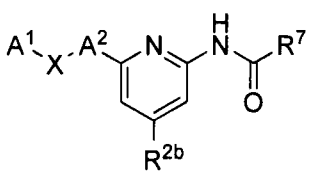
25. The compound of claim 24 wherein R^{10} is selected from the group consisting of optionally substituted alkyl, optionally substituted heteroaryl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocyclo, amino, alkoxyalkyl, alkylamino, heterocycloalkyl, hydroxyalkyl, heteroalkyl and alkoxy.

26. The compound of claim 24 or 25, wherein R^{8a} is selected from the group consisting of carboxamido, optionally substituted alkyl, aralkyl, (heteroaryl)alkyl, hydrogen, (carboxamido)alkyl and hydroxyalkyl.

27. The compound of any one of claims 20 to 22,wherein R^{9a} is $-SO_2R^{11}$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

28. The compound of claim 27, wherein R^{11} is optionally substituted alkyl.

29. The compound of any one of claims 1, 3, and 4 having Formula **IX**:

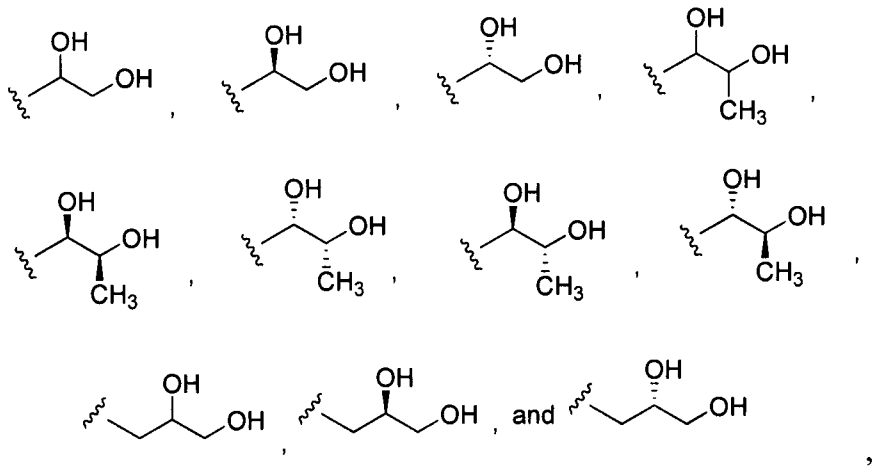


IX

wherein R^7 is hydroxyalkyl, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

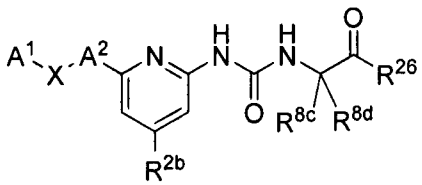
30. The compound of claim 29, wherein said hydroxyalkyl is a C_{2-4} dihydroxyalkyl, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

31. The compound of claim 30, wherein said hydroxyalkyl is selected from the group consisting of:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

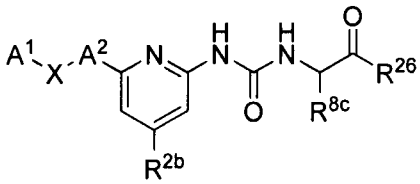
32. The compound of any one of claims 1, 3, or 4 having Formula **X**:



X

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

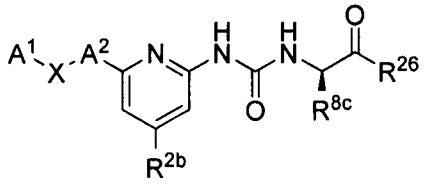
33. The compound of claim 1, 3, 4, and 32 having Formula **XI**:



XI

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

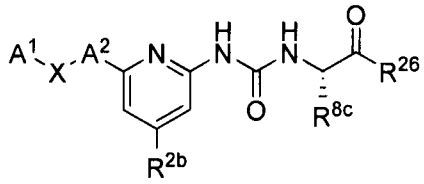
34. The compound of any one of claims 1, 3, 4, and 3334 having Formula **XII**:



XII

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

35. The compound of any one of claims 1, 3, 4, and 33 having Formula **XIII**:



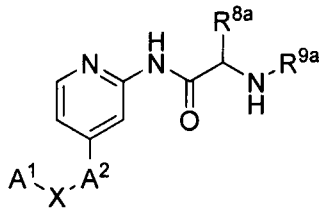
XIII

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

36. The compound of any one of claims 32-35, wherein R^{26} is selected from the group consisting of hydroxy, alkoxy, and amino, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

37. The compound of any one of claims 32 to 3637, wherein R^{8c} is selected from the group consisting of hydrogen, alkyl, (heterocyclo)alkyl, (heteroaryl)alkyl, and (carboxamido)alkyl, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

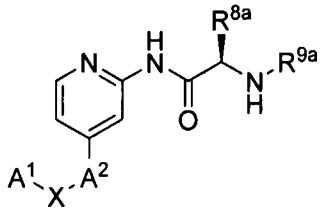
38. The compound of any one of claims 1, 3, and 4 having Formula Formula **XIV**:



XIV

or a pharmaceutically acceptable salt, solvate, or prodrugs thereof.

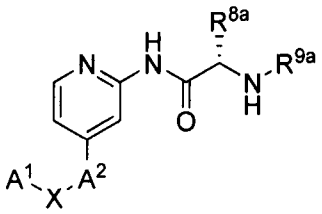
39. The compound of claim 1, 3, 4, and 38 having Formula **XV**:



XV

or a pharmaceutically acceptable salt, solvate, or prodrugs thereof.

40. The compound of any one of claims 1, 3, 4, and 38 having Formula **XVI**:



XVI

or a pharmaceutically acceptable salt, solvate, or prodrugs thereof.

41. The compound of any one of claims 38-40 wherein R^{9a} is $-COR^{10}$, or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

42. The compound of any one of claims 38-41, wherein R^{10} is optionally substituted alkyl and wherein R^{8a} is optionally substituted (heteroaryl)alkyl.

43. The compound of any one of claims 1-42, wherein R^{2b} is selected from the group consisting of halo, hydroxyalkyl and hydrogen.

44. The compound of any one of claims 1-43, wherein:

A^1 is selected from the group consisting of optionally substituted aryl and optionally substituted heteroaryl;

X is -O-; and

A^2 is optionally substituted phenyl,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

45. The compound of claim 44, wherein A^1 selected from the group consisting of:

a) optionally substituted phenyl;

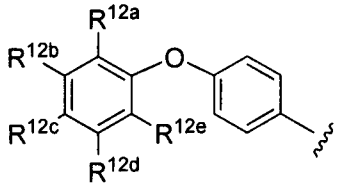
b) optionally substituted 2-pyridyl;

c) optionally substituted 3-pyridyl; and

d) optionally substituted 4-pyridyl,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

46. The compound of any one of claims 1-45, wherein A^1-X-A^2- is:



wherein:

R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e}, which can be identical or different, are selected from the group consisting of:

a) hydrogen;

b) halo;

c) nitro;

d) cyano;

e) hydroxy;

f) amino;

g) alkylamino;

h) dialkylamino;

i) haloalkyl;

j) hydroxyalkyl;

k) alkoxy;

l) haloalkoxy;

m) aryloxy;

n) aralkyloxy;

o) alkylthio;

p) carboxamido;

q) sulfonamido;

r) alkylcarbonyl;

s) arylcarbonyl;

t) alkylsulfonyl;
u) arylsulfonyl;
v) ureido;
w) guanidino;
x) carboxy;
y) carboxyalkyl;
z) alkyl;
aa) optionally substituted cycloalkyl;
bb) optionally substituted alkenyl;
cc) optionally substituted alkynyl;
dd) optionally substituted aryl;
ee) optionally substituted heteroaryl; and
ff) optionally substituted heterocyclo; or

R^{12a} and R^{12b}, or R^{12b} and R^{12c}, or R^{12c} and R^{12d}, or R^{12d} and R^{12e}, taken together with the carbon atoms to which they are attached form a 5- or 6-membered optionally substituted cycloalkyl or heterocyclo group,
or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

47. The compound of claim 46, wherein R^{12a} to R^{12e} is independently selected from the group consisting of hydrogen, halo, cyano, and haloalkyl.

48. The compound of claim 47, wherein R^{12c} is selected from the group consisting of hydrogen, fluoro, cyano, and triflouromethyl and wherein R^{12d} is selected from the group consisting of hydrogen, cyano, and trihalomethyl.

49. The compound of any one of claims 1-45, wherein A^1 is selected as 4-triflouromethyl-2-pyridine.

50. The compound of any one of claims 1-49, with the provisos that

i) when R^{1a} and R^{1b} taken together with the nitrogen atom to which they are attached form a 3- to 8-membered optionally substituted heterocyclo or when R^{1a} is selected as alkoxyalkyl, alkyl or alkylaminoalkyl, then X is selected from the group consisting of:

a) -O-;

b) -S-;

c) -SO-;

d) $-SO_2-$

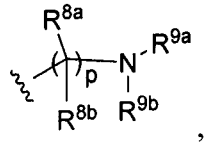
e) $-(CR^3R^4)_m-$;

f) $-SO_2NH-$; and

g) $-NHSO_2-$; or

ii) when A^2 is pyrrolopyridine and X is $C(R^3R^4)_m$, then m is selected from 1, 2, or 3; or

iii) when R^7 is:



,

and X is $-(CR^3R^4)_m-$, then m is 1, 2, or 3.

51. A compound selected from the group consisting of:

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methylpentanamide;

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-phenylpropanamide;

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide;

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-(2-methoxyethoxy)acetamido)-4-methylpentanamide;

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)nicotinamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(3-isopropylureido)-4-methylpentanamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-methyl-2-ureidopentanamide;

N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide;

(S)-N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-N-(2,3-dihydroxypropyl) methanesulfonamide;

N-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)sulfamide;

(S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl) methanesulfonamide;

(S)-N-(4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide;

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)methanesulfonamide;

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)cyclopropanesulfonamide;

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-imidazole-4-sulfonamide;

(S)-2-amino-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl) propanamide;

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)propanamide;

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide;

(S)-1-acetyl-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)piperidine-4-carboxamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(2-methoxyacetamido)propanamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-3-(1H-imidazol-4-yl)propanamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1H-imidazol-4-yl)propanamide;

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1H-imidazol-4-yl)-2-(methylsulfonamido)propanamide;

(S)-tert-butyl(1-amino-4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate;

(S)-tert-butyl(4-amino-1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-1,4-dioxobutan-2-yl)carbamate;

N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide;

N-((S)-1-((4-((S)-1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-4-methyl-1-oxopentan-2-yl)picolinamide;

2-(4-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)piperidin-1-yl)acetic acid;

1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)piperidine-4-carboxylic acid;

(2S,4R)-1-(3-chloro-5-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-hydroxypyrrolidine-2-carboxylic acid;

(2S,4R)-1-(4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-4-hydroxypyrrolidine-2-carboxylic acid;

1-(2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)ethyl)imidazolidin-2-one;

2-amino-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-6-hydroxypyrimidine-4-carboxamide;

(S)-1-(2-((4-(1,2-dihydroxyethyl)-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)ethyl)imidazolidin-2-one,

pyridine-2-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide,

cyclopropanecarboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide,

N-((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-nicotinamide,

N-((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-isonicotinamide,

5-methyl-isoxazole-3-carboxylic acid ((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-amide,

((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-hydroxy-ethyl)-carbamic acid tert-butyl ester,

(S)-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-(2-hydroxy-acetylamino)-propionamide,

(S)-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-2-ureido-propionamide,

((S)-1-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-ylcarbamoyl}-2-pyridin-3-yl-ethyl)-carbamic acid tert-butyl ester,

(S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide,

(S)-2-acetylamino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-hydroxy-butyramide,

(S)-2-amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pridin-2-yl}-3-hydroxy-propionamide, and

(S)-2-amino-N-{6-[4-(4-fluoro-phenoxy)-phenyl]-pyridin-2-yl}-3-pyridin-3-yl-propionamide,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

52. A compound selected from the group consisting of:

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide,

N-(6-(4-(4-cyanophenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide,

N-(6-(4-(3-cyano-4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide,

N-(6-(4-(4-cyano-3-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl)-2,3-dihydroxypropanamide,

2,3-dihydroxy-N-(6-(4-(4-(trifluoromethyl)phenoxy)phenyl)pyridin-2-yl) propanamide,

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide,

(R)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxy-2-methylpropanamido)-3-(1-methyl-1H-imidazol-4-yl)propanamide,

(S)-2-((4-chloro-6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino) propanamide,

(S)-2-((1-amino-1-oxopropan-2-yl)amino)-6-(4-(4-fluorophenoxy)phenyl) isonicotinamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-propionamidopropanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-isobutyramido-3-(1-methyl-1H-imidazol-4-yl)propanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)-2-pivalamidopropanamide,

(S)-2-acetamido-N-(4-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-4-yl)propanamide,

(S)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)cyclopropanecarboxamide,

(S)-3,3,3-trifluoro-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)propanamide,

(S)-2-acetamido-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-(1-methyl-1H-imidazol-5-yl)propanamide,

(R)-N-(1-((6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)amino)-3-(1-methyl-1H-imidazol-4-yl)-1-oxopropan-2-yl)-4-(trifluoromethyl)benzamide,

(S)-2-(3-(tert-butyl)ureido)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxypropanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-(2-hydroxyacetamido)-4-methylpentanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(3-isopropylureido)propanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxy-2-methylpropanamido)propanamide,

(S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-methoxyacetamido)propanamide,

(R)-2-acetamido-3-(1-methyl-1H-imidazol-4-yl)-N-(6-(4-((5-(trifluoromethyl) pyridin-2-yl)oxy)phenyl)pyridin-2-yl)propanamide,

(2S,3S)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-3-hydroxy-2-(2-hydroxyacetamido)butanamide,

2,3-dihydroxy-N-(6-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)pyridin-2-yl)propanamide,

(E)-N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-2-phenylethene sulfonamide,

N-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)-1-methyl-1H-benzo[d]imidazole-6-carboxamide,

(S)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanamide,

(S)-methyl 2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1-methyl-1H-imidazol-4-yl)propanoate,

(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-indol-2-yl) propanamide,

(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)succinamide, and

(R)-2-(3-(6-(4-(4-fluorophenoxy)phenyl)pyridin-2-yl)ureido)-3-(1H-imidazol-5-yl) propanamide,

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

53. A pharmaceutical composition comprising the compound of any one of claims 1-52 and a pharmaceutically acceptable carrier.

54. Use of a compound of any one of claims 1 to 52 or a pharmaceutically acceptable salt, solvate or prodrug thereof in the manufacture of a medicament for the treatment of stroke, neuronal damage resulting from head trauma, epilepsy, seizures, neuronal loss following global and focal ischemia, pain, migraine, primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, mental retardation, a neurodegenerative disorder, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia

55. The use of claim 54, in the manufacture of a medicament for the treatment of pain.

56. The use of claim 55, in the manufacture of a medicament for preemptive or palliative treatment of pain.

57. The use of claim 55, wherein said pain is selected from the group consisting of chronic pain, inflammatory pain, neuropathic pain, acute pain, and surgical pain.

58. A compound of any one of claims 1 to 53 or a pharmaceutically acceptable salt, solvate or prodrug thereof for use in the treatment of stroke, neuronal damage resulting from head trauma, epilepsy, seizures, neuronal loss following global and focal ischemia, pain, migraine,

primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, mental retardation, a neurodegenerative disorder, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia.

59. The compound of claim 58 for use in the treatment of pain.

60. The compound of claim 59 for use in the preemptive or palliative treatment of pain.

61. The compound of claim 59, wherein said pain is selected from the group consisting of chronic pain, inflammatory pain, neuropathic pain, acute pain, and surgical pain.

62. A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering from said disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound as claimed in of any one of claims 1-52.

63. The method of claim 62, wherein a disorder responsive to the blockade of TTX-resistant sodium channels is treated.

64. The method of claim 62, wherein a disorder responsive to the blockade of TTX-sensitive sodium channels is treated.

65. The method of claim 62, wherein a disorder responsive to the blockade of $Na_v1.7$ sodium channels is treated.

66. A method for treating stroke, neuronal damage resulting from head trauma, epilepsy, seizures, neuronal loss following global and focal ischemia, pain, migraine, primary erythromelalgia, paroxysmal extreme pain disorder, cerebellar atrophy, ataxia, mental retardation, a neurodegenerative disorder, manic depression, tinnitus, myotonia, a movement disorder, or cardiac arrhythmia, or providing local anesthesia in a mammal, comprising administering an effective amount of a compound as claimed in of any one of claims 1-52 to a mammal in need of such treatment.

67. The method of claim 66, wherein said method is for treating pain.

68. The method of claim 66, wherein said method is for preemptive or palliative treatment of pain.

69. The method of claim 67, wherein said pain is selected from the group consisting of chronic pain, inflammatory pain, neuropathic pain, acute pain, and surgical pain.

70. A method of modulating sodium channels in a mammal, comprising administering to the mammal at least one compound as claimed in of any one of claims 1-52.

71. The method of claim 70, wherein the $Na_v1.7$ sodium channel is modulated.

72. A pharmaceutical composition comprising the compound as claimed in of any one of claims 1-52 for treating a disorder responsive to the blockade of sodium ion channels.

73. A compound as claimed in any one of claims 1-52 for use in treating a disorder responsive to the blockade of sodium ion channels.

74. The compound as claimed in any one of claims 1-52, wherein the compound is ^{3}H, ^{11}C, or ^{14}C radiolabeled, or a pharmaceutically acceptable salt, prodrug, or solvate thereof.

75. A method of screening a candidate compound for the ability to bind to a binding site on a protein using a radiolabeled compound of claim 74, comprising a) introducing a fixed concentration of the radiolabeled compound to a soluble or membrane-associated protein or fragment thereof to form a mixture; b) titrating the mixture with a candidate compound; and c) determining the binding of the candidate compound to said binding site.

76. A method of preparing a pharmaceutical composition, comprising admixing a therapeutically effective amount of a compound of any one of claims 1-52, or a pharmaceutically acceptable salt, prodrug, or solvate thereof, with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/003137

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/75 C07D401/02 C07D401/12 C07D401/14 A61K31/44 A61K31/4439 A61P25/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 481 965 A1 (ENDO HITOSHI [JP]) 1 December 2004 (2004-12-01) tables 12,13; compounds 97,110	1,53
X	WO 2007/050348 A2 (MERCK & CO INC [US]; TROTTER WESLEY B [US]; NANDA KAUSIK K [US]; WOLKE) 3 May 2007 (2007-05-03) compounds I-340	1,53
X	WO 2005/070916 A1 (LILLY CO ELI [US]; CASTANO MANSANET ANA MARIA [ES]; DOMINGUEZ-MANZANAR) 4 August 2005 (2005-08-04) compounds A134, A135	1,53
X	US 2008/187575 A1 (KLEBL BERT [DE] ET AL) 7 August 2008 (2008-08-07) paragraph [0492]	1

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 March 2012	13/03/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Usuelli, Ambrogio

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/003137

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/030967 A1 (WYETH LLC [US]; TSOU HWEI-RU [US]; BIRNBERG GARY HAROLD [US]; MAC EWAN) 18 March 2010 (2010-03-18) compound 74	1,53
X	US 2004/054186 A1 (DAS JAGABANDHU [US] ET AL) 18 March 2004 (2004-03-18) compounds 476,477	1,53
X	WO 2009/140517 A1 (HYDRA BIOSCIENCES INC [US]; CHONG JAYHONG A [US]) 19 November 2009 (2009-11-19) figure 1	1,53
X	EP 1 402 900 A1 (TAKEDA CHEMICAL INDUSTRIES LTD [JP]) 31 March 2004 (2004-03-31)	1
X	US 2003/236256 A1 (EBERLE MARTIN [CH] ET AL) 25 December 2003 (2003-12-25) compounds 240,247	1,53
X	US 6 979 686 B1 (NARAIAN ASHOK S [US] ET AL) 27 December 2005 (2005-12-27) compounds A-268	1,53
X,P	WO 2011/019780 A1 (SQUIBB BRISTOL MYERS CO [US]; DUAN JINGWU [US]; JIANG BIN [US]; LU ZHO) 17 February 2011 (2011-02-17) paragraph [0163]	1,46,53
A	WO 2006/119390 A1 (VERTEX PHARMA [US]; WILSON DEAN [US]; TERMIN ANDREAS P [US]; FANNING L) 9 November 2006 (2006-11-09) paragraph [0021]	1-76
A	WO 2009/049181 A1 (VERTEX PHARMA [US]; CHEN WEICHUAN CAROLINE [US]; KRENITSKY PAUL [US];) 16 April 2009 (2009-04-16) the whole document	1-76
A	BIN SHAO ET AL: "Phenoxyphenyl Pyridines as novel State-Dependent, High-Potency Sodium Channel Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 47, no. 17, 1 January 2004 (2004-01-01), pages 4277-4285, XP002413029, ISSN: 0022-2623, DOI: 10.1021/JM040048D the whole document	1-76

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/003137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1481965 A1	01-12-2004	AU 2003208105 A1	02-09-2003
		CA 2475434 A1	14-08-2003
		CN 1630632 A	22-06-2005
		EP 1481965 A1	01-12-2004
		JP 4705756 B2	22-06-2011
		US 2005119256 A1	02-06-2005
		WO 03066574 A1	14-08-2003
WO 2007050348 A2	03-05-2007	AU 2006306542 A1	03-05-2007
		CA 2626496 A1	03-05-2007
		EP 1940406 A2	09-07-2008
		JP 2009512703 A	26-03-2009
		US 2009233897 A1	17-09-2009
		WO 2007050348 A2	03-05-2007
WO 2005070916 A1	04-08-2005	EP 1706395 A1	04-10-2006
		US 2007105852 A1	10-05-2007
		WO 2005070916 A1	04-08-2005
US 2008187575 A1	07-08-2008	CA 2578122 A1	02-03-2006
		EP 1786781 A2	23-05-2007
		JP 2008510766 A	10-04-2008
		US 2008187575 A1	07-08-2008
		WO 2006021458 A2	02-03-2006
WO 2010030967 A1	18-03-2010	US 2010068204 A1	18-03-2010
		WO 2010030967 A1	18-03-2010
US 2004054186 A1	18-03-2004	NONE	
WO 2009140517 A1	19-11-2009	NONE	
EP 1402900 A1	31-03-2004	CA 2450400 A1	19-12-2002
		EP 1402900 A1	31-03-2004
		US 2005080113 A1	14-04-2005
		WO 02100433 A1	19-12-2002
US 2003236256 A1	25-12-2003	AT 302549 T	15-09-2005
		AU 8384101 A	17-12-2001
		AU 2001283841 B2	05-05-2005
		BR 0111492 A	30-09-2003
		CA 2409877 A1	13-12-2001
		CN 1446048 A	01-10-2003
		DE 60112933 D1	29-09-2005
		DE 60112933 T2	09-03-2006
		EP 1292190 A1	19-03-2003
		ES 2245992 T3	01-02-2006
		JP 2003535109 A	25-11-2003
		MX PA02011919 A	13-09-2004
		PL 360434 A1	06-09-2004
		US 2003236256 A1	25-12-2003
		WO 0193682 A1	13-12-2001
US 6979686 B1	27-12-2005	NONE	
WO 2011019780 A1	17-02-2011	NONE	
WO 2006119390 A1	09-11-2006	EP 1877381 A1	16-01-2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/003137

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 2008540438 A	20-11-2008
		WO 2006119390 A1	09-11-2006
WO 2009049181 A1	16-04-2009	AU 2008310661 A1	16-04-2009
		CA 2701766 A1	16-04-2009
		CN 101855210 A	06-10-2010
		EP 2212292 A1	04-08-2010
		JP 2011500599 A	06-01-2011
		KR 20100066583 A	17-06-2010
		RU 2010118481 A	20-11-2011
		US 2009118333 A1	07-05-2009
		WO 2009049181 A1	16-04-2009