HETEROCYCLIC SUBSTITUTED 2- (4-PHENOXY) PYRIDINE DERIVATIVES AND RELATED COMPOUNDS AS SODIUM CHANNEL BLOCKERS FOR THE TREATMENT OF NEURONAL DAMAGE AND NEURODEGENERATIVE CONDITIONS

Field of the Invention

This invention is in the field of medicinal chemistry. In particular, the invention relates to novel aryl substituted pyridines and the discovery that these compounds act as blockers of sodium (Na^+) channels.

Related Art

Several classes of therapeutically useful drugs, including local anesthetics such as lidocaine and bupivacaine, antiarrhythmics such as propafenone and amioclarone, and anticonvulsants such as lamotrigine, phenytoin and carbamazepine, have been shown to share a common mechanism of action by blocking or modulating Na^+ channel activity (Catterall, W.A., *Trends Pharmacol. Sci. 8*:57-65 (1987)). Each of these agents is believed to act by interfering with the rapid influx of Na^+ ions.

Recently, other Na^+ channel blockers such as BW619C89 and lifarizine have been shown to be neuroprotective in animal models of global and focal ischemia and are presently in clinical trials (Graham *et al., J. Pharmacol. Exp. Ther.* 269:854-859 (1994); Brown *et al., British J. Pharmacol. 115*:1425-1432 (1995)).

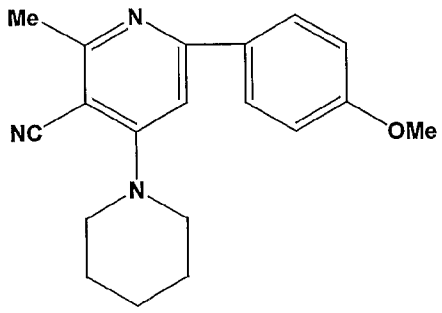
The neuroprotective activity of Na^+ channel blockers is due to their effectiveness in decreasing extracellular glutamate concentration during ischemia by inhibiting the release of this excitotoxic amino acid neurotransmitter. Studies have shown that unlike glutamate receptor antagonists, Na^+ channel blockers prevent hypoxic damage to mammalian white matter (Stys *et al., J. Neurosci. 12*:430-439 (1992)). Thus, they may offer advantages for treating certain types of strokes or neuronal trauma where damage to white matter tracts is prominent.

Another example of clinical use of a Na^+ channel blocker is riluzole. This drug has been shown to prolong survival in a subset of patients with ALS

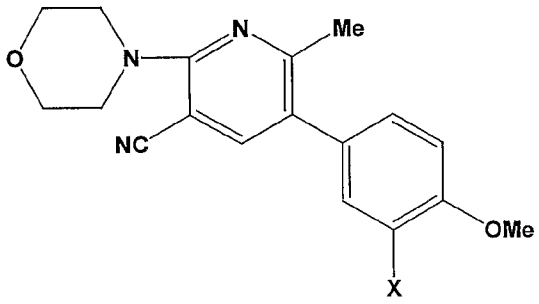
(Bensimm *et al., New Engl. J. Med. 330*:585-591 (1994)) and has subsequently been approved by the FDA for the treatment of ALS. In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are occasionally used to treat neuropathic pain, such as from trigeminal neurologia, diabetic neuropathy and other forms of nerve damage (Taylor and Meldrum, *Trends Pharmacol. Sci. 16*:309-316 (1995)), and carbamazepine and lamotrigine have been used for the treatment of manic depression (Denicott *et al., J. Clin. Psychiatry 55*: 70-76 (1994)). Furthermore, based on a number of similiarities between chronic pain and tinnitus, (Moller, A. R. *Am. J. Otol. 18:* 577-585 (1997); Tonndorf, *J. Hear. Res. 28:* 271-275 (1987)) it has been proposed that tinnitus should be viewed as a form of chronic pain sensation (Simpson, J. J. and Davies, E. W. *Tip. 20:* 12-18 (1999)). Indeed, lignocaine and carbamazepine have been shown to be efficacious in treating tinnitus (Majumdar, B. *et al. Clin. Otolaryngol. 8:* 175-180 (1983); Donaldson, I. *Laryngol. Otol. 95:* 947-951 (1981)).

It has been established that there are at least five to six sites on the voltage-sensitive Na^+ channels which bind neurotoxins specifically (Catterall, W.A., *Science 242*:50-61 (1988)). Studies have further revealed that therapeutic antiarrhythmics, anticonvulsants and local anesthetics whose actions are mediated by Na^+ channels, exert their action by interacting with the intracellular side of the Na^+ channel and allosterically inhibiting interaction with neurotoxin receptor site 2 (Catterall, W.A., *Ann. Rev. Pharmacol. Toxicol. 10*:15-43 (1980)).

Satayanarayana (*Synthesis 10*:889-890 (1991)) discloses a compound of formula:

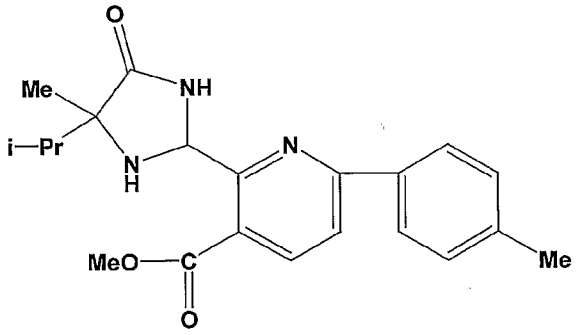


EP 200024 discloses compounds of formula:

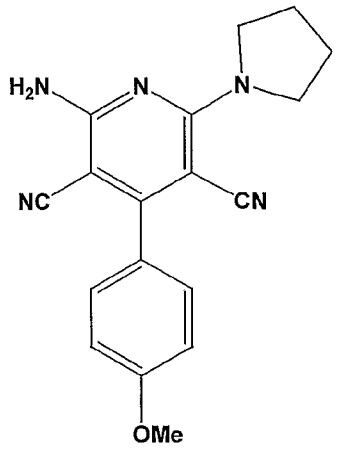


where X is H or OMe. These compounds are disclosed to be useful as potential cardiotonics.

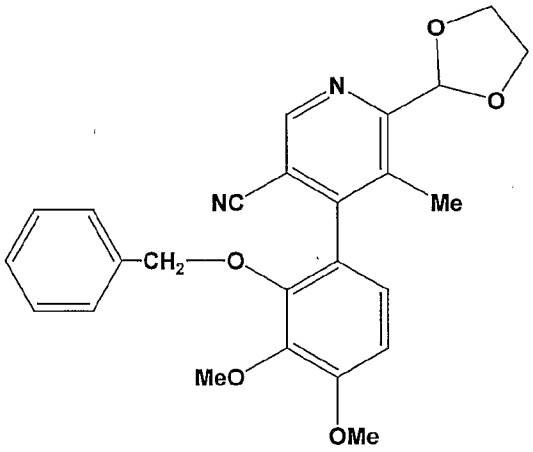
U.S. Patent No. 4,701,208 discloses a herbicidal compound of the following formula:



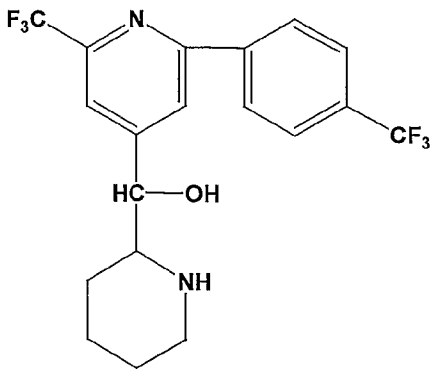
Fuentes *et al.* (*An. Quim., Ser. C.* 76:68-69 (1980)) disclose the following compound:



Liao *et al.* (*J. Heterocycl. Chem. 13*:1283-1288 (1976) disclose the formula:



U.S. Patent Nos. 3,940,404 and 3,886,167 disclose the following compound as an antimalarial:



SUMMARY OF THE INVENTION

The present invention is related to the discovery that aryl substituted pyridines represented by Formula **I** act as blockers of sodium (Na^+) channels.

The invention is also related with 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 Formula **I** as described herein.

The present invention is also directed to the use of a compound of Formula **I** for the treatment of neuronal damage following global and focal ischemia, and for the treatment or prevention of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS), for the treatment of tinnitus, as antimanic depressants, as local anesthetics, as antiarrhythmics, as anticonvulsants and for the treatment or prevention of diabetic neuropathy and for the treatment of pain including both acute and chronic pain and migraine headache.

A number of compounds useful in the present invention have not been heretofor reported. Thus, one aspect of the present invention is directed to the novel aryl substituted pyridines of Formula **I**.

Another aspect of the present invention is directed to the novel compounds of Formula **I** as blockers of sodium channels.

A further aspect of the present invention is to provide a method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating pain including acute and chronic pain, and neuropathic pain; treating, preventing or ameliorating convulsion and neurodegenerative conditions; treating, preventing or ameliorating manic depression; using as local anesthesics and anti-arrhythmics, and treating tinnitus by administering a compound of Formula **I** to a mammal in need of such treatment or use.

Also, an aspect of the present invention is to provide a pharmaceutical composition useful for treating disorders responsive to the blockade of sodium

ion channels, containing an effective amount of a compound of Formula **I** in a mixture with one or more pharmaceutically acceptable carriers or diluents.

Further, the present invention is directed to ^{3}H and ^{14}C radiolabeled compounds of Formula **I** and their use as radioligands for their binding site on the sodium channel.

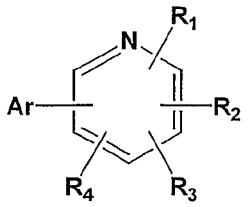
Additional embodiments and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

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

DETAILED DESCRIPTION OF THE INVENTION

The present invention arises out of the discovery that aryl substituted pyridines of Formula **I** are anticonvulsants and act as blockers of Na^{+} channels. In view of this discovery compounds of Formula **I** are useful for treating disorders responsive to the blockade of sodium ion channels.

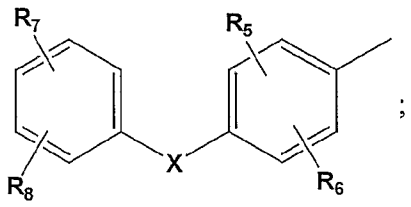
The compounds useful in this aspect of the present invention are aryl substituted pyridines represented by Formula **I**:

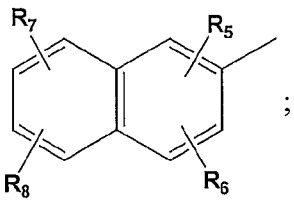


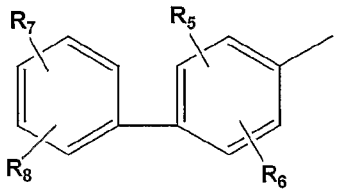
I

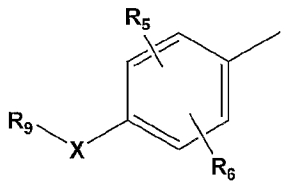
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl,

hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

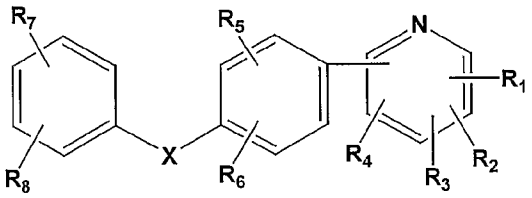
X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4.

Ar is preferably Ar_1. Preferably, Ar is at the 2-position of the pyridyl ring. R_1 is preferably at the 6-position of the pyridyl ring. Preferably, R_2 is at the 4-position of the pyridyl ring.

Since the compounds of Formula **I** are blockers of sodium (Na^+) channels, a number of diseases and conditions mediated by sodium ion influx can be treated employing these compounds. Therefore, the invention is related to a method of treating, preventing or ameliorating neuronal loss associated with stroke, global and focal ischemia, CNS trauma, hypoglycemia and surgery, spinal cord trauma; as well as treating or ameliorating neurodegenerative diseases including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, treating or ameliorating anxiety, convulsions, glaucoma, migraine headache, and muscle spasm. The compounds of Formula I are also useful as antitinnitus agents, antimanic depressants, as local anesthetics, and as antiarrhythmics; as well as for treating, preventing or ameliorating pain including surgical, chronic and neuropathic pain. In each instance, the methods of the present invention require administering to an

animal in need of such treatment an effective amount of a sodium channel blocker of the present invention, or a pharmaceutically acceptable salt or prodrug thereof.

Accordingly, compounds useful in the present invention are aryl substituted pyridines represented by Formula **II**:



II

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

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl,

cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2.

Preferably, R_1 is selected from the group consisting of an alkyl optionally substituted by halogen or hydroxy, thiomethyl, $C(O)R_{10}$, and SO_2R_{10}, wherein R_{10} is selected from the group consisting of alkyl, alkenyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, and heterocycloalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}.

Useful R_2 groups include, for example, N-morpholinyl, N-piperidinyl, N-piperazinyl, N-piperidinylmethoxy, 2-(N-piperidinyl)ethoxy, 3-(N-piperidinyl)propoxy, N-piperidinylmethylsulfide, 2-(N-piperidinyl)-ethylsulfide, and 3-(N-piperidinyl)propylsulfide.

Preferably, R_3 and R_4 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aminoalkyl, amino, hydroxyalkyl, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino, more preferably hydrogen, alkyl, alkoxy, aminoalkyl and aminocarbonyl. Preferably both R_3 and R_4 are hydrogen.

Preferably, R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, and cyano. More preferably, R_5, R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, alkyl, halogen, haloalkyl, and nitro. Preferred values of R_5-R_8 include hydrogen, halo, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 hydroxyalkyl, nitro, amino, ureido, cyano, C_1-C_6 acylamido, hydroxy, thiol, C_1-C_6 acyloxy, azido, C_1-C_6 alkoxy, or carboxy. The groups R_5-R_8 each

take the place of a hydrogen atom that would otherwise be present in any position on the aryl ring to which the R group is attached. Especially preferred are compounds where R_5 and R_6 are both hydrogen, R_7 is hydrogen and R_8 is a fluoro in the para-position.

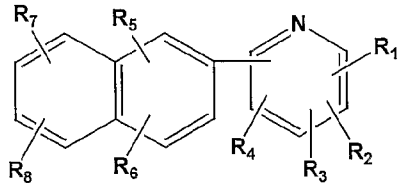
Preferably, R_9 is a branched alkyl group of C_{3-10} carbon atoms, more preferably C_{3-6} carbon atoms, optionally substituted with one or more of halogen, hydroxy, nitro, amino, cyano, and alkoxy.

Preferably, R_{10} is selected from the group consisting of alkyl, alkenyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, and heterocycloalkylamino, preferably piperidinylethylamino, especially 2-(N-piperidinyl)ethylamino, all of which can be optionally substituted, wherein R_{11} is as defined above, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}.

Preferably X is O or S, more preferably X is O.

In one aspect of the invention, preferred compounds falling within the scope of Formula **II** include compounds wherein X is O or S. In this aspect of the invention R_1 is preferably aminocarbonyl or methyl, and R_3 and R_4 both are preferably hydrogen. Preferred R_2 and R_5-R_8 groups are as described above.

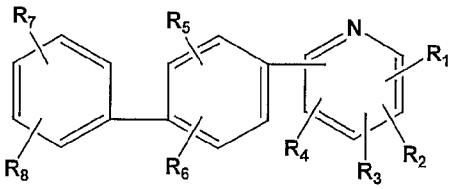
Further, compounds useful in the present invention are aryl substituted pyridines represented by Formula **III**:



III

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_8 are defined previously with respect to Formulae **I-II**. R_1 through R_8 have preferred values as described above for Formula **II**. Preferably both R_3 and R_4 are hydrogen.

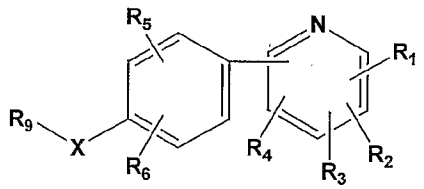
Further, compounds useful in the present invention are aryl substituted pyridines represented by Formula **IV**:



IV

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_8 are defined previously with respect to Formulae **I-II**. Preferably both R_3 and R_4 are hydrogen.

Also, compounds useful in the present invention are aryl substituted pyridines represented by Formula **V**:



V

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_6, and R_9 are defined previously with respect to Formulae **I-II**, and X is one of O, S, NH, or absent.

Another group of compounds useful in this aspect of the present invention are aryl substituted pyridines represented by the general Formula **V**, wherein R_1-R_6, R_9, and X are as described above, with the proviso that when R_1 is other than $C(O)R_{10}$, SO_2R_{10}, or $OC(O)NH_2$, then n is not 0 (zero).

Preferred compounds falling within the scope of Formula **V** include compounds wherein X is O, S, or absent. Preferably, R_9 is a branched chain C_{3-6} alkyl, more preferably C_{3-4} alkyl, optionally substituted with one or more of halogen, especially fluoro or chloro, or trihalomethyl, especially trifluoromethyl. R_5 and R_6 have preferred values as described above for Formula **II**.

Exemplary preferred compounds that may be employed in this method of invention include, without limitation:

2-[4-(4-fluorophenoxy)phenyl]-4-N-morpholinylpyridine-6-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)ethoxy]-pyridine;

2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-N-morpholinylpyridine;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

Useful aryl groups are C_{6-14} aryl, especially C_{6-10} aryl. Typical C_{6-14} aryl groups include phenyl, naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl and fluorenyl groups.

Useful cycloalkyl groups are C_{3-8} cycloalkyl. Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Useful halo or halogen groups include fluorine, chlorine, bromine and iodine.

Useful alkyl groups include straight-chained and branched C_{1-10} alkyl groups, more preferably C_{1-6} alkyl groups. Typical C_{1-10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, 3-pentyl, hexyl and octyl groups. Also contemplated is a trimethylene group substituted on two adjoining positions on the benzene ring of the compounds of the invention.

Useful alkenyl groups are C_{2-6} alkenyl groups, preferably C_{2-4} alkenyl. Typical C_{2-4} alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and *sec*-butenyl.

Useful alkynyl groups are C_{2-6} alkynyl groups, preferably C_{2-4} alkynyl. Typical C_{2-4} alkynyl groups include ethynyl, propynyl, butynyl, and 2-butynyl groups.

Useful arylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Useful values include benzyl, phenethyl and naphthylmethyl.

Useful arylalkenyl groups include any of the above-mentioned C_{2-4} alkenyl groups substituted by any of the above-mentioned C_{6-14} aryl groups.

Useful arylalkynyl groups include any of the above-mentioned C_{2-4} alkynyl groups substituted by any of the above-mentioned C_{6-14} aryl groups. Useful values include phenylethynyl and phenylpropynyl.

Useful cycloalkylalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned cycloalkyl groups.

Useful haloalkyl groups include C_{1-10} alkyl groups substituted by one or more fluorine, chlorine, bromine or iodine atoms, e.g. fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl and trichloromethyl groups.

Useful hydroxyalkyl groups include C_{1-10} alkyl groups substituted by hydroxy, e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups.

Useful alkoxy groups include oxygen substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful alkylthio groups include sulfur substituted by one of the C_{1-10} alkyl groups mentioned above.

Useful acylamino groups are any acyl group, particularly C_{2-6} alkanoyl or C_{6-10} aryl(C_{2-6})alkanoyl attached to an amino nitrogen, e.g. acetamido, propionamido, butanoylamido, pentanoylamido, hexanoylamido, and benzoyl.

Useful acyloxy groups are any C_{1-6} acyl (alkanoyl) attached to an oxy (-O-) group, e.g. acetoxy, propionoyloxy, butanoyloxy, pentanoyloxy, hexanoyloxy and the like.

The term heterocyclic is used herein to mean saturated or wholly or partially unsaturated 3-7 membered monocyclic, or 7-10 membered bicyclic ring system, which consists of carbon atoms and from one to four heteroatoms independently selected from the group consisting of O, N, and S, wherein the nitrogen and sulfur heteroatoms can be optionally oxidized, the nitrogen can be optionally quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples include, but are not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazoline, pyrazolidine, benzodiazepines, and the like.

Useful heterocycloalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned heterocyclic groups.

Useful heterocycloalkylamino groups include any of the above-mentioned heterocycloalkyl groups attached to an amino nitrogen, such as 2-(N-piperidinyl)ethylamino.

Useful alkylamino and dialkylamino groups are —NHR_{13} and —$NR_{13}R_{14}$, wherein R_{13} and R_{14} are C_{1-10} alkyl groups.

Useful dialkylaminoalkyl groups include any of the above-mentioned C_{1-10} alkyl groups substituted by any of the above-mentioned dialkylamino groups.

Useful dialkylaminoalkylamino groups include any of the above-mentioned dialkylaminoalkyl groups attached to an amino nitrogen, such as dimethylaminoethylamino.

Aminocarbonyl group is —$C(O)NH_2$.

Useful alkylaminocarbonyl groups are carbonyl groups substituted by —NHR_{13} and —$NR_{13}R_{14}$, wherein R_{13} and R_{14} are C_{1-10} alkyl groups.

Useful alkylthiol groups include any of the above-mentioned C_{1-10} alkyl groups substituted by a –SH group.

A carboxy group is –COOH.

An azido group is $-N_3$.

An ureido group is –NH-C(O)-NH_2.

An amino group is $-NH_2$.

An amide group is an organic radical having –NHC(O)– as a functional group.

Optional substituents on R_1-R_{11} include any one of halo, halo(C_{1-6})alkyl, aryl, heterocycle, cycloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, cycloalkyl(C_{1-6})alkyl, heterocyclo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, carboxy(C_{1-6})alkyl, alkoxy(C_{1-6})alkyl, nitro, amino, ureido, cyano, acylamino, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, aminocarbonyl, and C_{1-6}

alkylthiol groups mentioned above. Preferred optional substituents include: halo, halo(C_{1-6})alkyl, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, hydroxy, nitro, C_{1-6} alkyl, alkoxy and amino.

The invention disclosed herein is also meant to encompass prodrugs of the disclosed compounds. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug in vivo.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled compound of the invention, administering it parenterally in a detectable dose to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur and isolating its conversion products from the urine, blood or other biological samples.

The invention disclosed herein is also meant to encompass the disclosed compounds being isotopically-labelled 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, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

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 also meant to encompass all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers may be separated according to methods that are well known to those of ordinary skill in the art. When the

compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to 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 term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposeable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

The term "racemic" refers to a mixture of equal parts of enantiomers and which 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 invention disclosed is also meant to encompass all pharmaceutically acceptable salts thereof of the disclosed compounds. Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition 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 calsium 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

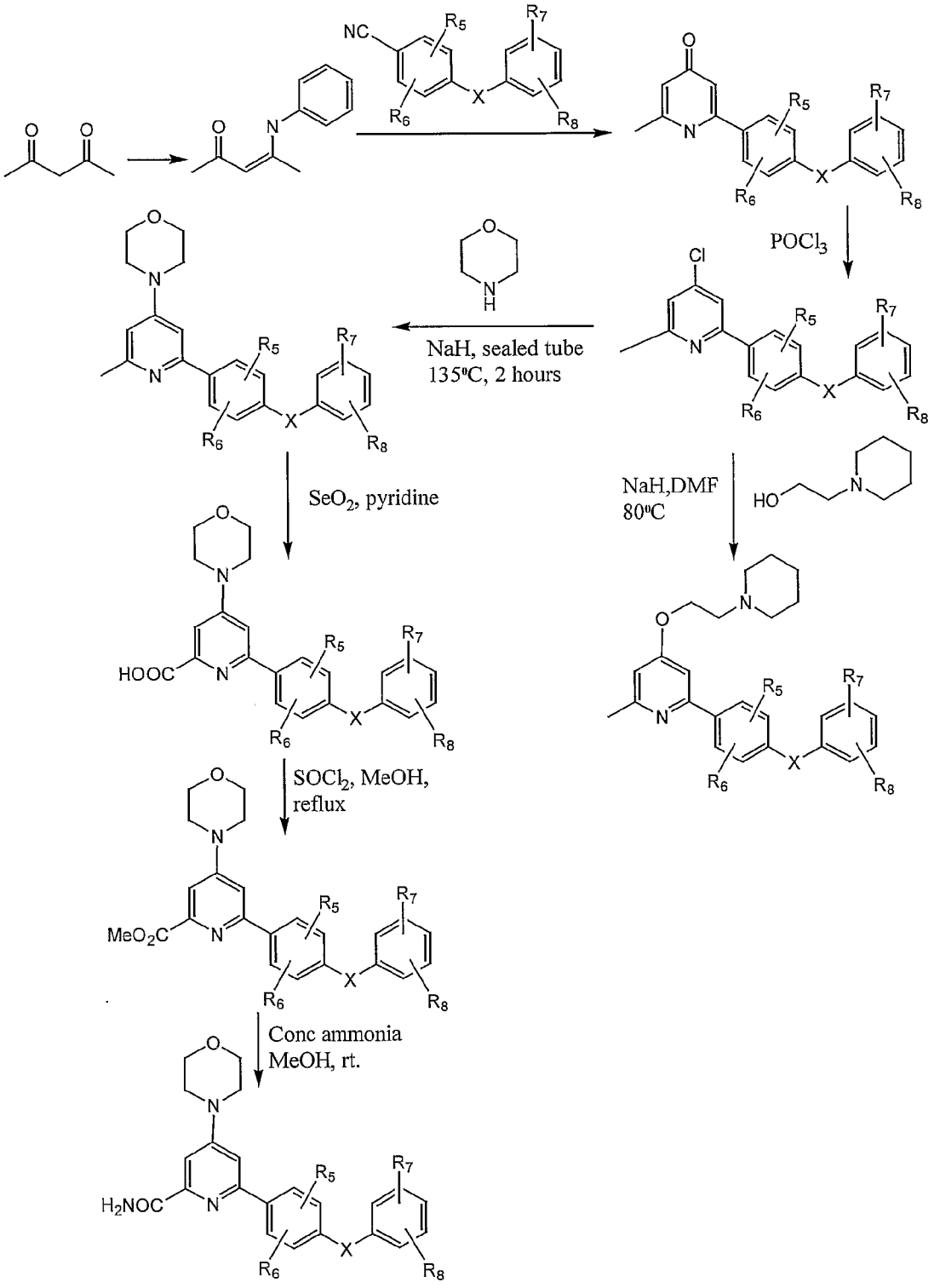
as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; and amino acid salts such as arginate, asparginate, glutamate and the like.

Examples of prodrugs include esters or amides of Formulae **I-V** with any of R_3-R_8 as hydroxyalkyl or aminoalkyl, and these may be prepared by reacting such compounds with anhydrides such as succinic anhydride.

The invention is also directed to a method for treating disorders responsive to the blockade of sodium channels in animals suffering thereof. Particular preferred embodiments of the aryl substituted pyridyl compounds for use in method of this invention are represented by previously defined Formulae **I-V**.

The compounds of this invention may be prepared using methods known to those skilled in the art. For example, compounds of the invention can be prepared according to Scheme 1.

Scheme I


NC
R5
R7
X
R6
R8
O
N
POCl3
Cl
NaH, sealed tube
135°C, 2 hours
NaH,DMF
80°C
HO
SeO2, pyridine
HOOC
SOCl2, MeOH,
reflux
MeO2C
Conc ammonia
MeOH, rt.
H2NOC

The invention is also directed to ^{3}H and ^{14}C radiolabeled compounds of Formula **I** and their use as radioligands for their binding site on the sodium channel. For example, one use of the labeled compounds of the invention is the characterization of specific receptor binding. Another use of the labeled compounds of the invention is an alternative to animal testing for the evaluation of structure-activity relationships. The receptor assay is performed at a fixed concentration of a labeled compound of Formula **I** and at increasing concentrations of a test compound in a competition assay.

Tritiated compounds of Formula **I** can be prepared by introducing tritium into the compound of Formula **I** by, for example, catalytic dehalogenation with tritium. This method includes reacting a suitably halogen-substituted precursor of a compound of Formula **I** 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. ^{14}C-labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

The compounds of the present invention were assessed by electrophysiological assays in dissociated hippocampal neurons for sodium channel blocker activity. These compounds also could be assayed for binding to the neuronal voltage-dependent sodium channel using rat forebrain membranes and [^{3}H]BTX-B.

Sodium channels are large transmembrane proteins that are expressed in various tissues. They are voltage sensitive channels and are responsible for the rapid increase of Na^{+} permeability in response to depolarization associated with the action potential in many excitable cells including muscle, nerve and cardiac cells.

One aspect of the present invention is the discovery of the mechanism of action of the compounds herein described as specific Na^{+} channel blockers. Based upon the discovery of this mechanism, these compounds are contemplated to be useful in treating or preventing neuronal loss due to focal

or global ischemia, and in treating or preventing neurodegenerative disorders including ALS, anxiety, and epilepsy. They are also expected to be effective in treating, preventing or ameliorating neuropathic pain, surgical pain, chronic pain and tinnitus. The compounds are also expected to be useful as antiarrhythmics, anesthetics and antimanic depressants.

The present invention is directed to compounds of Formulae **I-V** that are blockers of voltage-sensitive sodium channels. According to the present invention, those compounds having preferred sodium channel blocking properties exhibit an IC_{50} of about 100 μM or less in the electrophysiological assay described herein. Preferably, the compounds of the present invention exhibit an IC_{50} of 10 μM or less. Most preferably, the compounds of the present invention exhibit an IC_{50} of about 1.0 μM or less. Substituted heteroaryl compounds of the present invention may be tested for their Na^+ channel blocking activity by the following electrophysiological and binding assays.

Electrophysiological Assay:

Electrophysiological Assay was used to measure potencies of compounds of the present invention rBIIa/beta 1 sodium channels expressed in *Xenopus* oocytes.

Preparation of cRNA encoding cloned rat brain type IIa (rBIIa) and beta 1 (β1): cDNA clones encoding the rat brain beta 1 subunit were cloned in house using standard methods, and mRNA were prepared by standard methods. mRNA encoding rBIIa was provided by Dr. A. Golden (UC Irvine). The mRNAs were diluted and stored at -80°C in 1 μL aliquots until injection.

Preparation of oocytes: Mature female *Xenopus laevis* were anaesthetized (20-40 min) using 0.15 % 3-aminobenzoic acid ethyl ester (MS-222) following established procedures (Woodward, R. M., *et al.*, *Mol. Pharmacol. 41*:89-103 (1992)).

Two to six ovarian lobes were surgically removed. Oocytes at developmental stages V-VI were dissected from the ovary, oocytes were still surrounded by enveloping ovarian tissues. Oocytes were defolliculated on the day of surgery by treatment with collagenase (0.5 mg/mL Sigma Type I, or Boehringer Mannheim Type A, for 0.5-1 hr). Treated oocytes were vortexed to dislodge epithelia, washed repeatedly and stored in Barth's medium containing 88 mM NaCl, 1 mM KCl, 0.41 mM $CaCl_2$,, 0.33 mM $Ca(NO_3)_2$, 0.82 mM $MgSO_4$, 2.4 mM $NaHCO_3$, 5 mM HEPES, pH 7.4 adjusted with 0.1 mg/mL gentamycin sulphate.

Micro-injection of oocytes: Defolliculated oocytes were micro-injected using a Nanoject injection system (Drummond Scientific Co., Broomall, PA). Injection pipettes were beveled to minimize clogging. Tip diameter of injection pipettes was 15-35 μm. Oocytes were microinjected with approximately 50 nL 1:10 ratio mixtures of cRNAs for rBIIa and beta 1 respectively.

Electrophysiology: Membrane current responses were recorded in frog Ringer solution containing 115 mM NaCl, 2 mM KCl, 1.8 mM $CaCl_2$, 5 mM HEPES, pH 7.4. Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 1-7 days following injection. The recording chamber was a simple gravity fed flow-through chamber (volume 100-500 mL depending on adjustment of aspirator). Oocytes were placed in the recording chamber, impaled with electrodes and continuously perfused (5-15 mL min^{-1}) with frog Ringer's solution. The tested compounds were applied by bath perfusion.

Voltage protocols for evoking sodium channel currents: The standard holding potential for whole oocyte clamp was –120mV. Standard current-voltage relationships were elicited by 40ms depolarizing steps starting from –60mV to +50mV in 10mV increments. Peak currents were measured as the maximum negative current after depolarizing voltage steps. The voltage from maximum current response was noted and used for the next voltage protocol.

The purpose was to find compounds that are state dependent modifiers of neuronal sodium channels. Preferably, the compounds have a low affinity for the rested/closed state of the channel, but a high affinity for the inactivated state. The following voltage protocol was used to measure a compounds affinity for the inactivated state. Oocytes were held at a holding potential of –120mV. At this membrane voltage, nearly all of the channels would be in the closed state. Then a 4 second depolarization was made to the voltage where the maximum current was elicited. At the end of this depolarization, nearly all the channels would be in the inactivated state. A 10ms hyperpolarizing step was then made in order to remove some channels from the inactivated state. A final depolarizing test pulse was used to assay the sodium current after this prolonged depolarization (see analysis below). Sodium currents were measured at this test pulse before and after the application of the tested compound. Data was acquired using pClamp 8.0 software and analyzed with clampfit software (Axon instruments).

Data analysis: Apparent inhibition constants (K_i values) for antagonists were determined from single point inhibition data using the following equation (a generalized form of the Cheng-Prusoff equation) (Leff, P. and I. G. Dougall, *TiPS 14*:110-112 (1993)).

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

Where FR is the fractional response and is defined as sodium current elicited from the final depolarizing test pulse prior to application of the drug divided by the sodium current measured in the presence of the drug. [drug] is the concentration of the drug used.

Drugs: Drugs were initially made up at concentrations of 2-10 mM in DMSO. Dilutions were then made to generate a series of DMSO stocks over the range 0.3 μM to 10 mM - depending upon the potency of the compound. Working solutions were made by 1000-3000 fold dilution of stocks into Ringer. At these dilutions DMSO alone had little or no measurable effects on

membrane current responses. DMSO stocks of drugs were stored in the dark at 4 °C. Ringer solutions of drugs were made up fresh each day of use.

In vitro Binding Assay:

The ability of compounds of the present invention to modulate either site 1 or site 2 of the Na^+ channel was determined following the procedures fully described in Yasushi, *J. Biol. Chem. 261*:6149-6152 (1986) and Creveling, *Mol. Pharmacol. 23*:350-358 (1983), respectively. Rat forebrain membranes were used as sources of Na^+ channel proteins. The binding assays were conducted in 130 μM choline chloride at 37°C for 60-minute incubation with [^{3}H] saxitoxin and [^{3}H] batrachotoxin as radioligands for site 1 and site 2, respectively.

In vivo Pharmacology:

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

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

The compounds may be tested for their potential for the treatment of chronic pain (antiallodynic and antihyperalgesic activities) in the Chung model of peripheral neuropathy. Male Sprague-Dawley rats weighing between 200-225 g were anesthetized with halothane (1-3 % in a mixture of 70 % air and 30 % oxygen) and their body temperature controlled during anesthesia through use of a homeothermic blanket. A 2-cm dorsal midline incision was then made at the L5 and L6 level and the para-vertibral muscle groups retracted bilaterally. L5 and L6 spinal nerves were then be exposed, isolated, and tightly ligated with 6-0 silk suture. A sham operation was performed exposing the contralateral L5 and L6 spinal nerves as a negative control.

Tactile Allodynia: Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A series of Semmes-Weinstein monofilaments were applied to the plantar surface of the hindpaw to determine the animal's withdrawal threshold. The first filament used possessed a buckling weight of 9.1 gms (.96 log value) and was applied up to five times to see if it elicited a withdrawal response. If the animal had a withdrawal response then the next lightest filament in the series would be applied up to five times to determine if it could elicit a response. This procedure was repeated with subsequent lesser filaments until there was no response and the lightest filament that elicited a response was recorded. If the animal did not have a withdrawal response from the initial 9.1 gms filament then subsequent filaments of increased weight were applied until a filament elicited a response and this filament was then recorded. For each animal, three measurements were made at every time point to produce an average withdrawal threshold determination. Tests were performed prior to and at 1, 2, 4 and 24 hours post drug administration. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

Mechanical Hyperalgesia: Rats were transferred to an elevated testing cage with a wire mesh floor and allowed to acclimate for five to ten minutes. A slightly blunted needle was touched to the plantar surface of the hindpaw causing a dimpling of the skin without penetrating the skin. Administration of the needle to control paws typically produced a quick flinching reaction, too short to be timed with a stopwatch and arbitrarily given a withdrawal time of 0.5 second. The operated side paw of neuropathic animals exhibited an exaggerated withdrawal response to the blunted needle. A maximum withdrawal time of ten seconds was used as a cutoff time. Withdrawal times for both paws of the animals were measured three times at each time point with a five-minute recovery period between applications. The three measures were used to generate an average withdrawal time for each time point. Tactile allodynia and mechanical hyperalgesia tests were conducted concurrently.

The compounds may be tested for their neuroprotective activity after focal and global ischemia produced in rats or gerbils according to the procedures described in Buchan *et al.* (*Stroke*, Suppl. 148-152 (1993)) and Sheardown *et al.* (*Eur. J. Pharmacol. 236*:347-353 (1993)) and Graham *et al.* (*J. Pharmacol. Exp. Therap. 276*:1-4 (1996)).

The compounds may be tested for their neuroprotective activity after traumatic spinal cord injury according to the procedures described in Wrathall *et al.* (*Exp. Neurology 137*:119-126 (1996)) and Iwasaki *et al.* (*J. Neuro Sci. 134*:21-25 (1995)).

Compositions within the scope of this invention include all compositions wherein the compounds of the present invention are contained in an amount that is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, the compounds may be administered to mammals, e.g. humans, orally at a dose of 0.0025 to 50 mg/kg, or an equivalent amount of the pharmaceutically acceptable salt thereof, per day of the body weight of the mammal being treated for epilepsy, neurodegenerative diseases, anesthetic, arrhythmia, manic depression, and pain. For intramuscular injection, the dose is generally about one-half of the oral dose.

In the method of treatment or prevention of neuronal loss in global and focal ischemia, brain and spinal cord trauma, hypoxia, hypoglycemia, status epilepsy and surgery, the compound can be administrated by intravenous injection at a dose of about 0.025 to about 10 mg/kg.

The unit oral dose may comprise from about 0.01 to about 50 mg, preferably about 0.1 to about 10 mg of the compound. The unit dose may be administered one or more times daily as one or more tablets each containing from about 0.1 to about 10, conveniently about 0.25 to 50 mg of the compound or its solvates.

In addition to administering the compound as a raw chemical, the compounds of the invention may be administered as part of a pharmaceutical

preparation containing suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the compounds into preparations which can be used pharmaceutically. Preferably, the preparations, particularly those preparations which can be administered orally and which can be used for the preferred type of administration, such as tablets, dragees, and capsules, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by injection or orally, contain from about 0.01 to 99 percent, preferably from about 0.25 to 75 percent of active compound(s), together with the excipient.

Also included within the scope of the present invention are the non-toxic pharmaceutically acceptable salts of the compounds of the present invention. Acid addition salts are formed by mixing a solution of the particular heteroaryl compound of the present 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, and the like. Basic salts are formed by mixing a solution of the heteroaryl compound of the present 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 pharmaceutical compositions of the invention may be administered to any animal that may experience the beneficial effects of the compounds of the invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention may be administered by any means that achieve their intended purpose. For example, administration may be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes. Alternatively, or concurrently, administration may be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the

recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds 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 are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or 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, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may 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, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, poly-ethylene 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, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

Possible pharmaceutical preparations, which can be used rectally, include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, and include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered

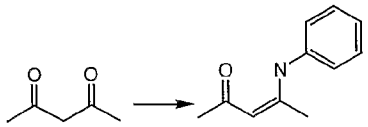
in clinical therapy and which are obvious to those skilled in the art are within the spirit and scope of the invention.

The yields of the following examples were not optimized, and MS spectra for all of the compounds were obtained with LCMS. The reactions were followed by either TLC or/and LCMS or/and ^{1}H NMR.

EXAMPLE 1

2-[4-(4-Fluorophenoxy)phenyl]-4-N-morpholinylpyridine-6-carboxamide (**10**)

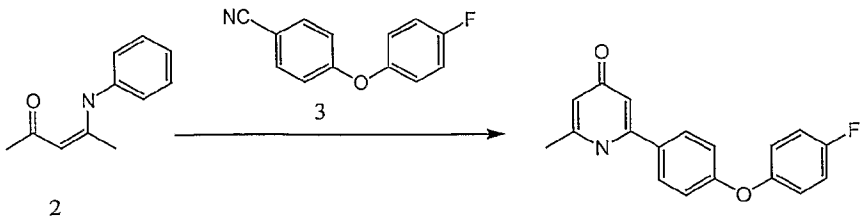
a) 2-(Pent-2-enyl-4-one)aniline (**2**):



1 2

A solution of 10 g (100 mmol) of 2,4-pentadione (1) and 11.2 g (120 mmol) of aniline in 100 ml toluene and a catalytical amount of p-toluenesulfonic acid monohydrate was refluxed in a round bottom flask equipped with azeotropic apparatus and condenser for 12 hours. The solution was concentrated to dryness and the product was used without purification. ^{1}H NMR ($CDCl_3$): δ 7.35(t, 2H, *J*=5.69 Hz), 7.19(t, 1H, *J*=6.4 Hz), 7.10(d, 2H, *J*=7.5 Hz), 5.19(s, 1H), 2.10(s, 3H), 1.99(s, 3H).

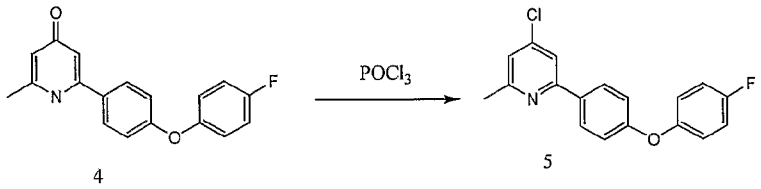
b) 2-Methyl-6-[4-(4-fluorophenoxy)phenyl]-4-pyridinone (**4**):



2 3 4

31 ml 1.6 M n-BuLi (50 mmol) was added dropwise to a solution of 7.21 g (51 mmol) of 2,2,6,6-tetrametylpiperidine in 80 ml THF at –78 °C under inert atomosphere. After the addition, the reaction mixture was stirred for 30 minutes at the same temperature. To this solution was added dropwise a solution of 3 g (17 mmol) of compound **2** in 10 ml THF at –78 °C. After the addition the reaction mixture was stirred for 30 minutes. To the resulting dark red solution was added dropwise a solution of 2.7 g (17 mmol) of compound **3** in 13 ml THF at –78 °C. After the addition the mixture was slowly warmed to –50 °C and stirred at that temperature for one hour. The reaction mixture was then poured into cold saturated NH_4Cl aqueous solution and extracted twice with ethyl acetate. The organic phase was washed with saturated brine, and dried with magnesium sulfate. After filtration the filtrate was concentrated to dryness. The material was used without purification. ^1H NMR ($CDCl_3$): δ 7.54 (d, 2H, *J*=3.8 Hz), 7.31 (m, 2H), 6.90-7.10 (m, 4H), 5.23 (s, 1H), 5.08 (s,1H), 2.03 (s, 3H).

c) 4-Chloro-2-[4-(4-fluorophenoxy)phenyl]-6-methylpyridine (**5**):

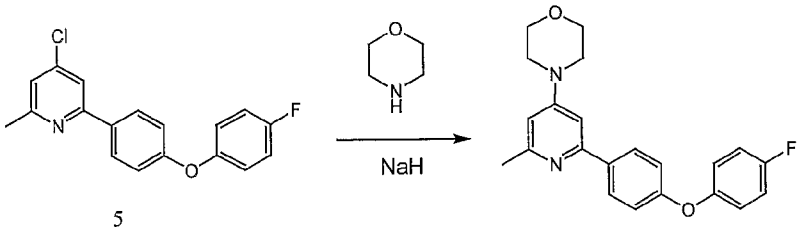


4 5

To a flask containing 20 ml of $POCl_3$ at 120 °C oil bath was carefully added a solution of 5 g (17 mmol) crude compound **4** and 2.6 ml of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (17 mmol) in 20 ml of methylene chloride. After the addition, the reaction mixture was refluxed for one hour. The resulting mixture was concentrated to dryness and diluted with ethyl acetate. Saturated aqueous $NaHCO_3$ was carefully added to the solution to adjust pH to 5-6. The organic phase was separated and the aqueous phase was extracted with the same volume of EtOAc. The combined organic phases were then washed with brine and dried with magnisium sulfate, filtered and

concentrated to dryness. The residue was purified with flash chromatography (silica gel, 5% EtOAc/hexane) to get 1.8 g of compound **5** and 850 mg of a mixture of compound **5** and unreacted compound **3**. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, 2H, *J*=6.7 Hz), 7.48 (d, 1H, *J*=1.36 Hz), 7.09 (d, 1H, *J*=1.5 Hz), 7.00 (m, 6H), 2.59 (s, 3H). MS: 314.1

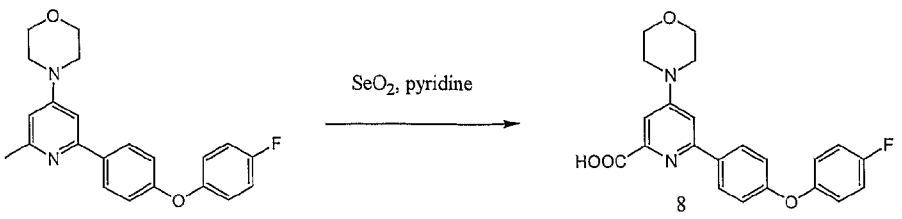
d) 2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-4-N-morpholinyl-pyridine (**7**):



5 7

A mixture of 2.6 g (8.8 mmol) compound **5** and 704 mg of 60 % NaH (17.6 mmol) in 8 ml morpholine was heated in a sealed tube at 135 °C oil bath for 2 hours. Methanol was carefully added to the cooled reaction mixture to quench NaH. The resulting mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 10% MeOH/CH_2Cl_2 with 1% NH_4OH) to get 3.2 g of compound **7**. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 2H, *J*=8.7 Hz), 7.00 (m, 6H), 6.86 (d, 1H, *J*=2.2 Hz), 6.52 (d, 1H, *J*=2.2 Hz), 3.85 (t, 4H, *J*=4.9 Hz), 3.33 (t, 4H, *J*=4.9 Hz), 2.52 (s, 3H). MS: 365.2 (M+1).

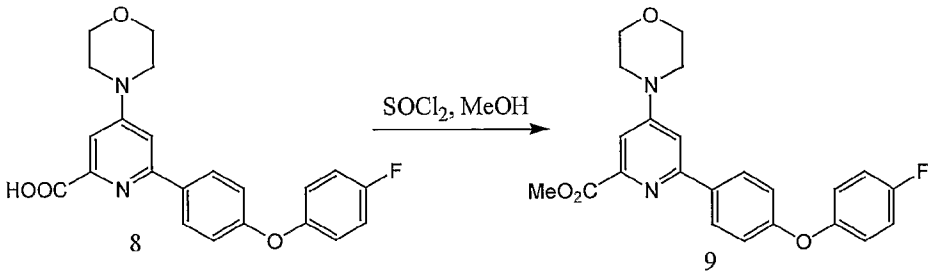
e) 2-[4-(4-Fluorophenoxy)phenyl]-4-N-morpholinylpyridine 6-carboxylic acid (**8**):



7 8

2 g of SeO_2 (18 mmol) was added to a solution of 3.2 g (8.7 mmol) of compound **7** in 90 ml pyridine and the resulting solution was refluxed for 2 days. The cooled reaction mixture was concentrated to dryness and diluted with methanol, filtered and concentrated. The crude product **8** was used without purification to convert to methyl ester. MS: 395.3(M+1).

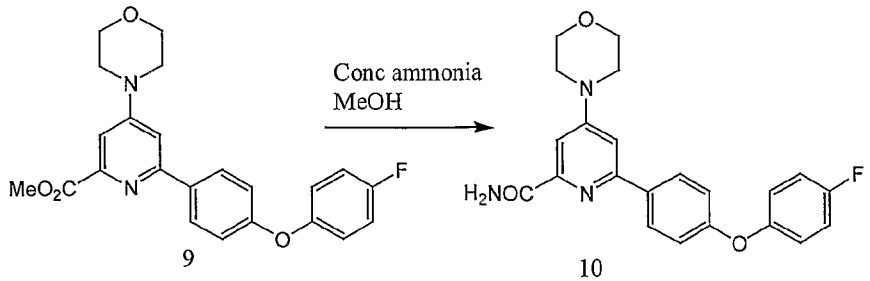
f) 2-[4-(4-Fluorophenoxy)phenyl]-4-N-morpholinylpyridine 6-carboxylic acid methyl ester (**9**):



8 9

32 ml (43.5 mmol) of thionyl chloride was slowly added carefully to the methanol solution of the crude compound **8**. After the addition, the resulting solution was refluxed for 12 hours. The cooled reaction mixture was filtered and concentrated to dryness. The residue was used without purification. ^1H NMR ($CDCl_3$): δ 7.95 (d, 2H, *J*=8.8 Hz), 7.55 (d, 1H, *J*=2.2 Hz), 7.15 (d, 1H, *J*=2.2 Hz), 7.04 (m, 6H), 4.12 (s, 3H), 3.89 (t, 4H, *J*=4.8 Hz), 3.44 (t, 4H, *J*=4.8 Hz). MS: 408.3 (M).

g) 2-[4-(4-Fluorophenoxy)phenyl]-4-N-morpholinylpyridine-6-carboxamide (**10**):

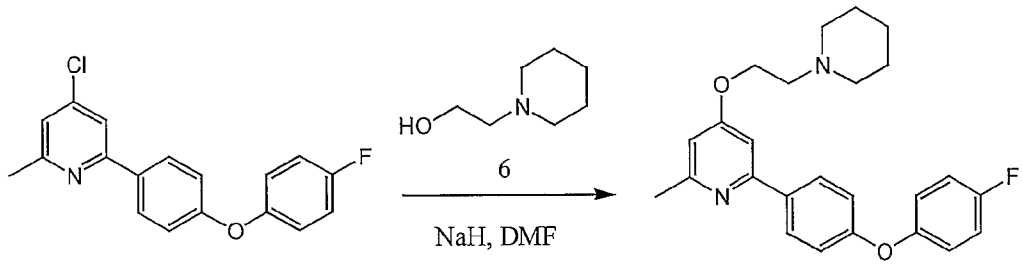


9 10

To a solution of 50 ml of 2M NH_3 in methanol was added the crude compound **9** and the resulting solution was stirred for 12 hours at room temperature. The mixture was then concentrated to dryness and the resulting solid was recrystalized in methanol to give 1.1 g of compound **10**. ^{1}H NMR (DMSO-D_6): δ 8.05 (b, 1H), 7.93 (d, 2H, *J*=8.8 Hz), 7.62 (d, 1H, *J*=2.5 Hz), 7.14 (d, 1H, *J*=2.5 Hz), 7.08 (m, 6H), 5.56 (b, 1H), 4.15 (t, 4H, *J*=5.1 Hz), 3.47 (t, 4H, *J*=5.1 Hz). MS: 394.2 (M+1).

EXAMPLE 2

2-[4-(4-Fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)ethoxy]-pyridine (**11**)



5 11

A solution of 157 mg (0.5 mmol) of compound **5**, 97 mg of compound **6** (0.75 mmol) and 40 mg of 60 % NaH (1 mmol) in 2.5 ml DMF was stirred at 80 °C for 16 hours. After standard aqueous workup with ethyl acetate and brine, the organic phase was dried with $MgSO_4$, filtered and concetrated. The crude product was purified with flash chromatography (silica gel column, 10:1 EtOAc/methanol) to give 87.1 mg of compound **11**. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, 2H, *J*=8.8 Hz), 7.03 (m, 7H), 6.63 (d, 1H, *J*=2.1 Hz), 4.19 (t, 2H, *J*=6.0 Hz), 2.81 (t, 2H, *J*=6.0 Hz), 2.57 (3, 3H), 2.51 (b, 4H), 1.61 (m, 4H), 1.42 (m, 2H). MS: 407.1(M+1).

EXAMPLE 3

Activity of 2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)-ethoxy]pyridine as Sodium Channel Blocker

2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)ethoxy]-pyridine was tested in the electrophysiological assay as described above. The result of 2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)-ethoxy]pyridine and other compounds are represented in Table 1.

Table 1
Evaluation of the Tested Compounds as Sodium Channel Blockers after an Electrophysiological in vitro Assay

Compound name	RBIIA/β1 K_i / μM
2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)ethoxy]pyridine	0.18
2-[4-(4-fluorophenoxy)phenyl]-4-N-morpholinylpyridine-6-carboxamide	0.29

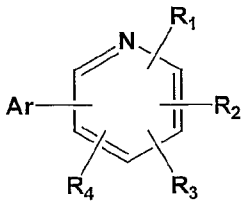
Having now fully described this invention, it will be understood by those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations and other parameters without affecting the scope of the invention or any embodiment thereof.

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.

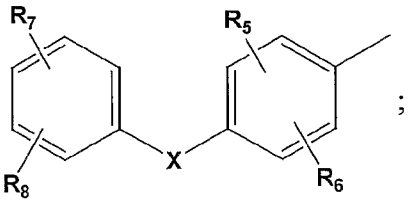
WHAT IS CLAIMED IS:

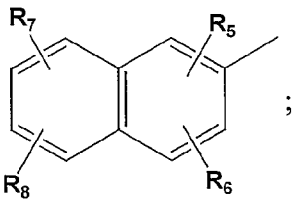
1. A compound having the Formula **I**:

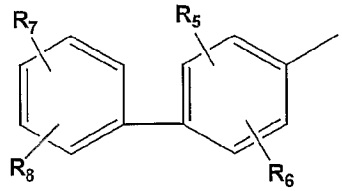


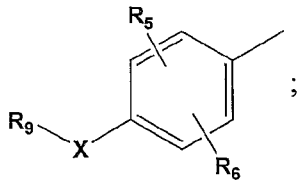
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

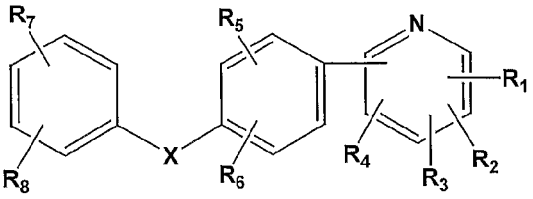
R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4,

with the proviso that when Ar is Ar_4 and R_1 is other than $C(O)R_{10}$, SO_2R_{10}, or $OC(O)NH_2$, then n is not 0 (zero).

2. A compound having the Formula **II**:



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

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol; and

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

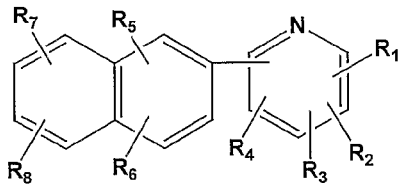
R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2.

3. The compound of claim 2, wherein R_1 is selected from the group consisting of an alkyl optionally substituted by halogen or hydroxy, $C(O)R_{10}$, and SO_2R_{10}, wherein R_{10} is as defined in claim 2, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}.

4. The compound of claim 3, wherein R_{10} is selected from the group consisting of alkyl, alkenyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, and heterocycloalkylamino, all of which can be optionally substituted, and wherein R_{12} is as defined in claim 2.

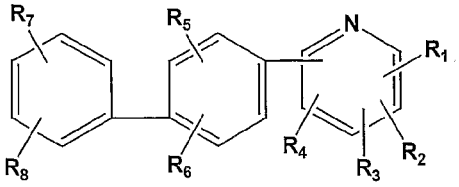
5. The compound of claim 1, having theFormula **III**:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_8 are defined in claim 1.

6. The compound of claim 5, wherein both R_3 and R_4 are hydrogen.

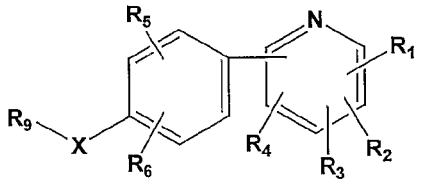
7. The compound of claim 1, having the Formula **IV**:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_8 are defined in claim 1.

8. The compound of claim 7, wherein both R_3 and R_4 hydrogen.

9. The compound of claim 1, having the Formula **V**:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein R_1-R_6, and R_9 are as defined in claim 1 and X is one of O, S, NH, or absent, with the proviso that when R_1 is other than $C(O)R_{10}$, SO_2R_{10}, or $OC(O)NH_2$, then n is not 0 (zero).

10. The compound of claim 2, wherein said compound is:

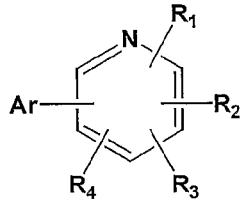
2-[4-(4-fluorophenoxy)phenyl]-4-N-morpholinylpyridine-6-carboxamide;

2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-[2-(N-piperidinyl)ethoxy]-pyridine;

2-[4-(4-fluorophenoxy)phenyl]-6-methyl-4-N-morpholinylpyridine;

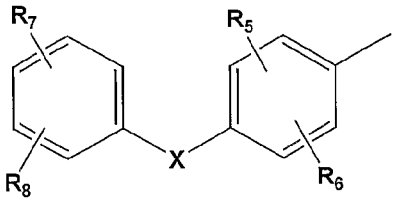
or a pharmaceutically acceptable salt, prodrug or solvate thereof.

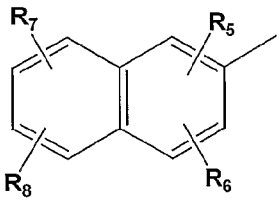
11. A pharmaceutical composition, comprising a compound of formula:

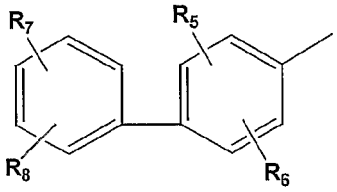


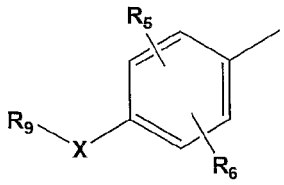
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl,

hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

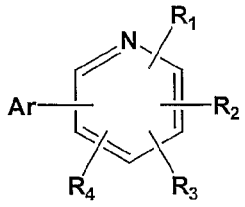
X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4,

a pharmaceutically acceptable carrier or diluent.

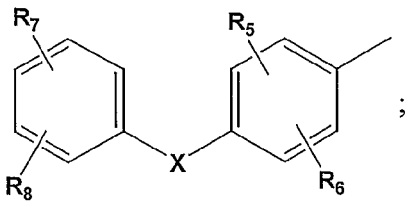
12. The composition of claim 11, wherein the compound is as claimed in any one of claims 1-10.

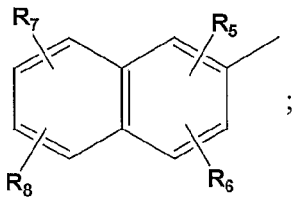
13. A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of a compound of formula:

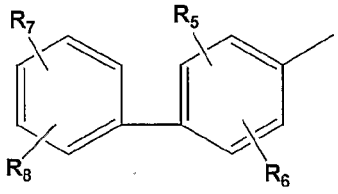


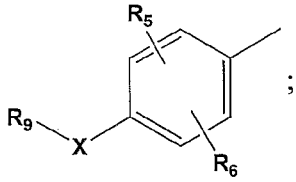
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl,

hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

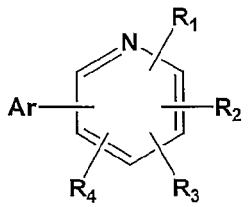
R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4.

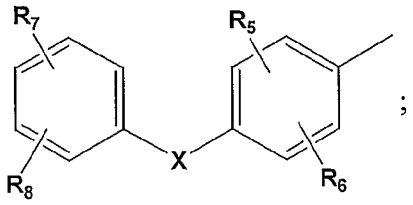
14. The method of claim 13, wherein the compound administered is as claimed in any one of the claims 1-10.

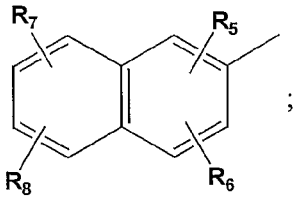
15. A method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating neurodegenerative conditions; treating, preventing or ameliorating pain or tinnitus; treating, preventing or ameliorating manic depression; providing local anesthesia; or treating arrhythmias, or treating convulsions, comprising administering to a mammal in need of such treatment an effective amount of a compound formula:

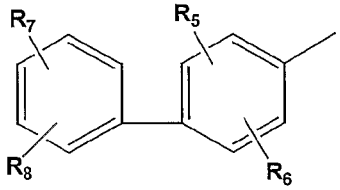


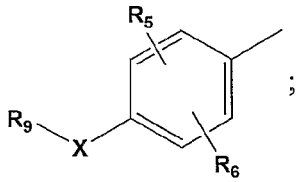
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

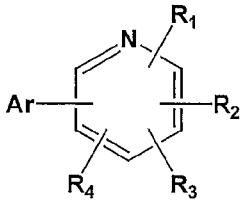
X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4

16. The method of claim 15, wherein the compound administered is as claimed in any one of claims 1-10.

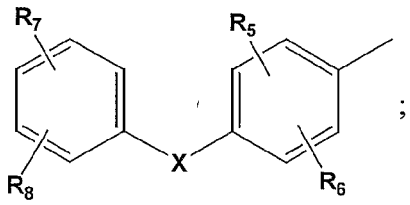
17. The method of claim 15, wherein the method is for treating, preventing or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

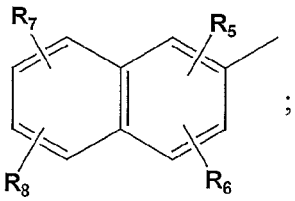
18. A method of alleviating or preventing seizure activity in an animal subject, comprising administering to said animal in need of such treatment an effective amount of a compound of formula:

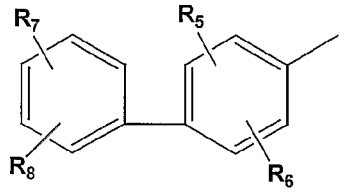


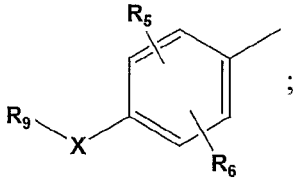
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

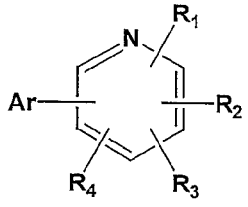
R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4.

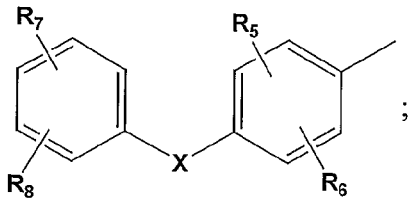
19. The method of claim 18, wherein the compound administered is as claimed in any one of claims 1-10.

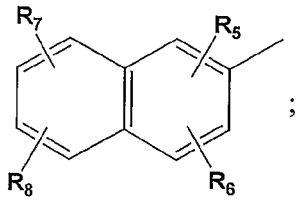
20. A compound having the Formula I:

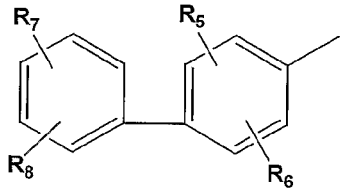


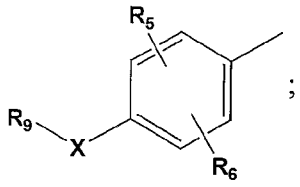
or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

Ar is selected from the group consisting of Ar_1, Ar_2, Ar_3 and Ar_4, wherein

Ar_1 is ;

Ar_2 is ;

Ar_3 is ; and

Ar_4 is ;

R_1 is selected from the group consisting of an optionally substituted alkyl, amino, alkylthiol, $C(O)R_{10}$, SO_2R_{10}, and $OC(O)NH_2$;

R_2 is $-Y_m-(CH_2)_n-Z$, wherein

Y is O, S or NR_{11}, wherein R_{11} is hydrogen or alkyl,

Z is a saturated heterocyclic ring optionally substituted at one or more carbon atoms,

m is 0 or 1, and n is 0-6;

R_3 and R_4 are independently selected from the group consisting of hydrogen, optionally substituted alkyl, alkenyl, or alkynyl, halogen, hydroxy, cycloalkyl, cyano, amino, alkylamino, dialkylamino, alkoxy, aminocarbonyl,

alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, and aralkylcarbonylamino;

R_5, R_6, R_7, and R_8 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, halogen, haloalkyl, hydroxyalkyl, hydroxy, nitro, amino, cyano, amide, carboxyalkyl, alkoxyalkyl, ureido, acylamino, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R_9 is an optionally substituted alkyl;

R_{10} is selected from the group consisting of alkyl, alkenyl, alkynyl, OR_{12}, amino, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, dialkylaminoalkylamino, dialkylaminoalkenylamino, alkylaminoalkenyl-amino, hydroxyaminoalkenylamino, cycloalkyl, heterocycloalkyl, cycloalkylalkylamino, heterocycloalkylamino, aryl, arylalkyl, arylalkenyl, arylalkynyl, and arylalkylamino, all of which can be optionally substituted, provided that R_{10} is not OR_{12} when R_1 is SO_2R_{10}; wherein

R_{12} is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal; and

X is one of O, S, NH, or CH_2 when Ar is Ar_1; or

X is one of O, S, NH, or absent (a covalent bond) when Ar is Ar_4,

wherein said compound is ^3H or ^{14}C radiolabeled.

21. Use of a compound of claim 20 as a radioligand for its binding site on the sodium channel.