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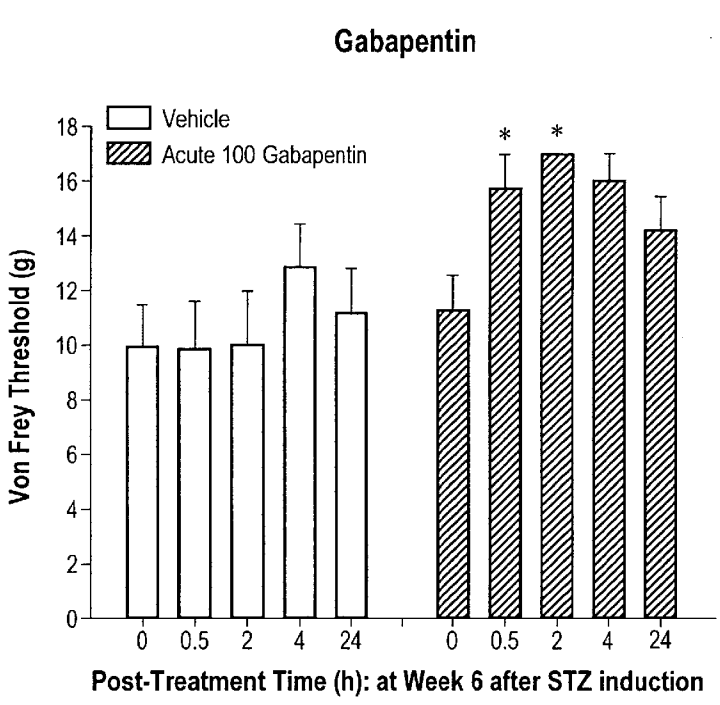

* P<0.05 compared to time-matched vehicle group

Fig. 1

(57) Abstract: The present invention includes methods and compositions for treating or preventing neuropathic pain. The present invention includes compounds for use in treating or preventing neuropathic pain. The present invention includes the use of compounds in the manufacture of a medicament for the treatment or prevention of neuropathic pain.

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METHODS OR USES AND COMPOSITIONS FOR TREATING OR PREVENTING NEUROPATHIC PAIN

Field of the Invention

The present invention includes methods and compositions for treating or preventing neuropathic pain. The present invention includes compounds for use in treating or preventing neuropathic pain. The present invention includes the use of compounds in the manufacture of a medicament for the treatment or prevention of neuropathic pain.

Background

Neuropathic pain syndromes include a variety of chronic or recurrent pain conditions resulting from trauma to, or dysfunction or sensitization of, the central or peripheral nervous system. As used herein, the phrase "neuropathic pain" includes but is not limited to neuralgia, neurodynia, dysesthesia (spontaneous or evoked unpleasant sensations), hyperalgesia (increased response to pain), allodynia (pain due to stimulus that does not normally provoke pain), and parethesia (chronic or recurrent non-painful abnormal sensations). The diversity of symptoms associated with these conditions make them difficult to diagnose, and their complex etiology make them difficult to treat effectively.

Neuropathies can develop following physical or biological insults to the central or peripheral nervous system, and often include a sensory, for example, pain, component. Following nerve injury, neurophysiological changes occur resulting in pain or unusual sensations that may persist, whether chronic or recurrent, for months or years beyond the healing of the original injury. Neuropathic pain can be triggered by a wide variety physical of biological causes such as trauma or surgery-related injury, for example. brachial plexus injury, tumor growth resulting in nerve compression or infiltration, inflammation, traumatic spinal cord injury, entrapment syndromes such as lumbar disk compression or carpel-tunnel syndrome, infections such as herpes or HIV-AIDS, neurological diseases such as Multiple Sclerosis, metabolic diseases such as diabetes, autoimmune diseases, nutritional deficiencies, alcoholism, stroke, chemotherapy, and toxins.

Present treatments used in control of neuropathic pain include anticonvulsants such as gabapentin, opioids such as morphine, antidepressants such as amitriptyline, NSAIDS such as ibuprofen, and topical anesthetics such as lidocaine. In general, these treatments may suffer from adverse side effects, for example addiction with opioids or gastric bleeding with NSAIDS. Also, such treatments may be based on a side effect profile, as opposed to the primary activity of the active ingredient, for example anticonvulsants and antidepressants, and, thus, are of limited efficacy.

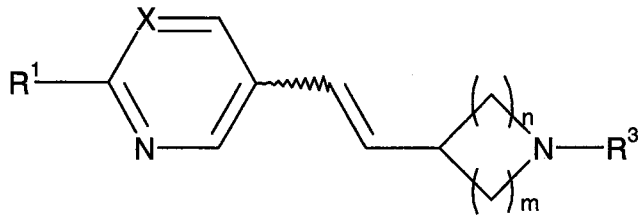
There remains a need for a highly targeted treatment of neuropathic pain. Preferably, such treatment neither relies upon, nor is characterized by, side effects.

Furthermore, there is a need for drugs which treat neuropathic pain through unique mechanisms of action.

The following references are each herein incorporated by reference for their background teaching: Agarwal M. Streptozotocin: Mechanisms of Action. *FEBS Letters* Volume 120, Number 1. October 1980; Bannon et al., *Brain Res.* **801**: 158-163 (1998) ; Calcutt N, et al., Tactile allodynia and formalin hyperalgesia in streptozotocin-diabetic rats: effects of insulin, aldose reductase inhibition and lidocaine. *Pain.* (1996) 68: 293 – 299; Chaplan, SR, et al., Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Methods.* (1994) 53: 55-63; Decker et al., *Curr. Top. Med. Chem.* **4**: 369-384 (2004); Flatters, SJL and Bennett, G.J. Ethosuximide reverses paclitaxel- and vincristine-induced painful peripheral neuropathy. *Pain*, 109: 150-161, 2004; Gilbert et al., *Pain* **89**: 159-165 (2001); Gilron, I and Flatters, SJL. Gabapentin and pregabalin for the treatment of neuropathic pain: A review of laboratory and clinical evidence. *Pain Res Manage,* 11, Suppl A: 16A-29A, Summer 2006; Jarvis MF, et al., ABT-627, an endothelin ET(A) receptor-selective antagonist attenuates tactile allodynia in a diabetic rat model of neuropathic pain. *Eur J Pharmacology.* (2000) 388:29-35; Lynch et al., *Eur. J. Pharmacol.* **509**: 43-48 (2005); Maneuf et al.,Reduction by gabapentin of K+-evoked release of [3H]-glutamate from the cudal trigeminal nucleus of the streptozotocin-treated rat. *Br. J. Pharmacol.* **141**: 574-579 (2004); Meyer, *Drug Dev. Res.* **67**: 355-359 (2006); Palomano, RC, et al., A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel. *Pain*, 94: 293-304, 2001; Rashid and Ueda, *Brain Res.* **953**: 53-62 (2002); Rittenhouse PA, et al., Streptozotocin-induced diabetes is associated with altered expression of peptide-encoding mRNAs in rat sensory neurons. *Peptides.* (1996) 17:1017-22; Rueter et al., *Pain* **103**: 269-276 (2003); Rueter et al., *Drug Disc. Today: Ther. Strat.* **1**: 89-96 (2004); WO03/097043; WO05/066166; WO05/066167; WO05/066168; WO07/018738; and WO07/024814.

Summary

In one aspect, the present invention relates to methods of treating neuropathic pain by administering vinylazacycloalkane compounds of Formula I:



Formula I

wherein:

variable geometry (E or Z) exists about the double bond as represented by the wavy line;

X is nitrogen or C-R^2;

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, halogen, -OR^4, -NR^4R^5, or -SR^4 when X is C-R^2, and

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cyclolalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, -OR^4, or -NR^4R^5 when X is nitrogen;

R^2 is hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, -$(CH_2)_qC_{3-8}$ polycycloalkyl, -OR^6, -NR^6R^7, -SR^6, -SOR^6, or -SO_2R^6;

wherein each R^2 can optionally be substituted with one or more substituent selected from halogen, -CN, -NO_2, -NH_2, -OH, -OR^6, -COOH, -C(O)OR^6, -O-C(O)R^6, -NR^6R^7, -NHC(O)R^6, -C(O)NR^6R^7, -SR^6, -S(O)R^6, -SO_2R^6, -$NHSO_2R^6$, -$SO_2NR^6R^6$, -C(S)NR^6R^6, -NHC(S)R^6, -O-SO_2R^6, aryl, heteroaryl, formyl, haloalkyl, haloalkylsulfanyl, haloalkoxy, and C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6} alkyl, -$(CH_2)_q$aryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl;

m is 1, 2, 3, or 4;

n is 1, 2, or 3;

each R^4, R^5, R^6, and R^7 is, independently, hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl, each of which can optionally be substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -CN, -NO_2, -NH_2, -OH, -C(O)OH, -C(O)O-C_{1-6} alkyl, -$CONH_2$, formyl, haloalkyl, and haloalkoxy,

wherein each of the C_{1-6}-alkyl, heterocyclyl, heteroaryl, and aryl groups can be substituted with from 1 to 6 substituents selected from the group consisting of F, Cl, Br, I, R^8, -NR^8R^9, haloalkyl, -CN, -NO_2, -C_2R^8, -N_3, -SO_2CH_3, -OR^8, -SR^8, -C(=O)NR^8R^9, -NR^8C(=O)R^8, -C(=O)R^8, -C(=O)OR^8, -$(CH_2)_qOR^8$, -OC(=O)R^8, -OC(=O)NR^8R^9, and -NR^8C(=O)OR^8,

wherein each R^8 and R^9 are individually hydrogen, C_{1-6} alkyl, an aromatic group-containing species, or a substituted aromatic group-containing species that is substituted with one or more of F, Cl, Br, I, R^{10}, -$NR^{10}R^{11}$, haloalkyl, -CN, -NO_2, -C_2R^{10}, -N_3, -SO_2CH_3, -OR^{10}, -SR^{10}, -C(=O)$NR^{10}R^{11}$, -NR^{10}C(=O)R^{10}, -C(=O)R^{10}, -C(=O)OR^{10}, -$(CH_2)_qOR^{10}$, -

$OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, or $-NR^{10}C(=O)OR^{10}$; wherein each of R^{10} and R^{11} individually is hydrogen or C_{1-6} alkyl; or

either R^6 and R^7 or R^8 and R^9 can combine together with the atoms to which they are attached to form a C_{1-10} cycloalkyl functionality; and

wherein each q independently is 1 to 6;

or a pharmaceutically acceptable salt thereof.

Exemplary cycloalkyl functionalities include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl.

Representative aromatic group-containing species include pyridyl, quinolinyl, pyrimidinyl, phenyl, and benzyl, where any of the foregoing can be suitably substituted with at least one substituent group as defined above, specifically including lower alkyl, halo, and/or amino substituents. Other representative aromatic ring systems are set forth in Gibson et al., *J. Med. Chem.* **39**:4065 (1996), herein incorporated by reference with regard to such aromatic ring systems.

Isomers, mixtures, including racemic mixtures, enantiomers, diastereomers and tautomers of these compounds as well as pharmaceutically acceptable salts thereof, are also included. Compounds of Formula I are reported in U.S. Patent 7,098,331 and in published PCT WO 04/078752, each of which is herein incorporated by reference in its entirety.

The present invention, more particularly, relates to use in treating neuropathic pain, of compounds of Formula I wherein:

in one embodiment, the geometry at the double bond is E;

in one embodiment, X is N

in one embodiment, X is C-R^2;

in one embodiment, R^1 is hydrogen;

in one embodiment, R^2 is $-OR^6$;

in one embodiment, R^3 is hydrogen;

in one embodiment, n is 1;

in one embodiment, m is 2; and

in one embodiment, R^6 is a alkyl, aryl or heterocyclyl.

Throughout the present specification, one or more aspects or embodiments may be combined to form still further an embodiment. All combinations of aspects and embodiments of the present invention are included within the scope of the present invention.

One embodiment of the invention includes methods of treating neuropathic pain by administering compounds of Formula I wherein: the geometry at the double bond is E; X is

N; R^1 is hydrogen; R^3 is hydrogen; n is 1; m is 2; or a pharmaceutically acceptable salt thereof.

In another aspect, the invention relates to a method of treating neuropathic pain by administering (R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine, (R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine, 5-((E)-2-piperidin-4-ylvinyl)pyrimidine, or 5-((E)-2-azetidin-3-ylvinyl)pyrimidine. The present invention should be interpreted to include geometric isomers, racemic mixtures, or enantiomers. In particular aspects, the methods comprise administration of (R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine, as a racemic mixture or as an enantiomerically enriched mixture. In further particular embodiments, the compound denoted (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine (Compound A) is administered.

In another aspect of the invention, the compounds herein are administered to a subject selected for treatment based on criteria which indicate that the subject is suffering from or will be subjected to conditions expected to lead to neuropathic pain states. In particular embodiments, the criteria indicate that the subject suffers from or is likely to experience neuropathic pain.

As noted, the scope of the present invention includes combinations of embodiments.

Description

Compounds of the present invention demonstrate efficacy in multiple animal models of neuropathic pain, including, for example, Chung spinal nerve ligation and streptozotocin (STZ)-induced and Paclitaxel (Taxol)-induced neuropathies, indicating promise of human efficacy for a variety of types of neuropathic pain states. In particular, the compound designated herein as Compound A has demonstrated efficacy in animal neuropathy models, including Chung spinal nerve ligation, STZ-induced diabetic neuropathy, and Taxol-induced neuropathy.

The compounds, compositions and methods described herein will be better understood with reference to the following preferred embodiments. The following definitions will be useful in defining the scope of the invention:

As used herein, "aromatic" refers to 3 to 10, preferably 5 and 6-membered ring aromatic and heteroaromatic rings.

As used herein, "aromatic group-containing species" refer to moieties that are or include an aromatic group. Accordingly, phenyl and benzyl moieties are included in this definition, as both are or include an aromatic group.

As used herein, C_{1-6} alkyl radicals, also referred to as lower alkyl radicals, contain from 1 to 6 carbon atoms in a straight or branched chain, which may be optionally substituted as herein further described, with multiple degrees of substitution being allowed. Examples of

"alkyl" as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, tert-butyl, isopentyl, and n-pentyl. As used throughout this specification, the preferred number of atoms, such as carbon atoms, will be represented by, for example, the phrase "C_{x-y} alkyl," which refers to an alkyl group, as herein defined, containing the specified number of carbon atoms. Similar terminology will apply for other preferred terms and ranges as well. One embodiment of the present invention includes so-called 'lower' alkyl chains of one to six carbon atoms. Thus, C_1-C_6 alkyl represents a lower alkyl chain as hereabove described.

As used herein, C_{1-6} alkoxy radicals contain from 1 to 6 carbon atoms in a straight or branched chain and refers to a group -OR^a, where R^a is alkyl as defined above.

As used herein, aryl radicals are selected from phenyl, naphthyl, and indenyl.

As used herein, heteroaryl radicals contain from 3 to 10 members, preferably 5 or 6 members, including one or more heteroatoms selected from oxygen, sulfur, and nitrogen. Examples of suitable five-membered ring heteroaryl moieties include furyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, thienyl, tetrazolyl, and pyrazolyl. Examples of suitable six- membered ring heteroaryl moieties include pyridinyl, pyrimidinyl, pyrazinyl, of which pyridinyl and pyrimidinyl are preferred.

As used herein, halogen is chlorine, iodine, fluorine or bromine.

As used herein the term "haloalkyl" refers to an alkyl group, as defined herein, that is substituted with at least one halogen. Examples of branched or straight chained "haloalkyl" groups as used herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, and t-butyl substituted independently with one or more halogens, for example, fluoro, chloro, bromo, and iodo. The term "haloalkyl" should be interpreted to include such substituents as perfluoroalkyl groups such as –CF_3.

As used herein, heterocyclyl radicals contain from 3 to 10 members including one or more heteroatoms selected from oxygen, sulfur and nitrogen. Examples of suitable heterocyclyl moieties include, but are not limited to, piperidinyl, morpholinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isothiazolidinyl, thiazolidinyl, isoxazolidinyl, oxazolidinyl, piperazinyl, tetrahydropyranyl, and tetrahydrofuranyl.

As used herein, cycloalkyl radicals contain from 3 to 8 carbon atoms. Examples of suitable cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

As used herein, polycycloalkyl radicals are fused cyclic ring structures. Representative polycycloalkyl radicals include, but are not limited to, adamantyl, bornanyl, norbornanyl, bornenyl, and norbornenyl. Polycycloalkyl radicals can also include one or more heteroatoms, such as N, O, or S.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of a hydrogen atom by a deuterium or tritium, or the replacement of a carbon atom by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the invention.

The compounds of the present invention may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature, pressure, or both. Polymorphism can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by the formulae of the present invention, as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted.

The present invention includes a salt, solvate, or prodrug of the compounds herein described, including combinations thereof such as a solvate of a salt.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention.

Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as chloride, bromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be

in some cases hydrates or ethanol solvates. Representative salts are provided as described in U.S. Patent Nos. 5,597,919 to Dull et al., 5,616,716 to Dull et al., and 5,663,356 to Ruecroft et al., each of which is incorporated by reference in its entirety.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute, namely in this invention, a compound of Formulae herein described, or a salt or prodrug thereof, and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably, the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid. Most preferably, the solvent used is water.

I. Compounds

The compounds of Formula I, as described in the various aspects of the invention set forth above in the Summary, can have one or more asymmetric carbons and can therefore exist in the form of isomers, racemic mixtures, enantiomers, and diastereomers. These individual compounds and their mixtures are intended to be within the scope of the present invention.

The following are representative compounds of Formula I:

(R)- and (S)-3-((E)-2-pyrrolidin-3-ylvinyl)-5-(tetrahydropyran-4-yloxy)pyridine

(R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine

(R)- and (S)-2-chloro-5-((E)-2-pyrrolidin-3-ylvinyl)pyridine

(R)- and (S)-3-isopropoxy-5-((E)-2-pyrrolidin-3-ylvinyl)pyridine

(R)- and (S)-3-isopropoxy-5-((E)-2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

(R)- and (S)-3-cyclopropylmethoxy-5-((E)-2-pyrrolidin-3-ylvinyl)pyridine

(R)- and (S)-5-((E)-2-(1-methylpyrrolidin-3-yl)vinyl)pyrimidine

(R)- and (S)-2-chloro-5-((E)-2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

(R)- and (S)-3-cyclopropylmethoxy-5-((E)-2-(1-methylpyrrolidin-3-yl)vinyl)pyridine

(R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine

(R)- and (S)-5-((E)-2-(1-methylpiperidin-3-yl)vinyl)pyrimidine

(R)- and (S)-2-chloro-5-((E)-2-piperidin-3-ylvinyl)pyridine

(R)- and (S)-2-chloro-5-((E)-2-(1-methylpiperidin-3-yl)vinyl)pyridine

(R)- and (S)-3-cyclopropylmethoxy-5-((E)-2-piperidin-3-ylvinyl)pyridine

(R)- and (S)-3-cyclopropylmethoxy-5-((E)-2-(1-methylpiperidin-3-yl)vinyl)pyridine

5-((E)-2-piperidin-4-ylvinyl)pyrimidine

5-((E)-2-(1-methylpiperidin-4-yl)vinyl)pyrimidine

2-chloro-5-((E)-2-piperidin-4-ylvinyl)pyridine
2-chloro-5-((E)-2-(1-methylpiperidin-4-yl)vinyl)pyridine
3-cyclopropylmethoxy-5-((E)-2-piperidin-4-ylvinyl)pyridine
3-cyclopropylmethoxy-5-((E)-2-(1-methylpiperidin-4-yl)vinyl)pyridine
5-((E)-2-azetidin-3-ylvinyl)pyrimidine
5-((E)-2-(1-methylazetidin-3-yl)vinyl)pyrimidine
5-((E)-2-azetidin-3-ylvinyl)-2-chloropyridine
5-((E)-2-(1-methylazetidin-3-yl)vinyl)-2-chloropyridine
3-((E)-2-azetidin-3-ylvinyl)-5-cyclopropylmethoxypyridine
3-((E)-2-(1-methylazetidin-3-yl)vinyl)-5-cyclopropylmethoxypyridine
(R)- and (S)-3-phenoxy-5-((E)-2-piperidin-3-ylvinyl)pyridine
(R)- and (S)-3-phenoxy-5-((E)-2-(1-methylpiperidin-3-yl)vinyl)pyridine
3-phenoxy-5-((E)-2-piperidin-4-ylvinyl)pyridine
3-phenoxy-5-((E)-2-(1-methylpiperidin-4-yl)vinyl)pyridine
3-phenoxy-5-((E)-2-azetidin-3-ylvinyl)pyridine; and
3-phenoxy-5-((E)-2-(1-methylazetidin-3-yl)vinyl)pyridine,
or a pharmaceutically acceptable salt thereof.

The scope of the present invention includes individual isomers, enriched mixtures, racemic mixtures, substantially pure enantiomers, substantially pure diastereomers, and substantially pure tautomers thereof.

The compounds preferably have the ability to pass across the blood-brain barrier of the patient. As such, such compounds have the ability to enter the central nervous system of the patient. The log P values of typical compounds, which are useful in carrying out the present invention are generally greater than about 0, often are greater than about 0.5, and frequently are greater than about 1. The log P values of such typical compounds generally are less than about 3.5, often are less than about 3, and sometimes are less than about 2.5. Log P values provide a measure of the ability of a compound to pass across a diffusion barrier, such as a biological membrane. See, Hansch, et al., J. Med. Chem. 11:1 (1968), herein incorporated by reference with regard to such analysis.

The compounds of the present invention have the ability to bind to, and in most circumstances, cause activation of, neuronal nicotinic receptors (NNRs) of the brain of the patient. As such, these compounds have the ability to express nicotinic pharmacology, and in particular, to act as nicotinic agonists or partial agonists. The receptor binding constants of typical compounds useful in carrying out the present invention generally are less than about 1 μM, and frequently are less than about 50 nM. Receptor binding constants provide a measure of the ability of the compound to bind to relevant receptor sites of certain brain

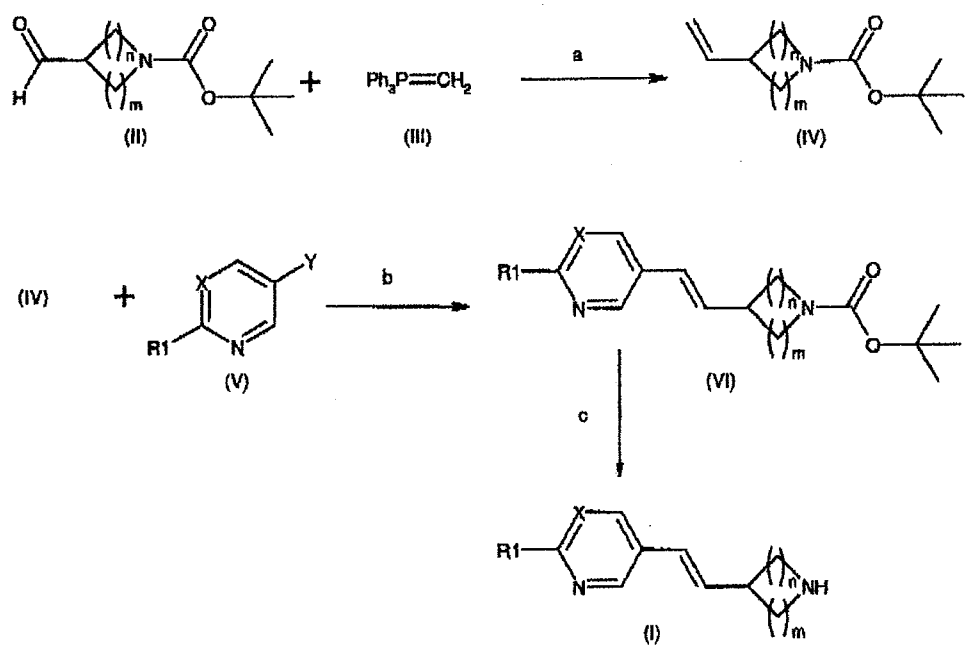
cells of the patient. See, Cheng, et al., Biochem. Pharmacol. 22:3099 (1973), herein incorporated by reference with regard to such pharmacology.

The compounds useful according to the method of the present invention have the ability to demonstrate a nicotinic function by effectively eliciting ion flux through, and/or neurotransmitter secretion from, nerve ending preparations, namely, thalamic or striatal synaptosomes. As such, such compounds have the ability to cause relevant neurons to become activated, and to release or secrete acetylcholine, dopamine, or other neurotransmitters. Generally, typical compounds useful in carrying out the present invention effectively provide for relevant receptor activation in amounts of at least about 30 percent, often at least about 50 percent, and frequently at least about 75 percent, of that maximally provided by (S)-(-)-nicotine. Generally, typical compounds useful in carrying out the present invention are more potent than (S)-(-)-nicotine in eliciting relevant receptor activation.

Effective amounts of the compounds are not believed to be sufficient to elicit any appreciable undesired nicotinic effects, as is demonstrated by decreased effects on preparations believed to reflect effects on the cardiovascular system or effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and undesired peripheral nicotinic effects, including side effects, are avoided. That is, an effective dose of a compound of the present invention is believed sufficient to provide the desired effects upon the CNS, but is believed insufficient, namely, not at a high enough level, to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/3, frequently less than 1/5, and often less than 1/10, that amount sufficient to cause any side effects to a significant degree.

II. Compound Preparation

While other synthetic strategies will be apparent to those of skill in the art, the compounds of Formula I wherein R^3 represents a hydrogen atom can be obtained from a compound of general formula II, illustrated below, in accordance with the following general synthesis scheme:



The general synthesis is as follows:

a) an aldehyde of general formula II is reacted with the phosphorane ylide III;

b) the vinylazacycloalkane of general formula IV is reacted with a heteroaryl halide of general formula (V, where Y=halogen); and

c) the tert-butoxycarbonyl group is eliminated from the compound of general formula VI; and the product is isolated and optionally converted into a pharmaceutically acceptable salt.

The reaction (a) between an aldehyde of general formula II and the phosphorane ylide III advantageously takes place under an inert atmosphere (for example under nitrogen or argon) in an inert solvent such as tetrahydrofuran at a temperature between -10°C and the boiling temperature of the reaction mixture, preferably at a temperature between around -5°C and around 22°C.

The reaction (b) between a vinylazacycloalkane of general formula IV and an appropriate heteroaryl halide of general formula V advantageously takes place under an inert atmosphere in the presence of a catalyst such as palladium acetate, a base such as diisopropylethylamine and an inorganic salt such as lithium chloride, in an inert solvent such as dimethylformamide at a temperature between 20°C and the boiling temperature of the reaction mixture. Ideally, the temperature of the reaction is in the region of about 110°C.

In another embodiment, the reaction (b) between a vinylazacycloalkane of general formula IV and an appropriate heteroaryl halide of general formula V can be performed preferably under an inert atmosphere (for example under nitrogen or under argon) in the

presence of a catalyst such as palladium acetate and a phosphine such as triphenylphosphine in basic medium, for example in the presence of a base such as triethylamine, at a temperature between 20°C and the boiling temperature of the reaction mixture, preferably at a temperature in the region of 110°C.

The reaction (c) takes place generally in accordance with the customary methods which do not adversely affect the rest of the molecule, in particular by applications of the methods described by T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd ed.), A. Wiley – Interscience Publication (1991), herein incorporated by reference with regard to such protecting groups.

For example, the reaction (c) of eliminating the tert-butoxycarbonyl group from the compound of general formula VI takes place preferably under an inert atmosphere (for example under nitrogen or under argon) in the presence of an acid such as trifluoroacetic acid in an inert solvent such as dichloromethane at a temperature between -10°C and the boiling temperature of the reaction mixture, preferably at a temperature between -5°C and a temperature in the region of 22°C.

Alternatively the reaction (c) of eliminating the tert-butoxycarbonyl group from the compound of general formula VI can be performed preferably under an inert atmosphere (for example under nitrogen or under argon) by the action of trimethylsilyl iodide in an inert solvent such as dichloromethane at a temperature between -10°C and the boiling temperature of the reaction mixture, preferably at a temperature in the region of 22°C.

The derivatives of general formula I in which R^3 does not represent a hydrogen can be obtained from a compound of general formula I in which R^3 represents a hydrogen atom in accordance with the customary methods of amine alkylation which do not adversely affect the rest of the molecule, in particular by applications of the methods described by R.C. Larock, Comprehensive Organic Transformations, VCH Publishers (1989), herein incorporated by reference with regard to such synthesis.

Alternatively the derivatives of general formula I in which R^3 represents a methyl can be obtained by reacting a compound of general formula I in which R^3 represents a hydrogen with a solution of formaldehyde in formic acid at a temperature between 22°C and the boiling temperature of the reaction mixture. The compounds of general formula II which are not commercially available can be obtained by applying or adapting methods described by Peschke B. et al., *Eur. J. Med. Chem.* **34**:363-380 (1999), the contents of which are hereby incorporated by reference.

The compounds of general formula V which are not commercially available can be obtained by applying or adapting methods described in PCT WO 00/75110, the contents of

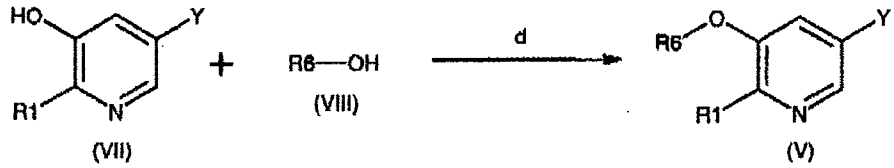
which are hereby incorporated by reference. Alternatively the compounds of general formula V in which:

X is C-R^2;

R^2 is -OR^6; and

R^6 is C_{1-6} alkyl, aryl-C_{1-6}alkyl, heteroaryl-C_{1-6}alkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl or polycycloalkyls, these radicals being optionally substituted by 1 or more substituents selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -CN, -NO_2, -NH_2, -OH, -COOH, -COO-C_{1-6} alkyl, -$CONH_2$, formyl, trifluoromethyl or trifluoromethoxy, can be obtained from a heteroaryl halide of general formula VII, where Y is a halogen and R^1 is as previously defined, and an alcohol of general formula VIII, where R^6 is as previously defined,

in accordance with the following general synthesis scheme:



The reaction (d) between heteroaryl alcohol of general formula VII and an appropriate alcohol of general formula VIII takes place preferably under an inert atmosphere in the presence of a diazene such as diethyl azodicarboxylate and a phosphine such as triphenylphosphine in an inert solvent such as toluene at a temperature between 0°C and the boiling temperature of the reaction mixture, preferably at a temperature between a temperature in the region of 22°C and the boiling temperature of the solvent.

The compounds of general Formula I can be isolated and purified using methods well known to those of skill in the art, including, for example, crystallization, chromatography, and/or extraction.

In the above-mentioned schemes, when any one or more of the R-groups are or contain reactive groups that are potentially reactive under the reaction conditions, for example, -OH, -SH, -NH_2, or –CO_2H, it will be readily apparent to those of skill in the art that these functional groups can require the use of suitable "protecting groups" during the reactions to "block" the reactivity of the R-group. These "protecting" groups can be chosen, introduced and cleaved in accordance to T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd ed.), A. Wiley – Interscience Publication (1991), herein incorporated by reference with regard to such protecting group chemistry.

The compounds of general formula I and the compounds of general formula IV can be obtained in optically pure form by separating their racemates in accordance with the customary methods, for example, resolution of enantiomers, or by using optically pure

starting materials. For example, the single enantiomer forms of 3-formylpyrrolidine-1-carboxylic acid tert-butyl ester, which is an intermediate useful in the synthesis of the compounds of Formula I, as taught in the examples herein, can be obtained as described in PCT WO 07/100670, herein incorporated by reference. Thus, itaconic acid is reacted with (S)-methylbenzylamine to form the diastereomeric (3S)- and (3R)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidinecarboxylic acids, from which the (3S)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidinecarboxylic acid can be separated by fractional crystallization in ethanol. Conversion of the (3S)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidinecarboxylic acid to the corresponding methyl ester, followed by reduction of the ester with lithium aluminium hydride, produces the corresponding alcohol, (3S)-1-[(S)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine. Exchange of protecting groups by hydrogenation, such as palladium hydroxide on carbon, of the (3S)-1-[(S)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine in the presence of di-tert-butyl dicarbonate produces tert-butyl (3S)-3-(hydroxymethyl)pyrrolidine-1-carboxylate, which is subsequently oxidized, using dimethylsulfoxide / oxalyl chloride / triethylamine (Swern conditions), to the aldehyde, tert-butyl (3S)-3-formylpyrrolidine-1-carboxylate. Thus prepared, tert-butyl (3S)-3-formylpyrrolidine-1-carboxylate, can be used to generate enantiomerically pure compounds of Formula I, via transformations, Wittig olefination, Heck coupling, and deprotection, such as those reported in the examples. The designation of absolute configuration changes (but the stereochemical configuration does not) as a result of the Wittig olefination, namely tert-butyl (3*S*)-3-formylpyrrolidine-1-carboxylate produces tert-butyl (3*R*)-3-vinylpyrrolidine-1-carboxylate.

In a useful variation in the synthesis reported immediately above, (3S)-1-[(S)-1-phenethyl]-5-oxo-3-pyrrolidinecarboxylic acid can be reduced directly, namely, without proceeding through the intermediacy of the ester, to (3S)-1-[(S)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine, as described in PCT WO 03/070728, herein incorporated by reference. This modification was used in the synthesis of (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine (Compound A).

The compounds of general Formula I can optionally be converted into addition salts with a mineral or organic acid by the action of such an acid in an appropriate solvent, for example, an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts likewise form part of the invention.

Representative pharmaceutically acceptable salts include, but are not limited to, benzenesulfonate, benzoate, bromide, chloride, citrate, ethanesulfonate, fumarate, gluconate, iodate, maleate, isethionate, methanesulfonate, methylenebis(β-oxynaphthoate),

nitrate, oxalate, palmoate, phosphate, salicylate, succinate, sulfate, tartrate, theophyllinacetate, p-toluenesulfonate, hemigalactarate and galactarate salts.

Synthetic Examples

The following synthetic examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, all parts and percentages are by weight, unless otherwise noted. Reaction yields are reported in mole percentages.

Example 1: Racemic 3-((E)-2-Pyrrolidin-3-ylvinyl)-5-(tetrahydropyran-4-yloxy)pyridine hemigalactarate:

Trifluoroacetic acid (0.91 cm^3, 11.7 mmol) was added drop-wise to a solution of 0.44 g (1.17 mmol) of racemic 3-{(E)-2-[5-(tetrahydropyran-4-yloxy)pyridin-3-yl]vinyl}pyrrolidine-1-carboxylic acid tert-butyl ester in 4.5 cm^3 of dichloromethane, which was under argon and was cooled to 0°C. The reaction mixture was stirred at this temperature for 0.5 h and then at a temperature in the region of 22°C for 20 h and was concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was taken up in 5 cm^3 of water and the resulting solution was rendered basic (pH=8) by adding 28% aqueous ammonia solution and then extracted with 3 times 25 cm^3 of dichloromethane. The combined organic phases were washed with 25 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.225 g of orange-colored oil, which was purified by chromatography on silica gel [eluent: dichloromethane/methanol (9/1 then 8/2 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 0.1 g (0.36 mmol) of orange-colored oil. Galactaric acid (0.038 g, 0.18 mmol) was added to a solution of this oil in 2 cm^3 of methanol to which 0.5 cm^3 of water has been added. The mixture was brought to reflux and cooled to a temperature in the region of 22°C and the insoluble material was removed by filtration. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) and the oily residue was taken up in 2 cm^3 of ethanol. The precipitated solid was filtered off, washed with 2 cm^3 of isopropyl acetate and 2 cm^3 of diisopropyl ether and then dried at 40°C under vacuum (2.7 kPa) to give 0.088 g of racemic 3-((E)-2-pyrrolidin-3-ylvinyl)-5-(tetrahydropyran-4-yloxy)pyridine hemigalactarate in the form of a beige solid. Mass spectrum (EI): m/z 274 (M^+), m/z 232. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with a few drops of CD_3COOD d4, δ in ppm): 1.61 (m: 2H); 1.82 (m: 1H); 1.98 (m: 2H); 2.17 (m: 1H); 2.96 (dd, J = 10.5 and 8.5 Hz: 1H); 3.07 (m: 1H); from 3.10 to 3.40 (m: 2H); 3.41 (dd, J = 10.5 and 7.5 Hz: 1H); 3.50 (ddd, J = 12 – 9.5 and 3 Hz: 2H); 3.79 (s: 1H); 3.87 (dt, J = 12 and 4.5 Hz: 2H); 4.24 (s: 1H);

4.69 (m: 1H); 6.43 (dd, J = 16 and 7 Hz: 1H); 6.56 (d, J = 16 Hz: 1H); 7.49 (m: 1H); 8.20 (m: 2H).

Racemic 3-{(E)-2-[5-(tetrahydropyran-4-yloxy)pyridin-3-yl]vinyl}pyrrolidine-1-carboxylic acid tert-butyl ester can be prepared as follows:

Palladium acetate (0.117 g, 0.52 mmol), 0.678 g (16 mmol) of lithium chloride and 7.25 cm^3 (42 mmol) of ethyldiisopropylamine were added in succession to a solution under argon of 1.33 g (5.17 mmol) of 3-bromo-5-(tetrahydropyran-4-yloxy)pyridine and 1.2 g (5.17 mmol) of racemic 3-vinylpyrrolidine-1-carboxylic acid tert-butyl ester in 15 cm^3 of dimethylformamide. After 3 hours of heating at 110°C with stirring, the reaction mixture was stirred for 2 hours at a temperature in the region of 22°C and then concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was taken up in 50 cm^3 of ethyl acetate and the resulting solution was washed in succession with 2 times 25 cm^3 of water, 25 cm^3 of saturated bicarbonate solution, 2 times 25 cm^3 of water and 25 cm^3 of saturated sodium chlorine solution and then was dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 1.4 g of brown oil. This residue was purified by chromatography on silica gel [eluent: cyclohexane/ethyl acetate (8/2 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 0.44 g of yellow oil which was used without further purification in the remainder of the synthesis.

3-Bromo-5-(tetrahydropyran-4-yloxy)pyridine can be prepared as follows:

Diethyl azodicarboxylate (7.1 cm^3, 45 mmol) was added drop-wise to a solution under argon of 5.22 g (30 mmol) of 5-bromopyridin-3-ol, 4.69 g (45 mmol) of tetrahydropyran-4-ol (45 mmol) and 11.8 g (45 mmol) of triphenylphosphine in 150 cm^3 of toluene. After 20 hours of heating under reflux with stirring, the reaction mixture was brought to a temperature in the region of 22°C and then washed in succession with 2 times 75 cm^3 of water, 2 times 75 cm^3 of saturated bicarbonate solution, 2 times 75 cm^3 of water and 75 cm^3 of saturated sodium chloride solution and then the organic solution was dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give an orange-colored oil. This residue was admixed with 100 cm^3 of diisopropyl ether and the solid formed was filtered off and washed with 2 times 25 cm^3 of diisopropyl ether. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) to give 10 g of an orange-colored oil. This residue was purified by chromatography on silica gel [eluent: cyclohexane/ethyl acetate (8/2 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 7.3 g of 3-bromo-5-(tetrahydropyran-4-yloxy)pyridine in the form of a yellow oil. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.59 (m: 2H); 1.99 (m: 2H); 3.49 (ddd, J = 12.5 – 9.5 and 3 Hz: 2H); 3.87 (dt, J = 12.5 and 4.5 Hz: 2H); 4.75 (m: 1H); 7.82 (dd, J = 2.5 and 2 Hz: 1H); 8.28 (d, J = 2 Hz: 1H); 8.33 (d, J = 2.5 Hz: 1H).

Racemic 3-vinylpyrrolidine-1-carboxylic acid tert-butyl ester can be prepared as follows:

n-Butyllithium in hexane (44 cm^3 of a 1.6 N solution) was added drop-wise to a suspension of 25.5 g (71 mmol) of triphenylmethylphosphonium bromide in 300 cm^3 of tetrahydrofuran, which was under argon and cooled to 0°C. The reaction mixture was stirred at 0°C for 0.5 h and then admixed with a solution of 7.1 g (35.6 mmol) of racemic 3-formylpyrrolidine-1-carboxylic acid tert-butyl ester in 100 cm^3 of tetrahydrofuran. After 2.5 hours of reaction at a temperature in the region of 22°C, the mixture was poured into 600 cm^3 of saturated aqueous ammonium chloride solution. Following addition of ethyl acetate the organic phase was taken off by decanting, washed twice with water and with saturated sodium chloride solution and then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The resulting oil was purified by chromatography on silica gel [eluent: cyclohexane/ethyl acetate (95/5 then 9/1 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 6.3 g of racemic 3-vinylpyrrolidine-1-carboxylic acid tert-butyl ester in the form of a colorless oil. Mass spectrum (ES): m/z 198 (MH^+), m/z=142.

Example 2: Racemic 5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine hemigalactarate:

Trifluoroacetic acid (1.2 cm^3, 15.6 mmol) was added drop-wise to a solution of 0.43 g (1.56 mmol) of racemic 3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester in 6 cm^3 of dichloromethane, which was under argon and cooled to 0°C. The reaction mixture was stirred at this temperature for 0.5 h then at a temperature in the region of 22°C for 20 hours and it was concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was taken up in 5 cm^3 of water and the resulting solution was rendered basic (pH=8) by adding 28% aqueous ammonia solution and was then extracted with 3 times 25 cm^3 of dichloromethane. The combined organic phases were washed with 25 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.126 g of orange-colored oil which was purified by chromatography on silica gel [eluent: dichloromethane/methanol (9/1 then 8/2 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 0.1 g (0.57 mmol) of orange-colored oil. Galactaric acid (0.06 g, 0.28 mmol) was added to a solution of this oil in 2 cm^3 of methanol to which 0.5 cm^3 of water has been added. The mixture was brought to reflux and cooled to a temperature in the region of 22°C and the insoluble material was removed by filtration. The filtrate was concentrated to dryness under reduced pressure (2.7 kPa) and the oily residue was taken up in 2 cm^3 of ethanol. The precipitated solid was filtered off, washed with 2 cm^3 of isopropyl acetate and 2 cm^3 of diisopropyl ether and then dried at 40°C under vacuum

(2.7 kPa) to give 0.1 g of racemic 5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine hemigalactarate in the form of an ochre solid. Mass spectrum (DCI): m/z 176 (MH^+). ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with a few drops of CD_3COOD d4, δ in ppm): 1.82 (m: 1H); 2.18 (m: 1H); 2.98 (dd, J = 11 and 8.5 Hz: 1H); 3.10 (m: 1H); 3.20 (m: 1H); 3.33 (m: 1H); 3.42 (dd, J = 11 and 7.5 Hz: 1H); 3.79 (s: 1H); 4.24 (s: 1H); 6.55 (limit AB: 2H); 8.87 (s: 2H); 9.04 (s: 1H).

Racemic 3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester can be prepared as follows:

Palladium acetate (0.117 g, 0.52 mmol), 0.678 g (16 mmol) of lithium chloride and 7.25 cm^3 (42 mmol) of ethyldiisopropylamine were added in succession to a solution under argon of 0.822 g (5.17 mmol) of 5-bromopyrimidine and 1.2 g (5.17 mmol) of racemic 3-vinylpyrrolidine-1-carboxylic acid tert-butyl ester in 15 cm^3 of dimethylformamide. After 3 hours of heating at 110°C with stirring, the reaction mixture was stirred for 2 hours at a temperature in the region of 22°C and then concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was taken up in 50 cm^3 of ethyl acetate and the resulting solution was washed in succession with 2 times 25 cm^3 of water, 25 cm^3 of saturated bicarbonate solution, 2 times 25 cm^3 of water and 25 cm^3 of saturated sodium chloride solution and was then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 1.1 g of brown oil. This residue was purified by chromatography on silica gel [eluent: cyclohexane/ethyl acetate (8/2 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 0.43 g of racemic 3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester in the form of an oil. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.42 (s: 9H); 1.78 (m: 1H); 2.05 (m: 1H); from 2.90 to 3.15 (m: 2H); from 3.15 to 3.60 (m: 3H); 6.51 (d, J = 16.5 Hz: 1H); 6.64 (dd, J = 16.5 and 7 Hz: 1H); 8.89 (s: 2H); 9.04 (s: 1H).

Example 3: (+)-5-((E)-2-Pyrrolidin-3-ylvinyl)pyrimidine galactarate:

Trimethylsilyl iodide (0.2 cm^3, 1.4 mmol) was added at a temperature in the region of 22°C to a solution under argon of 0.26 g (0.944 mmol) of (+)-3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester in 10 cm^3 of dichloromethane. After 2 hours of stirring at this temperature the reaction mixture was admixed with 15 cm^3 of 5% aqueous ammonia solution and stirred for 1 hour at a temperature in the region of 22°C and left to settle. The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were washed twice with water and with saturated aqueous sodium chloride solution and were then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.06 g of orange-colored oil. Galactaric acid (0.035 g, 0.16 mmol) was added to a solution of this oil in 6 cm^3 of methanol to which

0.6 cm^3 of water has been added. The mixture was brought to reflux, cooled to a temperature in the region of 22°C and concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was triturated in the presence of 5 cm^3 of diisopropyl ether and the solid formed was filtered off and then dried at 45°C under vacuum (2.7 kPa) to give 0.072 g of (+)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine galactarate in the form of a yellow solid. Mass spectrum (DCl): m/z = 176 (MH^+). ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with a few drops of CD_3COOD d4, δ in ppm): 1.81 (m: 1H); 2.19 (m: 1H); 2.98 (dd, J = 11 and 9 Hz: 1H); 3.10 (m: 1H); 3.21 (m: 1H); 3.33 (m: 1H); 3.43 (dd, J = 11 and 8 Hz: 1H); 3.79 (s: 2H); 4.25 (s: 2H); 6.56 (limit AB: 2H); 8.88 (s: 2H); 9.05 (s: 1H).

(+)-3-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester can be prepared as follows:

A racemic mixture of 3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester (0.5 g) was injected in two parts on a 8 cm diameter column containing 1.2 kg of chiral stationary phase CHIRALPAK AS ™ 20 µm [flow : 130 ml/min, eluent : heptane/methanol/ethanol (98/1/1 by volume)]. Concentration of the fractions under reduced pressure (2.7 kPa) gave 0.24 g of (+)-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester and 0.27 g of (-)-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester. (+)-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester was eluted in first position with a retention time of 14.2 min on a 4.6 mm diameter and 250 mm length CHIRALPAK AS ™ 20 µm column [flow : 1 ml/min, eluent : heptane/methanol/ethanol (98/1/1 by volume)]. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.43 (s: 9H); 1.79 (m: 1H); 2.06 (m: 1H); from 2.95 to 3.15 (m: 2H); from 3.20 to 3.35 (m: 1H); 3.44 (ddd, J = 11 – 8.5 and 3 Hz: 1H); 3.53 (broad dd, J = 10 and 7.5 Hz: 1H); 6.52 (d, J = 16.5 Hz: 1H); 6.63 (dd, J = 16.5 and 7 Hz: 1H); 8.89 (s: 2H); 9.04 (s: 1H). (-)-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester was eluted in second position with a retention time of 17 min on a 4.6 mm diameter and 250 mm length CHIRALPAK AS ™ 20 µm column [flow : 1 ml/min, eluent : heptane/methanol/ethanol (98/1/1 by volume)]. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.43 (s: 9H); 1.79 (m: 1H); 2.06 (m: 1H); from 2.95 to 3.15 (m: 2H); from 3.20 to 3.35 (m: 1H); 3.44 (ddd, J = 11 – 8.5 and 3 Hz: 1H); 3.53 (broad dd, J = 10 and 7.5 Hz: 1H); 6.52 (d, J = 16.5 Hz: 1H); 6.63 (dd, J = 16.5 and 7 Hz: 1H); 8.89 (s: 2H); 9.04 (s: 1H).

Example 4: (-)-5-((E)-2-Pyrrolidin-3-ylvinyl)pyrimidine galactarate:

Trimethylsilyl iodide (0.2 cm^3, 1.4 mmol) was added at a temperature in the region of 22°C to a solution under argon of 0.29 g (1.053 mmol) of (-)-3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester in 10 cm^3 of dichloromethane. After 2

hours of stirring at this temperature the reaction mixture was admixed with 15 cm^3 of 5% aqueous ammonia solution, stirred for 1 h at a temperature in the region of 22°C and left to settle. The aqueous phase was separated off and extracted with dichloromethane. The combined organic phases were washed twice with water and with saturated aqueous sodium chloride solution and then were dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.1 g of orange-colored oil. Galactaric acid (0.06 g, 0.28 mmol) was added to a solution of this oil in 10 cm^3 of methanol to which 1 cm^3 of water has been added. The mixture was brought to reflux, cooled to a temperature in the region of 22°C and concentrated to dryness under reduced pressure (2.7 kPa). The oily residue was triturated in the presence of 5 cm^3 of diisopropyl ether and the solid formed was filtered and then dried at 45°C under vacuum (2.7 kPa) to give 0.094 g of (-)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine galactarate in the form of a yellow solid. Mass spectrum (DCI): m/z = 176 (MH^+). ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with a few drops of CD_3COOD d4, δ in ppm): 1.82 (m: 1H); 2.19 (m: 1H); 2.98 (dd, J = 11 and 9 Hz: 1H); 3.10 (m: 1H); 3.21 (m: 1H); 3.32 (m: 1H); 3.43 (dd, J = 11 and 7.5 Hz: 1H); 3.79 (s: 2H); 4.24 (s: 2H); 6.57 (limit AB: 2H); 8.88 (s: 2H); 9.05 (s: 1H).

(-)-3-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine-1-carboxylic acid tert-butyl ester can be prepared as described in Example 3.

Example 5: (R)-5-((E)-2-Pyrrolidin-3-ylvinyl)pyrimidine hemigalactarate:

To a solution of (R)-3-((E)-2-pyrimidin-5-ylvinyl)pyrrolidine (15.7 g, 89.8 mmol) in ethanol (250 mL) at ambient temperature was sequentially added deionized water (70 mL) and 11.3 g of galactaric acid (53.7 mmol; 53.8 mmol). The mixture was refluxed for 30 min, and the insoluble material was filtered off at 65°C and rinsed with 85:15 ethanol/water (28 mL). The combined filtrates were refluxed for 30 min and cooled slowly (over several hours) first to ambient temperature and then to -5°C, at which temperature it was kept for 1 h. The (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine hemigalactarate product was collected by suction filtration and dried under vacuum. The white crystalline product was obtained in a yield of 55.6%. ^1H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6 with a few drops of CD_3COOD d4, δ in ppm): 1.81 (m: 1H); 2.19 (m: 1H); 2.98 (dd, J = 11 and 9 Hz: 1H); 3.10 (m: 1H); 3.21 (m: 1H); 3.33 (m: 1H); 3,43 (dd, J = 11 and 8 Hz: 1H); 3.79 (s: 1H); 4.25 (s: 1H); 6.56 (limit AB: 2H); 8.88 (s: 2H); 9.05 (s: 1H).

(R)-3-((E)-2-Pyrimidin-5-ylvinyl)pyrrolidine was made from tert-butyl (3S)-3-formylpyrrolidine-1-carboxylate (PCT WO 07/100670, incorporated by reference), via Wittig, Heck and deprotection reactions similar to those reported in previous examples.

III. Pharmaceutical Compositions

The present invention further provides pharmaceutical compositions that include effective amounts of compounds of the formulae of the present invention and salts or solvates or solvated salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formulae of the present invention, including salts, solvates, and solvates of salts thereof, are as herein described. The carrier(s), diluent(s), or excipient(s) must be acceptable, in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the present invention, including a salt, solvate, or solvated salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The pharmaceutical compositions according to the invention include a compound of Formula I or a salt thereof, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product, which can be inert or physiologically active. Such compositions can be administered, for example, orally, parenterally, rectally, or topically.

Examples of solid compositions for oral administration include, but are not limited to, tablets, pills, powders (gelatin capsules, cachets), and granules. In these compositions, the active compound is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose, or silica, ideally under a stream of an inert gas such as argon.

The compositions can also include substances other than diluents, for example, one or more lubricants such as magnesium stearate or talc, a colorant, a coating (coated tablets), or a varnish.

Examples of liquid compositions for oral administration include, but are not limited to, solutions, suspensions, emulsions, syrups, and elixirs that are pharmaceutically acceptable and typically contain inert diluents such as water, ethanol, glycerol, vegetable oils, or liquid paraffin. These compositions can comprise substances other than the diluents, for example, wetting agents, sweeteners, thickeners, flavors, and stabilizers.

Sterile compositions for parenteral administration can include, for example, aqueous or nonaqueous solutions, suspensions, and emulsions. Examples of suitable solvents and vehicles include, but are not limited to aqueous solutions, preferably buffered aqueous solutions, propylene glycol, a polyethylene glycol, vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, and other appropriate organic solvents. These compositions can also include adjuvants, especially wetting agents, isotonicity agents, emulsifiers, dispersants, and stabilizers. Such sterile compositions can be sterilized

in a number of ways, for example, by asepticizing filtration, by incorporating sterilizing agents into the composition, by irradiation, and by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Examples of compositions for rectal administration include, but are not limited to, suppositories and rectal capsules that, in addition to the active product, can include excipients such as cocoa butter, semi-synthetic glycerides, and polyethylene glycols.

Compositions for topical administration can, for example, be creams, lotions, eyewashes, collutoria, nasal drops, or aerosols.

The pharmaceutical compositions also can include various other components as additives or adjuncts. Exemplary pharmaceutically acceptable components or adjuncts which are employed in relevant circumstances include antioxidants, free radical scavenging agents, peptides, growth factors, antibiotics, bacteriostatic agents, immunosuppressives, anticoagulants, buffering agents, anti-inflammatory agents, anti-pyretics, time release binders, anesthetics, steroids, and corticosteroids. Such components can provide additional therapeutic benefit, act to affect the therapeutic action of the pharmaceutical composition, or act towards preventing any potential side effects which may be posed as a result of administration of the pharmaceutical composition. In certain circumstances, a compound of the present invention can be employed as part of a pharmaceutical composition with other compounds intended to prevent or treat a particular disorder.

The manner in which the compounds are administered can vary. The compounds can be administered by inhalation (e.g., in the form of an aerosol either nasally or using delivery articles of the type set forth in U.S. Patent No. 4,922,901 to Brooks et al.); topically (e.g., in lotion form); orally (e.g., in liquid form within a solvent such as an aqueous or non-aqueous liquid, or within a solid carrier); intravenously (e.g., within a dextrose or saline solution); as an infusion or injection (e.g., as a suspension or as an emulsion in a pharmaceutically acceptable liquid or mixture of liquids); intrathecally; intracerebroventricularly; or transdermally (e.g., using a transdermal patch).

Although it is possible to administer the compounds in the form of a bulk active chemical, it is preferred to present each compound in the form of a pharmaceutical composition or formulation for efficient and effective administration. Exemplary methods for administering such compounds will be apparent to the skilled artisan. For example, the compounds can be administered in the form of a tablet, a hard gelatin capsule or as a time-release capsule. As another example, the compounds can be delivered transdermally using the types of patch technologies available from Novartis and Alza Corporation.

The administration of the pharmaceutical compositions of the present invention can be intermittent, or at a gradual, continuous, constant or controlled rate to a warm-blooded animal, (e.g., a mammal such as a mouse, rat, cat, rabbit, dog, pig, cow, or monkey); but advantageously is preferably administered to a human being. In addition, the time of day and the number of times per day that the pharmaceutical formulation is administered can vary. Administration preferably is such that the active ingredients of the pharmaceutical formulation interact with receptor sites within the body of the subject that affect the functioning of the CNS or of the gastrointestinal (GI) tract. More specifically, in treating a CNS disorder administration preferably is such so as to optimize the effect upon those relevant receptor subtypes which have an effect upon the functioning of the CNS, while minimizing the effects upon muscle-type receptor subtypes. Other suitable methods for administering the compounds of the present invention are described in U.S. Patent No. 5,604,231 to Smith et al., the disclosure of which is incorporated herein by reference in its entirety.

The appropriate dose of the compound is that amount effective to prevent occurrence of the symptoms of the disorder or to treat some symptoms of the disorder from which the patient suffers. By "effective amount", "therapeutic amount" or "effective dose" is meant that amount sufficient to elicit the desired pharmacological or therapeutic effects, thus resulting in effective prevention or treatment of the disorder. Thus, when treating a CNS disorder, an effective amount of compound is an amount sufficient to pass across the blood-brain barrier of the subject, to bind to relevant receptor sites in the brain of the subject, and to activate relevant nicotinic receptor subtypes, namely, provide neurotransmitter secretion, thus resulting in effective prevention or treatment of the disorder. Prevention of the disorder is manifested by delaying the onset of the symptoms of the disorder. Treatment of the disorder is manifested by a decrease in the symptoms associated with the disorder or an amelioration of the recurrence of the symptoms of the disorder.

The effective dose can vary, depending upon factors such as the condition of the patient, the severity of the symptoms of the disorder, and the manner in which the pharmaceutical composition is administered. For human patients, the effective dose of typical compounds generally requires administering the compound in an amount sufficient to activate relevant receptors to effect neurotransmitter, such as dopamine, release but the amount should be insufficient to induce effects on skeletal muscles and ganglia to any significant degree. The effective dose of compounds will of course differ from patient to patient but in general includes amounts starting where CNS effects or other desired therapeutic effects occur, but below the amount where muscular effects are observed.

The doses depend on the desired effect, the duration of treatment and the administration route used; they are generally between 0.05 mg and 100 mg of active substance per day orally for an adult.

Generally speaking, a doctor will determine the appropriate dosage as a function of the age, weight, and all the other factors specific to the patient.

IV. Methods of Treatment

The compounds of Formula I are particularly useful in the treatment of neuropathic pain. As used herein, the phrase "neuropathic pain" includes various neuropathic pain states and neuropathic pain syndromes. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury can result from physical trauma, amputation, cancer, toxins, or chronic inflammatory conditions and may occur in the peripheral nerves, dorsal roots, spinal cord, or certain regions in the brain. Examples of common neuropathic pain states and syndromes include diabetic neuropathy, non-specific lower back pain, multiple sclerosis-related pain, fibromyalgia, HIV-related neuropathy including HIV myelopathy, post-herpetic neuralgia, trigeminal neuralgia, neuritis, causalgia, acute and chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, segmental neuropathy, ischemic optic neuropathy, geniculate neuralgia, occipital neuralgia, periodic migrainous neuralgia, chemotherapy-induced polyneuropathy, complex regional pain syndrome, entrapment neuropathies including carpal tunnel syndrome, brachial plexus avulsion, post-surgical neuropathy including post-mastectomy pain or post-thoracotomy pain, idiopathic sensory neuropathy, nerve compression including tumor infiltration, nutrition deficiency-related neuropathy, phantom limb pain, post-radiation plexopathy, radiculopathy, for example, sciatica, toxin exposure-related neuropathy, post-traumatic neuralgia, compressive myelopathy, Parkinson's disease-related neuropathy, post-ischemic myelopathy, post-radiation myelopathy, post-stroke pain, post-traumatic spinal cord injury pain, temporomandibular disorder, myofascial pain, and syringomyelia.

The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain or ongoing, burning pain or dysesthesia. Other symptoms include non-painful spontaneous abnormal sensations or paraesthesia, pain associated with normally non-painful stimulation such as clothing or light touch or allodynia, and increased sensitivity to mildly painful stimuli or hyperalgesia. The compounds of Formula I are also useful in treating reduction of sensitivity to normal and painful stimulation or hypoesthesia and hypoalgesia.

Neuropathic pain conditions are difficult to treat and, although several drugs are known to have some efficacy, complete pain control is only rarely achieved.

As used herein, the terms "prevention" or "prophylaxis" include any degree of reducing the progression of or delaying the onset of a disease, disorder, or condition, in this case, pain, specifically neuropathic pain. The term includes providing protective effects against a particular disease, disorder, or condition as well as amelioration of the recurrence of the disease, disorder, or condition. Thus, in another aspect, the invention provides a method for treating a subject having or at risk of developing or experiencing neuropathic pain. The compounds and pharmaceutical compositions of the invention may be used to achieve a beneficial therapeutic or prophylactic effect.

V. Pharmacological Examples

Example 1 – Acute Administration of Compound A for Allodynia in Streptozotocin-Induced Model of Diabetic Neuropathy

A major complication of diabetes is peripheral neuropathy, which is indicated by spontaneous pain and the perception of pain from a normally non-noxious stimulation. Streptozotocin (STZ) -induced diabetes in rats is a well-documented model in which a chemotherapeutic drug is administered peripherally, causing irreversible damage to the pancreatic β and α-cells and inhibiting islet synthesis of proinsulin. The model mimics clinical diabetes and onset of hyperglycemia can be seen in rats within 24 hours. Initial onset of peripheral neuropathy is typically demonstrated in control animals 3-4 weeks following STZ administration.

In this study, the compound was administered acutely, just before the test at Week 6. The test compound was evaluated for effects on mechanical allodynia, an assessment of pain response to a normally non-noxious stimulus, in the STZ animal model of peripheral neuropathy.

The results of this study indicate that, along with Gabapentin (positive control), acute administration of the test compound Compound A was effective in increasing the allodynia threshold in diabetic rats, thereby reducing the pain associated with diabetic neuropathy. Compound A, as its hemigalactarate salt, a powder, was formulated in deionized water to its highest concentration (1 mg/kg) and then serial dilutions were performed for remaining dose concentrations. Compound A had a Formula Weight of 280.302 with a salt/base ratio of 1.6, so the calculations for total amount of compound needed for the formulary took into account the multiplier of salt/base ratio. Doses are

expressed as the free-base equivalents. The materials, once formulated, were considered stable for the entire 6-week period of the study, when stored at 4° C.

The dose of 100 mg/kg Gabapentin is commonly used as a positive control in neuropathic pain models (Gilron and Flatters, 2006, herein incorporated by reference with regarding to gabapentin's use) and has previously been demonstrated to be an effective dose for reversing allodynia in pain models.

Animals

Adult male Sprague-Dawley rats were received from Harlan Sprague Dawley, Inc. (Indianapolis, Indiana, USA) for this study. The rats were specific pathogen free and approximately 8 weeks old upon arrival. Upon receipt the rats were unpacked and placed in cages. A visual health inspection was performed on each animal to include evaluation of the coat, extremities, and orifices. Each animal was also examined for any abnormal signs in posture or movement. The rats were acclimated for approximately one week prior to the commencement of the experimental procedures. No rats were found to be abnormal during the quarantine period. During the course of the study animals had *ad libitum* access to oval pellet Certified Picolab Rodent Diet 20 (PMI Feeds Inc., Richmond, Indiana, USA).

Allocation to Treatment Groups

As described in Table 1, rats were allocated to treatment groups, twelve (12) rats per group with the exception of satellite groups with six (6) rats in each group, based on baseline allodynia scores collected prior to the start of dosing. The mean allodynia scores for each group were reviewed to ensure that the mean values and standard deviation satisfy the assumption of homogeneity.

Table 1: Treatment Groups

Group	Injection	Dosing Regimen	Treatment	Dose and Route of Administration	n
1	STZ*	Chronic	Deionized water (Vehicle)	Vehicle, PO	12
2	STZ*	Acute#	Gabapentin	100 mg/kg IP	12
3	STZ*	Acute#	Compound A	0.01 mg/kg PO	12
4	STZ*	Acute#	Compound A	0.1 mg/kg PO	12

5	STZ*	Acute#	Comound A	1.0 mg/kg PO	12

* - Streptozotocin (75mg/kg)

- Groups received chronic vehicle until allodynia test day at week 6 post STZ

Disease Induction

On Day 1, the animals were dosed with an i.p. injection of 75mg/kg Streptozotocin.

Blood Glucose Monitoring

Diabetes was confirmed by assessing blood glucose levels. All groups had their glucose levels checked once between 3 and 5 days post STZ dosing. Approximately 50 μL of blood was collected via the tail vein for glucose level assessments. The animals were restrained and a needle was introduced into the tail vein to extract sufficient blood for the glucose strip. The glucose strip was inserted into the blood glucose meter and within 15 sec, the reading displayed on the meter was recorded on a Blood Glucose Test Record Form. The glucose levels had to be > 400 mg/dL for the animal to be considered diabetic. If the meter read "HI", it was considered to indicate that the glucose levels were above approximately 503 mg/dl, and therefore within the diabetic range. The reading of "HI" was recorded as the glucose level on the Blood Glucose Test Record Form.

Dosing

Starting at Day 0, all animals were dosed daily throughout the study by oral gavage with vehicle. On the day of allodynia testing at week 6, groups were dosed with vehicle (control group), the test article or reference article (Gabapentin) acutely.

Behavior

Acclimation

The animals were acclimated to the allodynia procedure approximately 2 to 3 days prior to testing. The rats were habituated to procedures in the testing devices in order to allow the animals to be calm enough to be properly tested.

Mechanical Allodynia (Von Frey)

At baseline (several days prior to the start of dosing), and at 6 weeks post STZ injections, the animals underwent Von Frey testing for mechanical allodynia. At 6 weeks the animals were tested prior to test compound dosing (time point = 0) and then dosed with test

compound, reference compound, or vehicle. Allodynia testing followed at 0.5, 2, 4, and 24-hour post test article dose. Tactile sensitivity (i.e., mechanical allodynia) was measured using calibrated filaments touched to the plantar surface of the affected limb. Any rat that showed allodynia (score of 5 or less) at baseline testing was not included in the study.

Procedurally, the rats were placed in a plexiglas cage with a wire mesh bottom and allowed to acclimate for at least 10 minutes. Once the animals were settled, the plantar surface of the right hind paw was touched with a 2.0 g Von Frey filament. In the absence of a paw withdrawal response to the initially selected filament, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. In this fashion, the resulting pattern of positive and negative responses was used to determine the paw withdrawal threshold, according to the method of Chaplan, et al., 1994, herein incorporated by reference with regard to such testing method.

Clinical Health

Body weights were measured prior to the start of the study and then weekly during the course of the study. Due to the dehydration and excessive urination associated with this model, all animals were given 5 mL of subcutaneous fluid up to twice daily starting at Day 14.

Animals were monitored for health and well-being throughout this study by clinical observations taken daily during dosing. The declining health of animals was noted on clinical observation forms. If the animal appeared moribund, it was documented and the animal was humanely euthanized.

Terminal Blood Collection

At 6 weeks, following the allodynia testing, blood was collected under isofluorane anesthetic via cardiac puncture from all animals for plasma. Animals were then euthanized by carbon dioxide asphyxiation.

Statistics

An initial one-way ANOVA was performed on baseline behavioral data to determine any differences in treatment group responses prior to STZ induction or treatment. Two-way ANOVAs were performed on the behavioral end points and evaluated for treatment and time to determine the effect of treatment on pain response. When there were overall significant differences by ANOVA, Holm-Sidak post-hoc analyses for multiple comparisons

versus a control group were used to evaluate individual treatment group differences from the vehicle-treated / time-matched controls.

Results

Non-diabetic animals excluded

Table 2 summarizes the percentage of animals that were excluded from the data analysis due to a clear or suspected non-diabetic state based on two sets of blood glucose readings. The glucose levels for each animal were measured at two time points. The first was taken at 4 days post-STZ injection and the second was from blood or plasma that was sampled at approximately 6 wk post-STZ injection. An animal was only accepted as diabetic, and included in the analyses if it had high (>400 mg/dl) readings for both samples. In the occasional cases where the 6 wk sample was missing, the animal was excluded. In any cases where a discrepancy existed regarding testing of 6 wk samples, animals were excluded.

The results in this table indicate that a large percentage of rats were eliminated from the group acutely dosed 0.01 and 0.1 mg/kg Compound A. Because the Compound A hadn't yet been dosed at the Day 4 time point, there is a likelihood of coincidence that these particular groups contained a large number of non-diabetic animals, rather than anything related to the test compound.

Table 2: Summary of non-diabetic rats removed from the study

Group	Injection	Dosing Regimen	Treatment	# non-diabetic removed /total n
1	STZ	Chronic	Deionized water (Vehicle)	3/12=25%
2	STZ	Acute#	Gabapentin	1/12=8%
3	STZ	Acute#	0.01 mg/kg Compound A	6/12=50%
4	STZ	Acute#	0.1 mg/kg Compound A	5/12=42%
5	STZ	Acute#	1 mg/kg Compound A	1/12=8%

- Groups received chronic vehicle until allodynia test day at week 6 post STZ

Mechanical allodynia

Mechanical allodynia was tested with Von Frey filaments to determine allodynia thresholds at baseline (prior to STZ administration) and at 6 weeks post-STZ. The baseline

data did not differ among any of the treatment groups [F(8,69)= 0.286; P=0.97)]. In contrast, an Overall Two-Way ANOVA on behavioral data collected at week 6 demonstrated significant effects of treatment group [F(8,349)=8.17; P<0.001] and time [F(4,349)=8.50; P<0.001].

Gabapentin

At the 6 week timepoint, the mechanical allodynia results for Gabapentin (100 mg/kg; i.p.) demonstrate a significant increase in allodynia thresholds at 0.5 and 2 hr post-dosing as compared to vehicle controls ($p<0.05$). See Figure 1, Gabapentin and vehicle-treated groups tested for allodynia at 6 weeks post-STZ treatment. Gabapentin significantly reversed the allodynia ($p<0.05$).

Compound A

Compound A was dosed using an acute regimen, just before testing at 6 weeks. This test compound had significant effects on allodynia at both 0.5 and 2 hr post-dosing at 0.1 mg/kg and 1 mg/kg in comparison with the vehicle-treated group ($p<0.05$; See Figure 2, Compound A and vehicle-treated groups tested for allodynia at 6 weeks post-STZ treatment. Compound A demonstrated a significantly increased allodynia threshold at both 0.5 and 2 hr post-dosing ($p<0.05$).

General animal health

The health of the diabetic rats in this study was generally poor. As is consistent with this model of progressive diabetes, the animals lost a lot of weight and appeared lethargic, unkempt, and weak. Several animals had to be euthanized during the study due to extreme weight loss (>40% vs vehicle-treated controls) and a small number of animals died for unidentified reasons. Just prior to the allodynia testing at 6 weeks, the technician stimulated the rats' paws using their fingers from below. Any animal that did not respond by moving away from this "poking" was eliminated from the study because it was reasoned that such a rat would not be able to demonstrate a proper withdrawal response during allodynia testing. The following symptoms were noted at the time of allodynia testing 6 wks post-STZ: inactivity, poorly groomed, constant rearing, excessive urination and defecation, hobbling, cupping the right foot to avoid placing weight, dragging feet, "dead foot" (which refers to an animal that doesn't respond when its foot is squeezed hard), wheezing, sleepy, and extreme difficulty walking and moving.

Conclusions

This study of STZ-induced diabetic neuropathy produced variable results regarding the incidence of diabetes and the reduced severity of the allodynia at 6 weeks post-STZ. It is not clear why this occurred but it resulted in fewer animals that could be tested for allodynia. Despite the smaller group size in several of the groups, it was still possible to determine significant effects for the test compound and positive control groups as compared to the vehicle-treated groups.

Compound A reversed allodynia at 0.5 and 2 hr post-dosing in the 0.1 and 1 mg/kg acute dosing groups. Similarly, Gabapentin (100 mg/kg) was also effective at reducing allodynia at 0.5 and 2 hr post-dosing vs the vehicle treated group. Compound A closely resembled the levels of allodynia and time course of effectiveness of Gabapentin in this model.

Example 2 – Chronic Administration of Compound A for Pain in Streptozotocin-Induced Model of Diabetic Neuropathy

In a study similar to the one described above, a second utilized the STZ rat model of diabetic neuropathy to investigate the effects of chronic administration of test compound on mechanical allodynia.

Test Article Formulation

The test material, Compound A as its hemigalactarate salt, was provided as a powder. The test article was formulated in deionized water to its highest concentration (3 mg/kg & 10 mg/kg respectively) and then serial dilutions were performed for remaining dose concentrations. The material, once formulated, was considered to be stable for the entire 6-week period of the study when stored at 4° C.

Animals

Adult male Sprague-Dawley rats were obtained from Harlan Sprague Dawley, Inc. for the purpose of conducting this study. Body weight range upon receipt of the animals was 188-238g. The rats were specific pathogen free and aged approximately 8 weeks upon arrival. The Sprague-Dawley rat is the strain of choice due to the availability of background data.

Allocation to Treatment Groups

Rats were randomly allocated to treatment group based on baseline allodynia scores collected prior to the initiation of dosing activities. Twelve (12) rats were assigned to each

treatment group (see Table 3 below). The group mean body weights were reviewed to ensure the mean values and standard deviations satisfied the assumption of homogeneity.

Table 3: Treatments Groups

Group	Injection	Treatment	Dose and Route of Administration	n
1	STZ*	Deionized water (Vehicle)	Vehicle, PO	12
2	STZ*	Insulin Implant (placed on Day 3), Subcutaneous	Vehicle, PO	12
3	STZ*	Compound A	0.1 mg/kg PO	12
4	STZ*	Compound A	1 mg/kg PO	12
5	STZ*	Compound A	10 mg/kg PO	12

* - Streptozotocin (75mg/kg)

Disease Induction

At time point Day 0, the animals were dosed with an i.p. injection of 75mg/kg Streptozotocin.

Blood Glucose Monitoring

At weekly time points, a minimal blood sample (<300µL) was collected via the tail vein for analysis of glucose levels. The animals were restrained and a needle was introduced into the tail vein to produce sufficient blood to collect on a glucose test strip. The glucose test strip was then inserted into the blood glucose meter to produce a reading that was recorded in the study records.

The glucose levels were required to be $\geq$ 400mg/dL for the animal to be considered diabetic. If the meter read "HI", this was an indication that the glucose levels were above 600 mg/dl, considered to be within the diabetic range, and the reading of "HI" was recorded as the glucose level, and this was translated as 601 mg/dl for the purposes of data averaging. The glucose levels were determined prior to STZ dosing, 3 days later, and again at 1, 2, 3, 4, 5, and 6 weeks post-STZ dosing.

Subcutaneous Implants

On Day 3, animals in Group 2 received a subcutaneous implant of insulin. The animals were briefly sedated with inhalation anesthetic and 1½ insulin pellets (approximately 3 IU/day) were introduced subcutaneously.

Dosing

Beginning the day before STZ injection, all animals were dosed daily throughout the study by oral gavage with test or control article.

Behavior

Acclimation

All animals were subjected to chamber acclimation for the von Frey test of mechanical allodynia. The acclimation was performed 2 and 3 days prior to testing, in order to habituate the rats to the testing environment and allow the animals to be calm enough to be properly tested.

Mechanical Allodynia (Von Frey)

At baseline, several days prior to the start of dosing, and at 4 and 6 weeks post STZ injections, the animals were subjected to von Frey testing for mechanical allodynia. Tactile sensitivity, namely mechanical allodynia, was measured using calibrated filaments touched to the plantar surface of the affected limb. No animal showed significant allodynia (score of 5 or less) at baseline testing, and thus no animal was excluded from the study.

Procedurally, the animal was placed in a Plexiglas cage with a wire mesh bottom and allowed to acclimate for at least 10 minutes. Once the animals settled, the plantar surface of the right hind paw was touched with a 2.0g Von Frey filament. In the absence of a paw withdrawal response to the initially selected filament, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. In this fashion, the resulting pattern of positive and negative responses is used to determine the paw withdrawal threshold, according to the method of Chaplan, et al., 1994, incorporated by reference.

Clinical Health

Animals were monitored for health and well-being throughout this study by weekly body weights and clinical observations during daily dosing. Animals that were found to be in a state of dehydration were treated with subcutaneous fluids. The declining health of any

animals was noted on a form and if the animal appeared moribund, this was documented and the rat was humanely euthanized.

Blood Collection

Following the behavior testing at Week 6, a cardiac puncture was performed, and the animals were humanely euthanized by carbon dioxide asphyxiation. Blood was collected and processed for plasma, frozen at –80° degrees, and shipped to the sponsor on dry ice.

Statistics

A one-way ANOVA was performed on the behavioral endpoints at each time point to determine the effect of treatment on pain response. In instances of overall significant differences by ANOVA, then post-hoc analyses were used to evaluate individual treatment group differences.

Results

Blood Glucose Levels

Blood glucose levels were determined each week by tail vein puncture. The upper limits of the glucometer were typically reached for many of the STZ-treated rats; the glucose level for these animals was recorded as 601 mg/dl. The insulin pump was effective in reducing the glucose levels to baseline levels in Group 2 (data not shown). A one-way ANOVA of the Week 6 data was highly significant ($p<0.0001$) with a Dunnett's post-hoc test confirming that only the insulin-treated group significantly differed from the vehicle group ($p<0.001$).

Mechanical Allodynia

Mechanical allodynia was measured using Von Frey filaments to assess sensitivity to a tactile stimulus. Rats were first tested for mechanical allodynia at baseline, prior to STZ administration and then allocated to treatment groups on the basis of their baseline allodynia results, ensuring homogeneity across groups.

Compound A

At Week 4, there was a significant overall effect for mechanical allodynia ($p<0.05$) but a Dunnett's Multiple Comparison test did not indicate any group differences. As illustrated in Figure 3, allodynia testing at Week 6 revealed a highly significant overall effect ($p<0.01$) with a post-hoc Dunnett's test for Multiple Comparisons demonstrating significant group

differences for all three Compound A dose groups tested($p<0.05$ for the low and high doses, $p<0.01$ for the medium dose group).

General Animal Health

Due to the dehydration and excessive urination associated with this model, extra care was performed in an effort to improve the health and well-being of the animals. Beginning the week after STZ injection, cages were changed daily. In addition, the animals were injected with 5 ml subcutaneous fluids (Ringer's Lactate) to rehydrate the rats. This occurred for most animals on a daily basis beginning around Week 3. Clinical observations were noted for any animal that was suffering from symptoms associated with the diabetes. The following clinical symptoms were noted in many of the diabetic animals: severe weight loss and dehydration, ascites, gait problems, distended stomach, lack of muscle tone, general weakness, or pitting edema in the tail.

Conclusions

The rat Streptozotocin-induced diabetic neuropathy model is a clinically relevant model of diabetic neuropathy, which replicates elements of the human situation diabetic condition such as high glucose levels, neuropathic pain in the extremities, and generally poor health. This study demonstrated progressive pain sensitivity, as measured by allodynia testing of the hindpaw at Weeks 4 and 6, and significant reversal of this pain at Week 6 by the test article, in the absence of any changes to blood glucose levels in these groups. The insulin-treated group did show reduced blood glucose levels but did not have significant improvement in pain sensitivity compared in comparison with vehicle-treated animals. This demonstrates a lack of correspondence between blood glucose levels and allodynia levels in this diabetic neuropathy model, and is consistent with reports in the literature (Maneuf, et al, 2004, herein incorporated by reference with regard to such model). The results demonstrated in this study are indicative of Compound A at all three doses tested in the STZ-rat model of diabetic neuropathy.

Example 3 - Compound A for Pain in an Animal Model of Taxol®-Induced Sensory Neuropathy

Peripheral neuropathies are chronic conditions that arise when nerves are damaged by trauma, disease, metabolic insufficiency, or by certain drugs and toxins. The sensory disturbances associated with chemotherapeutic agents, such as Paclitaxel (sold under the brand name Taxol®), range from mild tingling to spontaneous burning, typically in the hands

and feet. Symptoms become more intense with continued therapy and can lead to weakness, ataxia, numbness and pain.

In this study, an animal model of Taxol®-induced sensory neuropathy was employed to evaluate the effects of test compounds for response to tactile sensitivity using the Von Frey test for mechanical allodynia. Animals were administered Taxol® and then dosed with vehicle, acute Gabapentin, or one of three doses of the test compound daily, throughout the course of the study. Testing for mechanical allodynia was performed at three weeks and four weeks post-Taxol®. After the final behavioral test, the sciatic nerve and hind paw were harvested and retained for possible histological analysis. Results demonstrated significant effects of both test compounds in reversing the allodynia levels associated with Taxol®-induced neuropathy.

Disease Induction Agent Preparation

A stock Taxol® solution of 6.0 mg/mL was prepared by the following methods. A quantity of 299.9mg of Taxol® was weighed on analytical balance and transferred to a container with a stir bar; then 25 mL of Cremaphor (Cremaphor EL, Sigma Aldrich) was added using a syringe and stirred until dissolved; then 25mL of Ethyl alcohol was added and stirred for approximately 5 min.

The dosing solution was prepared by diluting the stock solution with deionized water for a concentration of 1 mg/mL. 208.33 mL of saline was added to 41.67 mL of stock Taxol® solution. The Dosing solution was aliquoted into four conical tubes and placed in 2-8 °C storage until used for dose administration.

Animals

Animals were obtained, selected, and maintained as indicated in Pharmacological Example 1 above.

Allocation to Treatment Groups

Rats were randomly allocated to treatment group based on their baseline Von Frey scores. The group means were reviewed to ensure that mean values and standard deviations satisfied the assumption of homogeneity.

As described in Table 4, rats were allocated to treatment groups, ten (10) rats per group, based on allodynia scores collected prior to the start of dosing. The mean allodynia

scores for each group were reviewed to ensure that the mean values and standard deviation satisfied the assumption of homogeneity.

Table 4: Treatments Groups

Group	Injection	Treatment	Dose and Route of Adminstration
1	Taxol	Deionized water (Vehicle)	Vehicle, PO
2	Taxol	*Gabapentin	100mg/kg IP
3	Taxol	Compound A	0.01 mg/kg PO
4	Taxol	Compound A	0.1 mg/kg PO
5	Taxol	Compound A	1.0 mg/kg PO

*Group 2 — Gabapentin, reference article, was administered 90 minutes prior to the scheduled three and four week Von Frey testing time points. On all other days these animals were orally gavaged with water.

Dosing

Animals in Groups 1-8 were given Taxol® (2mg/kg) i.p. on Days 1, 3, 5 & 7. Animals received daily oral gavage of test compound or vehicle (5 mL/kg), starting the day of the first Taxol® injection and continuing once daily for the entire 4 weeks of the study. On the four days that Taxol® was administered, the test article was dosed approximately 60 min after Taxol®. Following dosing, animals were observed for signs of abnormal reaction to the Taxol® or test treatments. The reference compound was given by IP injection at a volume of 2 mL/kg, 90 minutes prior to the allodynia testing only on the day of testing at weeks 3 and 4.

Behavioral Testing

Acclimation

The animals were acclimated to the allodynia procedure. The acclimation to the apparatus occurred approximately 2 to 3 days prior to initial testing, as this habituated the rats to the testing devices and allowed the animals to be calm enough to be properly tested.

Mechanical Allodynia (Von Frey)

At baseline and at week three and week four post-Taxol injection, the animals underwent Von Frey testing for mechanical allodynia. At the three and four week time points, testing began 30 minutes after dosing with the test compound except for Group 2 which was tested at 90 minutes post-dosing. Tactile sensitivity (i.e. mechanical allodynia) was measured using calibrated filaments touched to the plantar surface of the affected limb. Procedurally, the rats were placed in a plexiglas cage with a wire mesh bottom and allowed to acclimate for at least 10 minutes. Once the animals settled, the plantar surface of the right hind paw was touched with a 2.0g Von Frey filament. In the absence of a paw withdrawal response to the initially selected filament, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. In this fashion, the resulting pattern of positive and negative responses was used to determine the paw withdrawal threshold, according to the method of Chaplan, et al., herein incorporated by reference. The optimal threshold calculation by this method requires six responses in the immediate vicinity of the 50% threshold. The resulting pattern of positive and negative responses is tabulated using the convention, X=withdrawal; 0=no withdrawal, and the 50% response threshold is interpolated using the formula:

$$50\% \text{ gram threshold} = (10\ [X_f + k\delta])/10{,}000$$

where:

X_f = value (in log units) of the final Von Frey hair used

k = value for the pattern of positive/negative responses

δ = mean difference (in log units) between stimuli.

Statistics

The data were analyzed using two-way ANOVAs to determine the effects of test compound on mechanical allodynia at two time points (3 and 4 weeks post-Taxol® treatment initiation). Appropriate post-hoc tests were used when the data were significant. Statistical significance was accepted when $p<0.05$.

Results

The allodynia data, tested at 3 weeks and 4 weeks post-Taxol® dosing, were significantly reduced from baseline levels in the vehicle treated group, indicating onset of neuropathic pain by these time points.

Positive control / Validation of Assay

A two-way ANOVA for all the data indicated a treatment effect, an effect of time, and an interaction (all $p<0.0001$). Gabapentin at 100 mg/kg, was effective at reversing the allodynia observed in the vehicle-treated groups when delivered acutely 90 min prior to testing ($p<0.001$; Bonferroni post-hoc test) at both Weeks 3 and 4. See Figure 4, Gabapentin and vehicle-treated groups tested for allodynia at baseline, 3 and 4 weeks post-Taxol® administration. Gabapentin significantly reversed the allodynia ($p<0.001$).

Compound A

Chronically administered Compound A, as its hemigalactarate salt, at all doses significantly reduced allodynia as compared with the vehicle-treated group at 4 weeks post-Taxol® dosing but at 3 weeks post-dosing, only the 0.1 mg/kg dose was significantly different from vehicle (see figure below). A two-way ANOVA revealed overall significance for Compound A for treatment ($p<0.001$) and time ($p<0.0001$). A Bonferroni post-hoc test demonstrated effects for the 0.1 mg/kg dose at three weeks ($p<0.05$) and at 4 weeks, in a dose-dependent manner (0.01 mg/kg, $p<0.05$, 0.1 mg/kg, $p<0.01$, 1 mg/kg, $p<0.001$). See Figure 5, Compound A and vehicle-treated groups tested for allodynia at baseline, 3 and 4 weeks post-Taxol® administration. All three doses were effective at week 4 ($p<0.05$ for 0.01 mg/kg Compound A, $p<0.01$ for 0.1 mg/kg Compound A, and $p<0.001$ for 0.1 mg/kg Compound A).

Conclusions

This study of Taxol®-induced neuropathy demonstrated an analgesic effect of the chronically administered test compound (Compound A) as well as acutely administered Gabapentin. Notably, at the 4 week allodynia assessment, the vehicle allodynia response had dropped compared to the 3 week assessment indicating a greater degree of allodynia from which alleviation could be demonstrated. Thus, at three weeks following Taxol®, significant reversal of allodynia demonstrated by the vehicle group was achieved at a 50% threshold of about 10 g force whereas only about 7.5 g was required by week 4.

Example 4 - Compound A in Chung Model of Neuropathic Pain

The aim of this study was to examine the analgesic potential of Compound A in the Chung Model of neuropathic pain.

Animals

Adult male Sprague-Dawley rats (Elevage Janvier, France) were stabilized for at least 5 days in macrolon cages (41 x 25 x 18 cm, 4 per cage) on wood litter with free access to food and water. The rats had a body weight range of 268-334 g on day 1 of dosing and 375-493 g on day 21 of the study.

Substances

The test substance, Compound A, provided as its hemigalactarate salt, a white powder, was dissolved in distilled water. It was administered p.o. at 0.01, 0.1 and 1 mg/kg (free base) 30 min before the test on day 1 (acute evaluation) or once daily from day 1 to day 20 and once 30 min before the test on day 21 (evaluation after 21 days of chronic administration).

The control substance was vehicle (distilled water).

The comparison substance was gabapentin (Toronto Research Chemicals), provided as a white powder and dissolved in distilled water. It was administered p.o. at 100 mg/kg 60 min before the test on day 1 (acute evaluation) or once on day 1 and once 60 min before the test on day 21 (with vehicle administration once daily from day 2 to day 20) (evaluation on day 21).

The reference substance was morphine hydrochloride. It was administered p.o. at 128 mg/kg 60 min before the test on day 1 (acute evaluation) or once on day 1 and once 60 min before the test on day 21 (with vehicle administration once daily from day 2 to day 20) (evaluation on day 21).

Evaluation and Statistical Analysis

The effects of the test substance were compared to those of the control substance. Paired and unpaired Student's t-test were used.

Results

Acute Evaluation

In vehicle controls, the force inducing paw-withdrawal and paw-withdrawal latency were both decreased in the lesioned paw as compared with the non-lesioned paw (-82% and -58% respectively, $p<0.001$), demonstrating allodynia and thermal hyperalgesia respectively.

Compound A (0.01, 0.1 and 1 mg/kg) globally increased the force inducing paw-withdrawal (tactile allodynia) in the lesioned paw, as compared with vehicle control (+35%, +74% and +35%, respectively), significantly so at 0.1 mg/kg ($p<0.05$). It did not affect paw-withdrawal latency (thermal hyperalgesia) in the lesioned paw. It significantly deceased the

force inducing paw-withdrawal in the non-lesioned paw at 0.1 mg/kg (-11%, $p<0.05$) but had no effect at 0.01 or 1 mg/kg and did not affect paw-withdrawal latency at any dose.

Gabapentin (100 mg/kg) did not affect the force inducing paw-withdrawal but tended to increase paw-withdrawal latency in the lesioned paw, as compared with vehicle controls (=48%, $p=0.0943$). It had no effects on the non-lesioned paw.

Morphine (128 mg/kg) increased the force inducing paw-withdrawal and paw-withdrawal latency in the lesioned paw, as compared with vehicle control(+119% and +192%, respectively, $p<0.001$). It did not affect the force inducing paw-withdrawal but significantly increased paw-withdrawal latency in the non-lesioned paw (+29%, $p<0.01$).

Evaluation after 21 days chronic administration

In vehicle controls, the force inducing paw-withdrawal and paw-withdrawal latency were both decreased in the lesioned paw as compared with the non-lesioned paw (-85%, $p<0.001$, and -53%, $p<0.01$, respectively), demonstrating allodynia and thermal hyperalgesia respectively.

Compound A at 0.1 mg/kg, but not at 0.01 or 1 mg/kg, tended to increase the force inducing paw-withdrawal in the lesioned paw, as compared with the vehicle controls (+85%, $p=0.0903$). It tended to dose-dependently increase paw-withdrawal latency in the lesioned paw (+12%, +58% and +61%, respectively). It significantly the force inducing paw-withdrawal in the non-lesioned paw at 0.1 mg/kg (-10%, $p<0.05$) and had a similar tendency at 0.01 mg/kg (-10%, $p=0.0951$) but had no effect at 1 mg/kg. It did not affect paw-withdrawal latency in the non-lesioned paw.

Gabapentin (100 mg/kg) did not affect the force inducing paw-withdrawal or paw-withdrawal latency in the lesioned paw, as compared with vehicle controls. It had no effects on the non-lesioned paw.

Morphine (128 mg/kg) increased the force inducing paw-withdrawal and clearly increased paw-withdrawal latency in the lesioned paw, as compared with vehicle control(+239%, $p<0.001$, and +110%, $p<0.01$, respectively). It significantly decreased the force inducing paw-withdrawal (-13%, $p<0.05$) but had no effect on paw-withdrawal latency in the non-lesioned paw.

Conclusions

Taken together, these results demonstrate the presence of analgesic activity for Compound A against tactile allodynia, but not against thermal hyperalgesia, at 0.1 mg/kg p.o. after acute administration, in the Chung model of neuropathic pain in the rat. Compound A had a similar tendency after repeated (21 days) administration, with a dose-dependent, although statistically non-significant, effects on thermal hyperalgesia. The comparison

compound, gabapentin, was devoid of clear analgesic activity against tactile allodynia or thermal hyperalgesia when evaluated after either acute administration or after 20 days repeat vehicle administration in the same test.

The specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

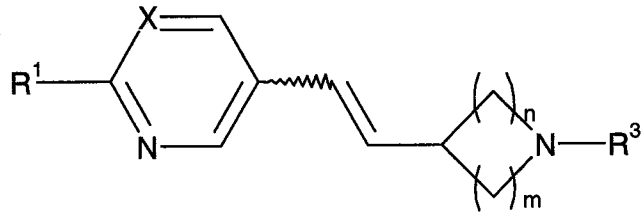
Test compounds were employed in free or salt form.

Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the spirit of the invention are intended to be included with the scope of the appended claims.

What is Claimed is:

1. A methods for treating or preventing neuropathic pain comprising:

administering a vinylazacycloalkane compound of Formula I:



Formula I

wherein:

variable geometry (E or Z) exists about the double bond as represented by the wavy line;

X is nitrogen or C-R^2;

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, halogen, -OR^4, -NR^4R^5, or -SR^4 when X is C-R^2, and

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cyclolalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, -OR^4, or -NR^4R^5 when X is nitrogen;

R^2 is hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, -$(CH_2)_qC_{3-8}$ polycycloalkyl, -OR^6, -NR^6R^7, -SR^6, -SOR^6, or -SO_2R^6;

wherein each R^2 can optionally be substituted with one or more substituent selected from halogen, -CN, -NO_2, -NH_2, -OH, -OR^6, -COOH, -C(O)OR^6, -O-C(O)R^6, -NR^6R^7, -NHC(O)R^6, -C(O)NR^6R^7, -SR^6, -S(O)R^6, -SO_2R^6, -$NHSO_2R^6$, -$SO_2NR^6R^6$, -C(S)NR^6R^6, -NHC(S)R^6, -O-SO_2R^6, aryl, heteroaryl, formyl, haloalkyl, haloalkylsulfanyl, haloalkoxy, and C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6} alkyl, -$(CH_2)_q$aryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl;

m is 1, 2, 3, or 4;

n is 1, 2, or 3;

each R^4, R^5, R^6, and R^7 is, independently, hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl, each of which can optionally be substituted with one or more substituents selected from the group consisting of halogen, C_{1-6}

alkyl, C_{1-6} alkoxy, -CN, $-NO_2$, $-NH_2$, -OH, -C(O)OH, $-C(O)O-C_{1-6}$ alkyl, $-CONH_2$, formyl, haloalkyl, and haloalkoxy,

wherein each of the C_{1-6}-alkyl, heterocyclyl, heteroaryl, and aryl groups can be substituted with from 1 to 6 substituents selected from the group consisting of F, Cl, Br, I, R^8, $-NR^8R^9$, haloalkyl, -CN, $-NO_2$, $-C_2R^8$, $-N_3$, $-SO_2CH_3$, $-OR^8$, $-SR^8$, $-C(=O)NR^8R^9$, $-NR^8C(=O)R^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-(CH_2)_qOR^8$, $-OC(=O)R^8$, $-OC(=O)NR^8R^9$, and $-NR^8C(=O)OR^8$,

wherein each R^8 and R^9 are individually hydrogen, C_{1-6} alkyl, an aromatic group-containing species, or a substituted aromatic group-containing species that is substituted with one or more of F, Cl, Br, I, R^{10}, $-NR^{10}R^{11}$, haloalkyl, -CN, $-NO_2$, $-C_2R^{10}$, $-N_3$, $-SO_2CH_3$, $-OR^{10}$, $-SR^{10}$, $-C(=O)NR^{10}R^{11}$, $-NR^{10}C(=O)R^{10}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-(CH_2)_qOR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, or $-NR^{10}C(=O)OR^{10}$; wherein each of R^{10} and R^{11} individually is hydrogen or C_{1-6} alkyl; or

either R^6 and R^7 or R^8 and R^9 can combine together with the atoms to which they are attached to form a C_{1-10} cycloalkyl functionality; and

wherein each q independently is 1 to 6;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein:

the geometry at the double bond is E;

R^1 is hydrogen;

X is N or CR^2;

when X is CR^2, then R^2 is $-OR^6$;

R^3 is hydrogen;

n is 1;

m is 2; and

R^6 is a alkyl, aryl, or heterocyclyl.

3. The method of claim 1 wherein:

the geometry at the double bond is E;

X is N;

R^1 is hydrogen;

R^3 is hydrogen;

n is 1; and

m is 2.

4. The method of claim 1 wherein the compound is

(R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine,
(R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine,
5-((E)-2-piperidin-4-ylvinyl)pyrimidine, or
5-((E)-2-azetidin-3-ylvinyl)pyrimidine

5. The method of claim 1 wherein the compound is (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine.

6. The method of claim 1 wherein the neuropathic pain is associated with injury.

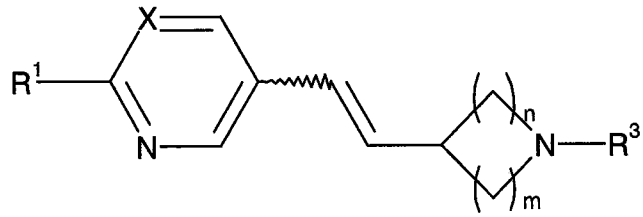
7. The method of claim 6 wherein the injury is associated with physical trauma, amputation, disease or condition, one or more toxin, or inflammation.

8. The method of claims 6 or 7 wherein the neuropathic pain effects a subject's peripheral nerves, dorsal roots, spinal cord, or regions of the brain.

9. The method of claims 6 – 8 wherein the neuropathic pain is neuralgia, neurodynia, spontaneous, lancinating, dysesthesia, paraesthesia, allodynia, hyperalgesia, hypoesthesia, or hypoalgesia.

10. The method of claims 6 – 9 wherein the neuropathic pain is associated with diabetic neuropathy, non-specific lower back pain, multiple sclerosis-related pain, fibromyalgia, HIV-related neuropathy including HIV myelopathy, post-herpetic neuralgia, trigeminal neuralgia, neuritis, causalgia, acute or chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, segmental neuropathy, ischemic optic neuropathy, geniculate neuralgia, occipital neuralgia, periodic migrainous neuralgia, chemotherapy-induced polyneuropathy, complex regional pain syndrome, entrapment neuropathies, carpal tunnel syndrome, brachial plexus avulsion, post-surgical neuropathy, post-mastectomy pain or post-thoracotomy pain, idiopathic sensory neuropathy, nerve compression, tumor infiltration, nutrition deficiency-related neuropathy, phantom limb pain, post-radiation plexopathy, radiculopathy, sciatica, toxin exposure-related neuropathy, post-traumatic neuralgia, compressive myelopathy, Parkinson's disease-related neuropathy, post-ischemic myelopathy, post-radiation myelopathy, post-stroke pain, post-traumatic spinal cord injury pain, temporomandibular disorder, myofascial pain, or syringomyelia.

11. A pharmaceutical composition for the treatment or prophylaxis of neuropathic pain comprising one or more carrier and a vinylazacycloalkane compound of Formula I:



Formula I

wherein:

variable geometry (E or Z) exists about the double bond as represented by the wavy line;

X is nitrogen or C-R^2;

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, halogen, -OR^4, -NR^4R^5, or -SR^4 when X is C-R^2, and

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cyclolalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, -OR^4, or -NR^4R^5 when X is nitrogen;

R^2 is hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, -$(CH_2)_qC_{3-8}$ polycycloalkyl, -OR^6, -NR^6R^7, -SR^6, -SOR^6, or -SO_2R^6;

wherein each R^2 can optionally be substituted with one or more substituent selected from halogen, -CN, -NO_2, -NH_2, -OH, -OR^6, -COOH, -C(O)OR^6, -O-C(O)R^6, -NR^6R^7, -NHC(O)R^6, -C(O)NR^6R^7, -SR^6, -S(O)R^6, -SO_2R^6, -$NHSO_2R^6$, -$SO_2NR^6R^6$, -C(S)NR^6R^6, -NHC(S)R^6, -O-SO_2R^6, aryl, heteroaryl, formyl, haloalkyl, haloalkylsulfonyl, haloalkoxy, and C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6} alkyl, -$(CH_2)_q$aryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl;

m is 1, 2, 3, or 4;

n is 1, 2, or 3;

each R^4, R^5, R^6, and R^7 is, independently, hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl, each of which can optionally be substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -CN, -NO_2, -NH_2, -OH, -C(O)OH, -C(O)O-C_{1-6} alkyl, -$CONH_2$, formyl, haloalkyl, and haloalkoxy,

wherein each of the C_{1-6}-alkyl, heterocyclyl, heteroaryl, and aryl groups can be substituted with from 1 to 6 substituents selected from the group consisting of F, Cl, Br, I, R^8, $-NR^8R^9$, haloalkyl, -CN, $-NO_2$, $-C_2R^8$, $-N_3$, $-SO_2CH_3$, $-OR^8$, $-SR^8$, $-C(=O)NR^8R^9$, $-NR^8C(=O)R^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-(CH_2)_qOR^8$, $-OC(=O)R^8$, $-OC(=O)NR^8R^9$, and $-NR^8C(=O)OR^8$,

wherein each R^8 and R^9 are individually hydrogen, C_{1-6} alkyl, an aromatic group-containing species, or a substituted aromatic group-containing species that is substituted with one or more of F, Cl, Br, I, R^{10}, $-NR^{10}R^{11}$, haloalkyl, -CN, $-NO_2$, $-C_2R^{10}$, $-N_3$, $-SO_2CH_3$, $-OR^{10}$, $-SR^{10}$, $-C(=O)NR^{10}R^{11}$, $-NR^{10}C(=O)R^{10}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-(CH_2)_qOR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, or $-NR^{10}C(=O)OR^{10}$; wherein each of R^{10} and R^{11} individually is hydrogen or C_{1-6} alkyl; or

either R^6 and R^7 or R^8 and R^9 can combine together with the atoms to which they are attached to form a C_{1-10} cycloalkyl functionality; and

wherein each q independently is 1 to 6;

or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition of claim 11 wherein:
the geometry at the double bond is E;
R^1 is hydrogen;
X is N or CR^2;
when X is CR^2, then R^2 is $-OR^6$;
R^3 is hydrogen;
n is 1;
m is 2; and
R^6 is alkyl, aryl, or heterocyclyl.

13. The pharmaceutical composition of claim 11 wherein:
the geometry at the double bond is E;
X is N;
R^1 is hydrogen;
R^3 is hydrogen;
n is 1; and
m is 2.

14. The pharmaceutical composition of claim 11 wherein the compound is
(R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine,
(R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine,

5-((E)-2-piperidin-4-ylvinyl)pyrimidine, or
5-((E)-2-azetidin-3-ylvinyl)pyrimidine

15. The pharmaceutical composition of claim 11 wherein the compound is (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine.

16. The pharmaceutical composition of claim 11 wherein the neuropathic pain is associated with injury.

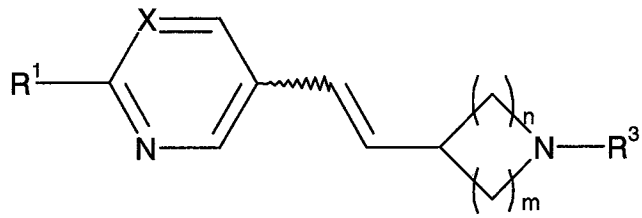
17. The pharmaceutical composition of claim 16 wherein the injury is associated with physical trauma, amputation, disease or condition, one or more toxin, or inflammation.

18. The pharmaceutical composition of claims 16 or 17 wherein the neuropathic pain effects a subject's peripheral nerves, dorsal roots, spinal cord, or regions of the brain.

19. The pharmaceutical composition of claims 16 – 18 wherein the neuropathic pain is neuralgia, neurodynia, spontaneous, lancinating, dysesthesia, paraesthesia, allodynia, hyperalgesia, hypoesthesia, or hypoalgesia.

20. The pharmaceutical composition of claims 16 – 19 wherein the neuropathic pain is associated with diabetic neuropathy, non-specific lower back pain, multiple sclerosis-related pain, fibromyalgia, HIV-related neuropathy including HIV myelopathy, post-herpetic neuralgia, trigeminal neuralgia, neuritis, causalgia, acute or chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, segmental neuropathy, ischemic optic neuropathy, geniculate neuralgia, occipital neuralgia, periodic migrainous neuralgia, chemotherapy-induced polyneuropathy, complex regional pain syndrome, entrapment neuropathies, carpal tunnel syndrome, brachial plexus avulsion, post-surgical neuropathy, post-mastectomy pain or post-thoracotomy pain, idiopathic sensory neuropathy, nerve compression, tumor infiltration, nutrition deficiency-related neuropathy, phantom limb pain, post-radiation plexopathy, radiculopathy, sciatica, toxin exposure-related neuropathy, post-traumatic neuralgia, compressive myelopathy, Parkinson's disease-related neuropathy, post-ischemic myelopathy, post-radiation myelopathy, post-stroke pain, post-traumatic spinal cord injury pain, temporomandibular disorder, myofascial pain, or syringomyelia.

21. A vinylazacycloalkane compound for use in the treatment or prevention of neuropathic pain of Formula I:



Formula I

wherein:

variable geometry (E or Z) exists about the double bond as represented by the wavy line;

X is nitrogen or C-R^2;

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, halogen, -OR^4, -NR^4R^5, or -SR^4 when X is C-R^2, and

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cyclolalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, -OR^4, or -NR^4R^5 when X is nitrogen;

R^2 is hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, -$(CH_2)_qC_{3-8}$ polycycloalkyl, -OR^6, -NR^6R^7, -SR^6, -SOR^6, or -SO_2R^6;

wherein each R^2 can optionally be substituted with one or more substituent selected from halogen, -CN, -NO_2, -NH_2, -OH, -OR^6, -COOH, -C(O)OR^6, -O-C(O)R^6, -NR^6R^7, -NHC(O)R^6, -C(O)NR^6R^7, -SR^6, -S(O)R^6, -SO_2R^6, -NHSO_2R^6, -$SO_2NR^6R^6$, -C(S)NR^6R^6, -NHC(S)R^6, -O-SO_2R^6, aryl, heteroaryl, formyl, haloalkyl, haloalkylsulfonyl, haloalkoxy, and C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6} alkyl, -$(CH_2)_q$aryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl;

m is 1, 2, 3, or 4;

n is 1, 2, or 3;

each R^4, R^5, R^6, and R^7 is, independently, hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl, each of which can optionally be substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -CN, -NO_2, -NH_2, -OH, -C(O)OH, -C(O)O-C_{1-6} alkyl, -$CONH_2$, formyl, haloalkyl, and haloalkoxy,

wherein each of the C_{1-6}-alkyl, heterocyclyl, heteroaryl, and aryl groups can be substituted with from 1 to 6 substituents selected from the group consisting of F, Cl, Br, I, R^8,

$-NR^8R^9$, haloalkyl, -CN, $-NO_2$, $-C_2R^8$, $-N_3$, $-SO_2CH_3$, $-OR^8$, $-SR^8$, $-C(=O)NR^8R^9$, $-NR^8C(=O)R^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-(CH_2)_qOR^8$, $-OC(=O)R^8$, $-OC(=O)NR^8R^9$, and $-NR^8C(=O)OR^8$,

wherein each R^8 and R^9 are individually hydrogen, C_{1-6} alkyl, an aromatic group-containing species, or a substituted aromatic group-containing species that is substituted with one or more of F, Cl, Br, I, R^{10}, $-NR^{10}R^{11}$, haloalkyl, -CN, $-NO_2$, $-C_2R^{10}$, $-N_3$, $-SO_2CH_3$, $-OR^{10}$, $-SR^{10}$, $-C(=O)NR^{10}R^{11}$, $-NR^{10}C(=O)R^{10}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-(CH_2)_qOR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, or $-NR^{10}C(=O)OR^{10}$; wherein each of R^{10} and R^{11} individually is hydrogen or C_{1-6} alkyl; or

either R^6 and R^7 or R^8 and R^9 can combine together with the atoms to which they are attached to form a C_{1-10} cycloalkyl functionality; and

wherein each q independently is 1 to 6;

or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21 wherein:

the geometry at the double bond is E;

R^1 is hydrogen;

X is N or CR^2;

when X is CR^2, then R^2 is $-OR^6$;

R^3 is hydrogen;

n is 1;

m is 2; and

R^6 is alkyl, aryl, or heterocyclyl.

23. The compound of claim 21 wherein:

the geometry at the double bond is E;

X is N;

R^1 is hydrogen;

R^3 is hydrogen;

n is 1; and

m is 2.

24. The compound of claim 21 wherein the compound is

(R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine,

(R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine,

5-((E)-2-piperidin-4-ylvinyl)pyrimidine, or

5-((E)-2-azetidin-3-ylvinyl)pyrimidine

25. The compound of claim 21 wherein the compound is (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine.

26. The compound of claim 21 wherein the neuropathic pain is associated with injury.

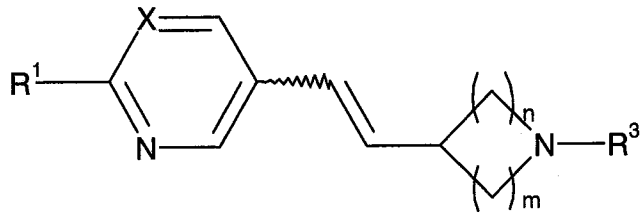
27. The compound of claim 26 wherein the injury is associated with physical trauma, amputation, disease or condition, one or more toxin, or inflammation.

28. The compound of claims 26 or 27 wherein the neuropathic pain effects a subject's peripheral nerves, dorsal roots, spinal cord, or regions of the brain.

29. The compound of claims 26 – 28 wherein the neuropathic pain is neuralgia, neurodynia, spontaneous, lancinating, dysesthesia, paraesthesia, allodynia, hyperalgesia, hypoesthesia, or hypoalgesia.

30. The compound of claims 26 – 29 wherein the neuropathic pain is associated with diabetic neuropathy, non-specific lower back pain, multiple sclerosis-related pain, fibromyalgia, HIV-related neuropathy including HIV myelopathy, post-herpetic neuralgia, trigeminal neuralgia, neuritis, causalgia, acute or chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, segmental neuropathy, ischemic optic neuropathy, geniculate neuralgia, occipital neuralgia, periodic migrainous neuralgia, chemotherapy-induced polyneuropathy, complex regional pain syndrome, entrapment neuropathies, carpal tunnel syndrome, brachial plexus avulsion, post-surgical neuropathy, post-mastectomy pain or post-thoracotomy pain, idiopathic sensory neuropathy, nerve compression, tumor infiltration, nutrition deficiency-related neuropathy, phantom limb pain, post-radiation plexopathy, radiculopathy, sciatica, toxin exposure-related neuropathy, post-traumatic neuralgia, compressive myelopathy, Parkinson's disease-related neuropathy, post-ischemic myelopathy, post-radiation myelopathy, post-stroke pain, post-traumatic spinal cord injury pain, temporomandibular disorder, myofascial pain, or syringomyelia.

31. Use of a vinylazacycloalkane compound of Formula I in the manufacture of a medicament for the treatment or prevention of neuropathic pain



Formula I

wherein:

variable geometry (E or Z) exists about the double bond as represented by the wavy line;

X is nitrogen or C-R^2;

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, halogen, -OR^4, -NR^4R^5, or -SR^4 when X is C-R^2, and

R^1 is hydrogen, C_{1-6} alkyl, C_{3-8} cyclolalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, -OR^4, or -NR^4R^5 when X is nitrogen;

R^2 is hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, C_{3-8} cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, -$(CH_2)_qC_{3-8}$ polycycloalkyl, -OR^6, -NR^6R^7, -SR^6, -SOR^6, or -SO_2R^6;

wherein each R^2 can optionally be substituted with one or more substituent selected from halogen, -CN, -NO_2, -NH_2, -OH, -OR^6, -COOH, -C(O)OR^6, -O-C(O)R^6, -NR^6R^7, -NHC(O)R^6, -C(O)NR^6R^7, -SR^6, -S(O)R^6, -SO_2R^6, -$NHSO_2R^6$, -$SO_2NR^6R^6$, -C(S)NR^6R^6, -NHC(S)R^6, -O-SO_2R^6, aryl, heteroaryl, formyl, haloalkyl, haloalkylsulfonyl, haloalkoxy, and C_{1-6} alkyl;

R^3 is hydrogen, C_{1-6} alkyl, -$(CH_2)_q$aryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl;

m is 1, 2, 3, or 4;

n is 1, 2, or 3;

each R^4, R^5, R^6, and R^7 is, independently, hydrogen, C_{1-6} alkyl, aryl, -$(CH_2)_q$aryl, heteroaryl, -$(CH_2)_q$heteroaryl, heterocyclyl, -$(CH_2)_q$heterocyclyl, cycloalkyl, -$(CH_2)_qC_{3-8}$ cycloalkyl, polycycloalkyl, or -$(CH_2)_qC_{3-8}$ polycycloalkyl, each of which can optionally be substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, -CN, -NO_2, -NH_2, -OH, -C(O)OH, -C(O)O-C_{1-6} alkyl, -$CONH_2$, formyl, haloalkyl, and haloalkoxy,

wherein each of the C_{1-6}-alkyl, heterocyclyl, heteroaryl, and aryl groups can be substituted with from 1 to 6 substituents selected from the group consisting of F, Cl, Br, I, R^8,

$-NR^8R^9$, haloalkyl, -CN, $-NO_2$, $-C_2R^8$, $-N_3$, $-SO_2CH_3$, $-OR^8$, $-SR^8$, $-C(=O)NR^8R^9$, $-NR^8C(=O)R^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-(CH_2)_qOR^8$, $-OC(=O)R^8$, $-OC(=O)NR^8R^9$, and $-NR^8C(=O)OR^8$,

wherein each R^8 and R^9 are individually hydrogen, C_{1-6} alkyl, an aromatic group-containing species, or a substituted aromatic group-containing species that is substituted with one or more of F, Cl, Br, I, R^{10}, $-NR^{10}R^{11}$, haloalkyl, -CN, $-NO_2$, $-C_2R^{10}$, $-N_3$, $-SO_2CH_3$, $-OR^{10}$, $-SR^{10}$, $-C(=O)NR^{10}R^{11}$, $-NR^{10}C(=O)R^{10}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-(CH_2)_qOR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)NR^{10}R^{11}$, or $-NR^{10}C(=O)OR^{10}$; wherein each of R^{10} and R^{11} individually is hydrogen or C_{1-6} alkyl; or

either R^6 and R^7 or R^8 and R^9 can combine together with the atoms to which they are attached to form a C_{1-10} cycloalkyl functionality; and

wherein each q independently is 1 to 6;

or a pharmaceutically acceptable salt thereof.

32. The use of claim 31 wherein:

the geometry at the double bond is E;

R^1 is hydrogen;

X is N or CR^2;

when X is CR^2, then R^2 is $-OR^6$;

R^3 is hydrogen;

n is 1;

m is 2; and

R^6 is alkyl, aryl, or heterocyclyl.

33. The use of claim 31 wherein:

the geometry at the double bond is E;

X is N;

R^1 is hydrogen;

R^3 is hydrogen;

n is 1; and

m is 2.

34. The use of claim 31 wherein the compound is

(R)- and (S)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine,

(R)- and (S)-5-((E)-2-piperidin-3-ylvinyl)pyrimidine,

5-((E)-2-piperidin-4-ylvinyl)pyrimidine, or

5-((E)-2-azetidin-3-ylvinyl)pyrimidine

35. The use of claim 31 wherein the compound is (R)-5-((E)-2-pyrrolidin-3-ylvinyl)pyrimidine.

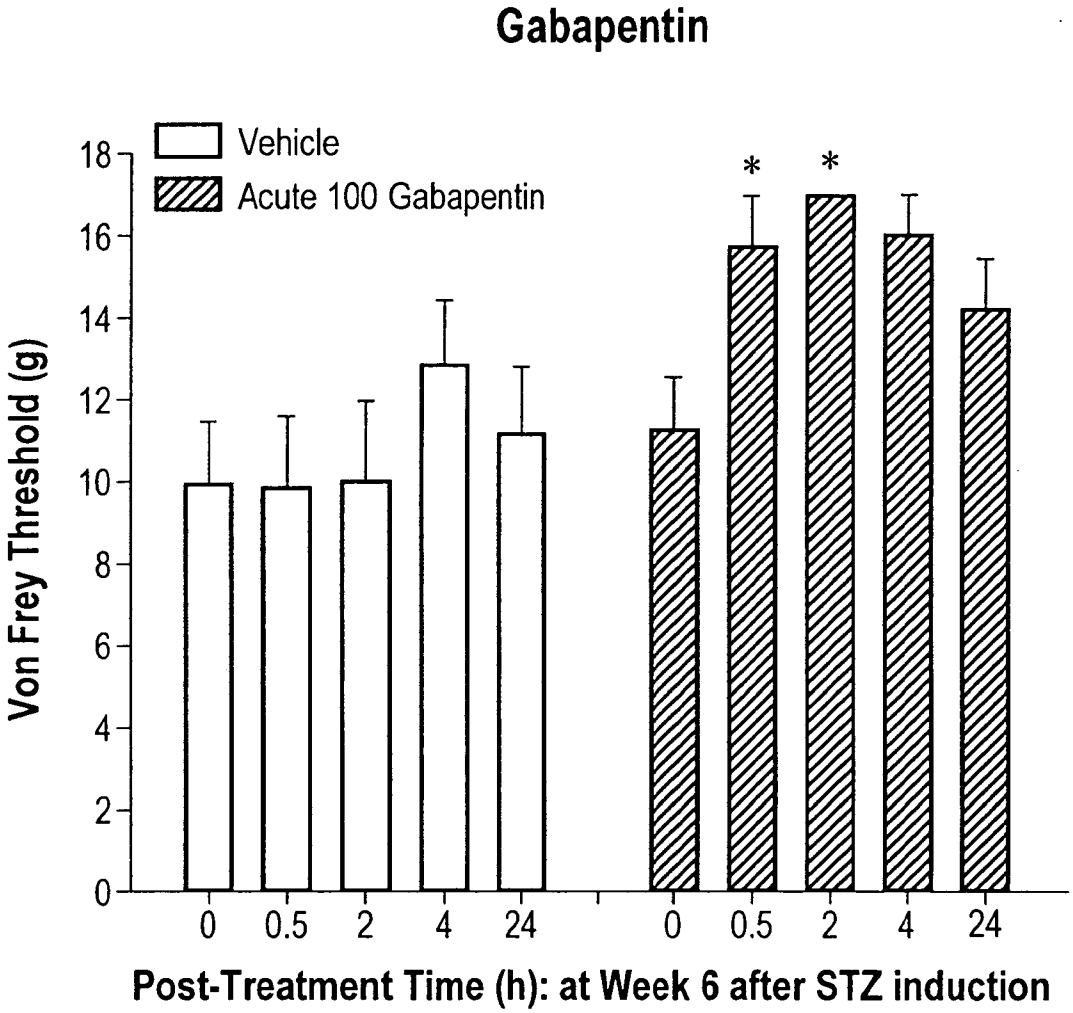
36. The use of claim 31 wherein the neuropathic pain is associated with injury.

37. The use of claim 36 wherein the injury is associated with physical trauma, amputation, disease or condition, one or more toxin, or inflammation.

38. The use of claims 36 or 37 wherein the neuropathic pain effects a subject's peripheral nerves, dorsal roots, spinal cord, or regions of the brain.

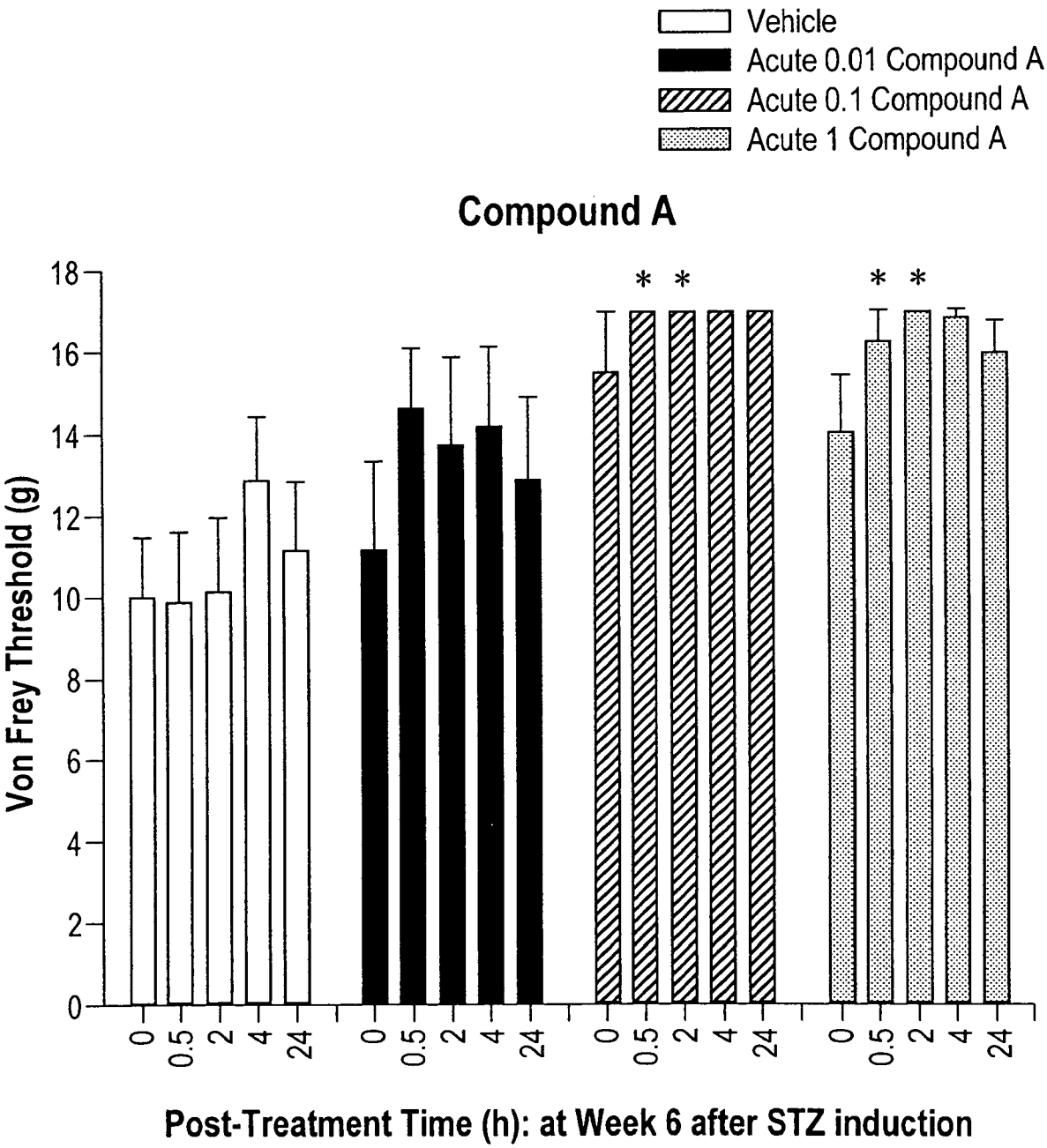
39. The use of claims 36 – 38 wherein the neuropathic pain is neuralgia, neurodynia, spontaneous, lancinating, dysesthesia, paraesthesia, allodynia, hyperalgesia, hypoesthesia, or hypoalgesia.

40. The use of claims 36 – 39 wherein the neuropathic pain is associated with diabetic neuropathy, non-specific lower back pain, multiple sclerosis-related pain, fibromyalgia, HIV-related neuropathy including HIV myelopathy, post-herpetic neuralgia, trigeminal neuralgia, neuritis, causalgia, acute or chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, segmental neuropathy, ischemic optic neuropathy, geniculate neuralgia, occipital neuralgia, periodic migrainous neuralgia, chemotherapy-induced polyneuropathy, complex regional pain syndrome, entrapment neuropathies, carpal tunnel syndrome, brachial plexus avulsion, post-surgical neuropathy, post-mastectomy pain or post-thoracotomy pain, idiopathic sensory neuropathy, nerve compression, tumor infiltration, nutrition deficiency-related neuropathy, phantom limb pain, post-radiation plexopathy, radiculopathy, sciatica, toxin exposure-related neuropathy, post-traumatic neuralgia, compressive myelopathy, Parkinson's disease-related neuropathy, post-ischemic myelopathy, post-radiation myelopathy, post-stroke pain, post-traumatic spinal cord injury pain, temporomandibular disorder, myofascial pain, or syringomyelia.



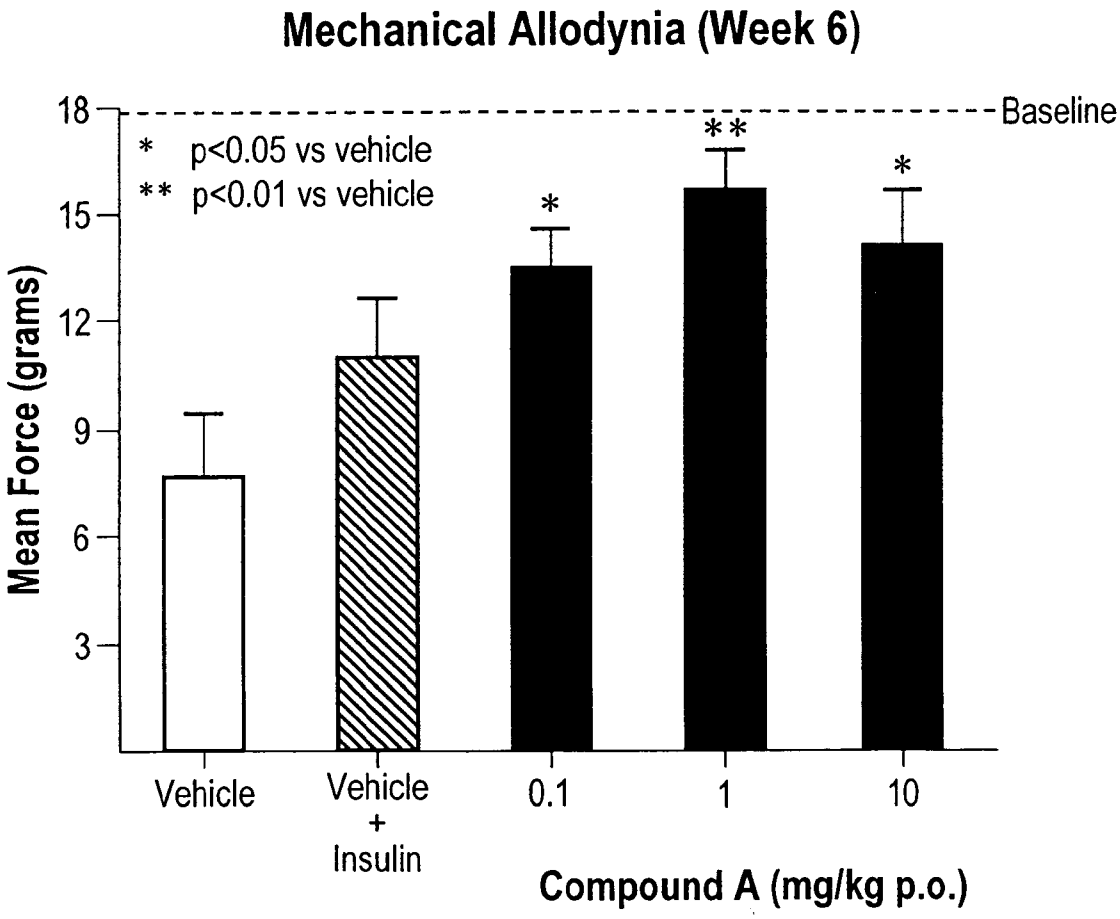
* P<0.05 compared to time-matched vehicle group

Fig. 1



* P<0.05 compared to time-matched vehicle group

Fig. 2



Note: Gabapentin was tested in a separate study @ 100 mg/kg - Mean Force = 17.5

Fig. 3

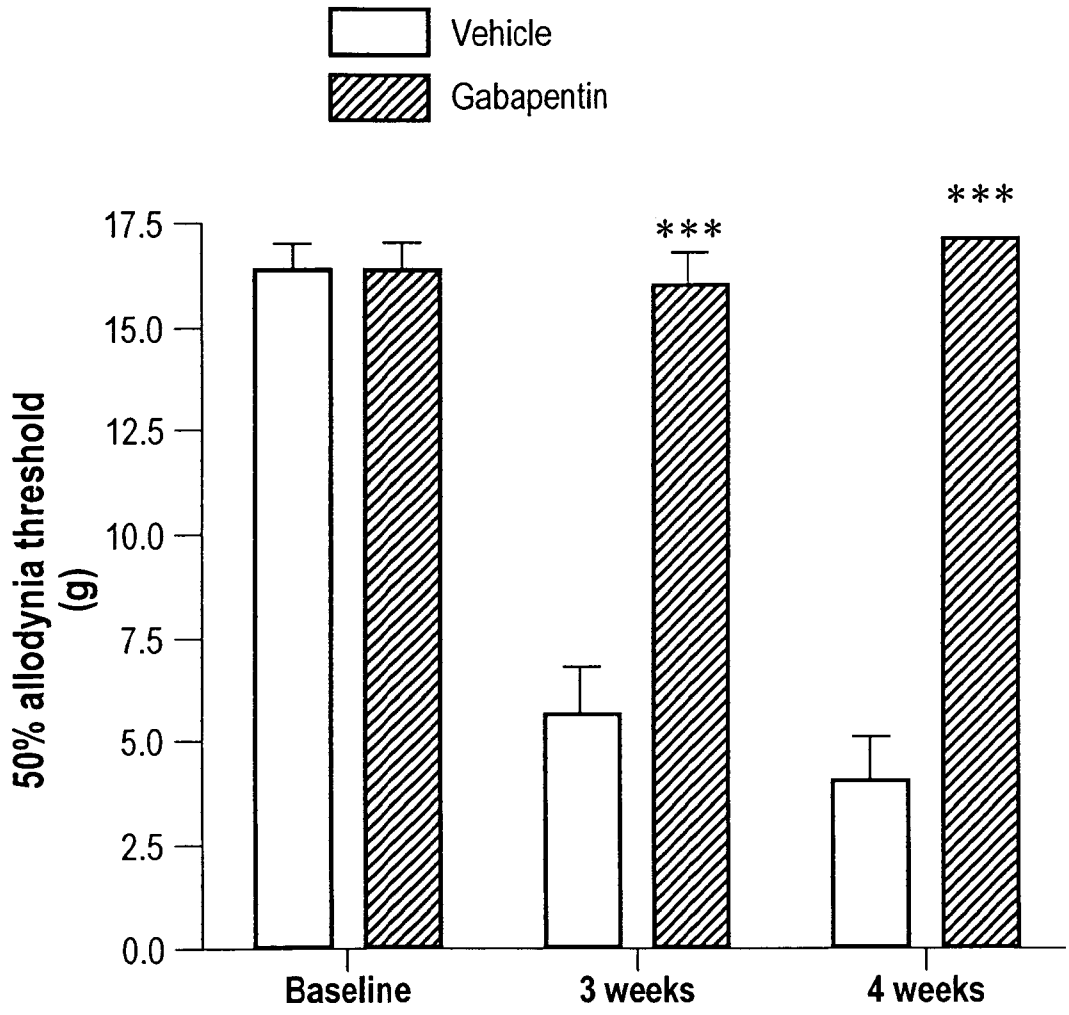

Vehicle
Gabapentin
50% allodynia threshold (g)
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
***
***
Baseline
3 weeks
4 weeks

Fig. 4

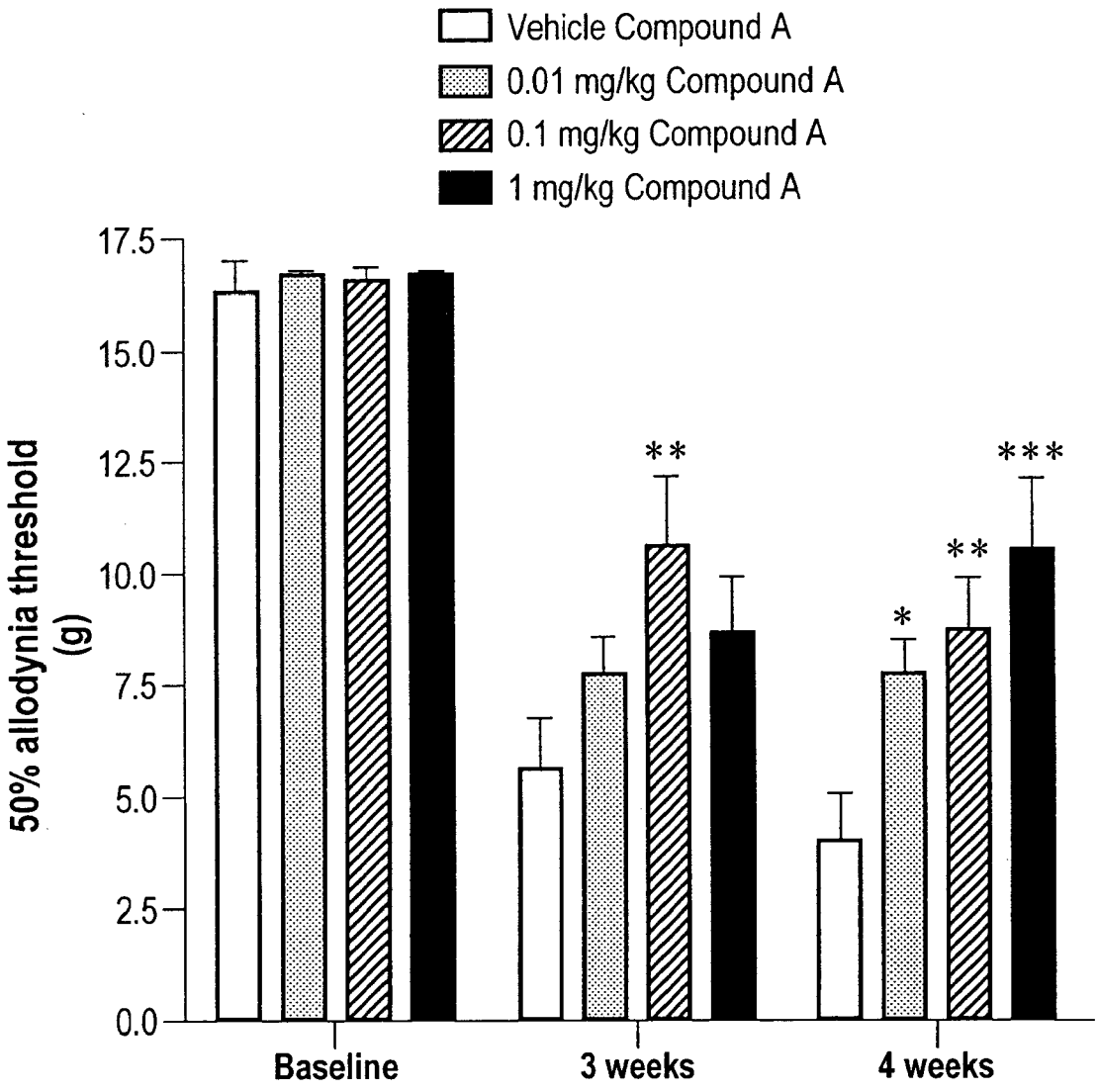

Vehicle Compound A
0.01 mg/kg Compound A
0.1 mg/kg Compound A
1 mg/kg Compound A
50% allodynia threshold (g)
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
**
*
**
***
Baseline
3 weeks
4 weeks

Fig. 5