PHARMACEUTICAL COMPOSITIONS OF SPIRO-OXINDOLE COMPOUND FOR TOPICAL ADMINISTRATION AND THEIR USE AS THERAPEUTIC AGENTS

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition for topical administration to a mammal, preferably a human, comprising one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a spiro-oxindole compound that is a sodium channel blocker, preferably a neuronal voltage-gated sodium channel antagonist. In particular, the present invention relates to pharmaceutical compositions for treating diseases or conditions, such as pain, preferably post-herpetic neuralgia (PHN), osteoarthritis, and persistent post-operative pain, which is alleviated by the inhibition of a sodium channel, preferably a neuronal voltage-gated sodium channel. However, other neurological disorders unrelated to pain could similarly be treated as part of this invention, for example, alleviation of symptoms of myotonia and multiple sclerosis.

BACKGROUND OF THE INVENTION

Diseases and conditions which are alleviated by the inhibition (or "blocking") of sodium channels, particularly neuronal voltage-gated sodium channels, include acute and chronic pain, particularly neuropathic and inflammatory pain. Persistent (chronic) neuropathic pain occurs in a wide range of clinical conditions, including post-herpetic neuralgia (PHN), trigeminal neuralgia, painful diabetic neuropathy (PDN), lower back pain, post-operative pain, chemotherapy-related and HIV infection. Estimates of the prevalence of chronic neuropathic pain vary greatly by geographical region, ranging from approximately 11% of the population of the U.S. to estimates that 20% of all European adults suffer with moderate to severe chronic pain (see, for example, Hall, G.C. *et al.*, "Primary Care Incidence and Treatment of Four Neuropathic Pain Conditions: A Descriptive Study, 2002-2005," *BMC Fam. Pract.* (2008); Vol. 9, No. 26; and Hardt, J. *et al.*, "Prevalence of Chronic Pain in a Representative Sample in the United States," *Pain Medicine* (2008), Vol. 9, No. 7, pp. 803-812). In the U.S., the most common chronic neuropathic pain conditions, PHN and PDN, are thought to affect 1 million and 3 million people, respectively (see, for example, Dworkin, R.H. *et al.*, "Advances in Neuropathic Pain Diagnosis, Mechanism, and Treatment Recommendations," *Arch. Neurol.* (2003), Vol. 60, pp. 1524-1534).

Numerous pharmacological agents are available for the treatment of

neuropathic pain, including tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, anticonvulsants (*e.g.*, gabapentin and pregabalin), local anaesthetics and opioids (*e.g.*, morphine). However, these treatments offer sub-optimal efficacy and/or have unacceptable side effects in a chronic setting, with adequate relief of neuropathic pain reported in only approximately 50% of patients (see, for example, Moulin, D.E., "The Clinical Management of Neuropathic Pain," *Pain Res. Manag.* (2006), Vol. 11 (Supplement A), pp. 30A-36A). Frequently, multiple drug therapy with tricyclic antidepressants, anticonvulsants and local anaesthetics is necessary for relief of neuropathic pain.

The Lidoderm® patch (5% lidocaine) belongs to a class of local and topical anaesthetic medications and is approved for the treatment of PHN. However, while lidocaine may have local effects, it is systemically absorbed and must be used with extreme caution when administered topically, as applying to too large a surface area can result in severe systemic toxicity and death.

Voltaren® (diclofenac sodium gel) is a non-steroidal anti-inflammatory agent (NSAID) in a topical formulation. It is a marketed treatment option for osteoarthritis patients. While the risk of gastrointestinal side effects for NSAID topical use is lower than it is for NSAID oral use, these serious side effects remain a concern for topical diclofenac. Furthermore, meaningful elevation of hepatic enzymes has recently been reported in some patients on long-term topical diclofenac, necessitating regular monitoring for hepatotoxicity in this patient population (see, FDA website, MedWatch, 2009; Volteren Gel (diclofenac sodium) 1% topical gel; Safety Labeling Changes Approved by FDA Center for Drug Evaluation and Research -- September 2009).

Neuronal voltage-gated sodium channels (Na_v's) are well-known to modulate the transmission of pain signals. For example, loss-of-function mutations of $Na_v1.7$, which is expressed primarily in sensory neurons of the peripheral nervous system and is upregulated by both nerve injury and inflammation, cause a human condition known as congenital indifference to pain, which is characterized by an inability to sense pain (see, for example, Goldberg, Y.P. *et al.*, *Clin. Genet.* (2007), Vol. 71, No. 4, pp. 311-119). Lidocaine and other local anaesthetics act mainly by inhibiting Na_v's.

PCT Published Patent Application No. WO 06/110917 is directed to spiro-oxindole compounds which are disclosed as being useful as sodium channel blockers. These compounds, *inter alia*, inhibit sodium ion flux through sodium channels. As such, the compounds are considered to be sodium channel blockers and are therefore useful for treating diseases and conditions in mammals, preferably humans, which are

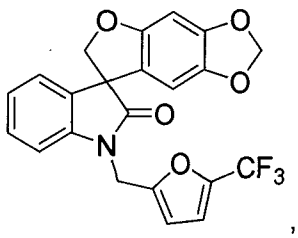
the result of aberrant voltage-dependent sodium channel biological activity or which may be ameliorated by modulation of the biological activity of sodium channels.

There exists, therefore, a need for a topical pharmaceutical composition comprising a compound that is a sodium channel blocker, preferably a neuronal voltage-gated sodium channel antagonist, for the treatment of pain having minimal systemic exposure of the compound and that is cosmetically and pharmaceutically acceptable for chronic application of the compound to the skin (*i.e.*, non-irritating, non-stinging and non-sensitizing).

SUMMARY OF THE INVENTION

The present invention is directed to pharmaceutical compositions comprising one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a spiro-oxindole compound, or a pharmaceutically acceptable salt thereof. In particular, the present invention is directed to pharmaceutical compositions comprising one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a spiro-oxindole compound that is a sodium channel blocker. Such pharmaceutical compositions are useful in the treatment and/or prevention of diseases or conditions mediated by sodium channels and are topically administered to a mammal, preferably a human, in need thereof, with minimal systemic exposure of the spiro-oxindole compound.

Accordingly, in one aspect, the invention is directed to a pharmaceutical composition for topical administration to a mammal, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a spiro-oxindole compound having the following formula:



as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides a method for the treatment of pain in a mammal, preferably a human, wherein the method comprises administering to the

mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

In another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of neuronal voltage-gated sodium channels selected from $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.5$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, or $Na_V1.9$ is implicated in the disease, condition or disorder, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

In another aspect, the invention provides a method of treating a range of sodium channel-mediated diseases or conditions, preferably neuronal voltage-gated sodium channel-mediated diseases or conditions, wherein the diseases or conditions are selected from, but are not limited to, pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia (PHN), familial erythromelalgia, primary erythromelalgia, familial rectal pain, eudynia, heat sensitivity, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), painful diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, tendonitis, bursitis, musculoskeletal sprains, tenosinovitis, chondromalacia patellae, myositis, myotonia (including but not limited to SCN4A-related myotonia), paramyotonia, rhabdomyolysis, paroxysmal dystonia, myasthenia syndromes, malignant hyperthermia, sodium channel toxin related illnesses, cancer pain, restless leg syndrome, fibromyalgia, and neurodegenerative disease, as well as other neurological disorders including multiple sclerosis, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

In another aspect, the invention provides a method of treating a range of sodium channel-mediated diseases or condition, preferably neuronal voltage-gated sodium channel-mediated diseases or condition, in a mammal, preferably a human, wherein the diseases or conditions are selected from, but are not limited to, neuroprotection under ischaemic conditions caused by stroke or neural trauma, neurodegenerative disease, as well as other neurological disorders including multiple sclerosis, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

In another aspect, the invention provides a method of treating a range of

sodium channel-mediated diseases or conditions, preferably neuronal voltage-gated sodium channel-mediated diseases or conditions, in a mammal, preferably a human, wherein the diseases or conditions are selected from, but are not limited to, pruritis (itch), dermatitis, contact dermatitis, allergic dermatitis, eczema, acne, and inflammatory skin disorders, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

In another aspect, the invention provides a method of treating a range of sodium channel-mediated diseases or condition, preferably neuronal voltage-gated sodium channel-mediate diseases or condition, in a mammal, preferably a human, through inhibition of ion flux through a voltage-dependent sodium channel in the mammal, preferably a neuronal voltage-gated sodium channel, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

A further aspect of this invention is a process for the preparation of the pharmaceutical composition of this invention.

Specific embodiments of these aspects of the invention are described in more detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

Figure 1 is a graph showing the mean percent change from baseline (CFB) for each dosage group described in the CFA-induced chronic inflammatory pain study in Example 1. Data are expressed as Mean ± SD change from baseline values.

Figure 2 is a graph showing the mean paw withdrawal threshold expressed as percent change from baseline (CFB) for each treatment group described in the neuropathic pain model study in Example 2. Data are plotted as Mean ± SEM.

Figure 3 is a graph showing 30-minute post-dosing von Frey Change from Baseline (CFB) for treated paw from the diabetic neuropathy study in Example 4.

Figure 4 is a graph showing the mean percent change from baseline (CFB) for each dosage group described in the CCI model for neuropathic pain study in Example 5. Data are expressed as Mean ± SD change from baseline values.

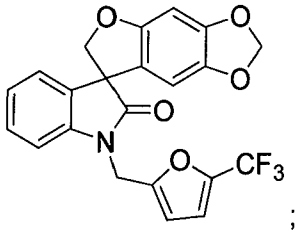
Figure 5 is a graph showing the mean plasma concentration of COMPOUND A for each treatment group described in the CCI model study in Example 5.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

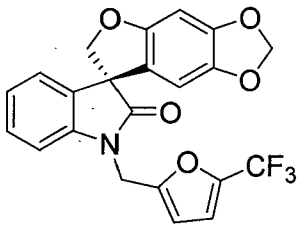
Unless defined otherwise in the specification, the following terms and phrases shall have the following meaning:

"Spiro-oxindole compound" refers to a compound having the following formula:



;

or a pharmaceutically acceptable salt thereof. This compound is disclosed in PCT Published Patent Application No. WO 06/110917, which is incorporated in full by reference herein. The spiro-oxindole compound may exist as a single enantiomer, a racemate or as a non-racemic mixture of enantiomers. One of the enantiomers of the spiro-oxindole compound has the following formula:



and is named herein as (*S*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one. This enantiomer is also identified herein as "COMPOUND A". The use of the "COMPOUND A" identifier herein is intended to include the enantiomer as a free base or as a pharmaceutically acceptable salt.

The term "about" when placed before a numerical value "X" herein refers to an interval extending from X minus 10% of X to X plus 10% of X and preferably to an interval extending from X minus 5% of X to X plus 5% of X.

The expression "% w/w" refers to a percentage by weight compared to the total weight of the composition being considered.

The expression "% w/v" refers to a weight of a solute in a given volume of

solvent. For example, 50% w/v of PEG is 50 grams of PEG in 100 mL solvent

"Clathrates" refers to substances which fix gases, liquids or compounds as inclusion complexes so that the complex may be handled in solid form and the included constituent (or "guest" molecule) subsequently releases by the action of a solvent or by melting. The term "clathrate" can be used interchangeably with the phrase "inclusion molecule" or with the phrase "inclusion complex". Clathrates contemplated for use in the instant invention are prepared from cyclodextrins. Cyclodextrins are widely known as having the ability to form clathrates (*i.e.*, inclusion compounds) with a variety of molecules. See, for example, *Inclusion Compounds*, edited by J.L. Atwood, J.E.D. Davies, and D.D. MacNicol, London, Orlando, Academic Press, 1984; Goldberg, I., "The Significance of Molecular Type, Shape and Complementarity in Clathrate Inclusion", *Topics in Current Chemistry* (1988), Vol. 149, pp. 2-44; Weber, E. *et al.*, "Functional Group Assisted Clathrate Formation - Scissor-Like and Roof-Shaped Host Molecules", *Topics in Current Chemistry* (1988), Vol. 149, pp. 45-135; and MacNicol, D.D. *et al.*, "Clathrates and Molecular Inclusion Phenomena", *Chemical Society Reviews* (1978), Vol. 7, No. 1, pp. 65-87. Conversion into cyclodextrin clathrates is known to increase the stability and solubility of certain compounds, thereby facilitating their use as pharmaceutical agents. See, for example, Saenger, W., "Cyclodextrin Inclusion Compounds in Research and Industry", *Angew. Chem. Int. Ed. Engl.* (1980), Vol. 19, pp. 344-362; U.S. Patent No. 4,886,788 (Schering AG); U.S. Patent No. 6,355,627 (Takasago); U.S. Patent No. 6,288,119 (Ono Pharmaceuticals); U.S. Patent No. 6,14,969 (Ono Pharmaceuticals); U.S. Patent No. 6,235,780 (Ono Pharmaceuticals); U.S. Patent No. 6,262,293 (Ono Pharmaceuticals); U.S. Patent No. 6,225,347 (Ono Pharmaceuticals); and U.S. Patent No. 4,935,446 (Ono Pharmaceuticals).

"Mammal" includes humans and both domestic animals such as laboratory animals and household pets, (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, and rabbits), and non-domestic animals such as wildlife and the like.

"Pharmaceutically acceptable excipient" or "excipient" includes without limitation any inactive material that is combined with a spiro-oxindole compound of the invention in order to produce a drug dosage form for topical administration. The term "pharmaceutically acceptable excipient" is intended to include, but is not limited to, any solvents, penetration enhancing agents, antioxidants, stiffening agents (*i.e.*, thickeners), ointment bases, protectives, adsorbents, demulcents, emollients, preservatives, moisturizers, buffers, adjuvants, bioavailability enhancers, carriers,

glidants, sweetening agents, diluents, dye/colorants, flavor enhancers, solubilizers (including surfactants), wetting agents, dispersing agents, suspending agents, stabilizers and isotonic agents, which have been approved by a regulatory agency, such as for example, but is not limited to, the United States Food and Drug Administration, the European Medicines Agency or Health Canada, as being acceptable for use in a formulation for the topical administration of a pharmacologically active ingredient, and/or are considered as Generally Recognized As Safe materials (GRAS materials), and/or are listed in the Inactive Ingredients Guide published by the United States Food and Drug Administration. "Pharmaceutically acceptable excipient" can also comprise the acceptable excipients listed in *Remington: The Science and Practice of Pharmacy*, Fox, 21st ed. 2005. Exemplary pharmaceutically acceptable excipients include, but are not limited to, the following:

ascorbic acid and esters;
benzyl alcohol;
benzyl benzoate;
butylated hydroxytoluene ("BHT");
butylated hydroxyanisole ("BHA");
caprylic/capric triglyceride;
cetyl alcohol;
chelating agents (*e.g.*, EDTA and citric acid);
cholesterol;
cross-linked acrylic acid based polymers (*e.g.*, Carbopol®);
decyl methyl sulfoxide;
diethyl sebacate;
dimethylamine ("DMA");
dimethicone;
dimethyl sulfoxide;
diethylene glycol mono ether (*e.g.*, Transcutol® P);
diisopropyl adipate (*e.g.*, Ceraphyl® 230);
ethanol;
flavinoid;
glutathione;
glycerine;
glycerol oleate/propylene glycol (*e.g.*, Arlacel 186);
glycerol monooleate;

glyceryl caprylate/caprate and PEG-8 (polyethylene glycol) caprylate/caprate complex; carpylocaproyl macrogolglycerides (*e.g.*, Labrasol®);
glyceryl monocaprylate (*e.g.*, Capmul® MCM C8);
glyceryl monolinoleate (*e.g.*, Maisine™ 35-1);
glyceryl monooleate (*e.g.*, Peceol™);
glyceryl monostearate;
hexylene glycol;
hydroxypropyl-β-cyclodextrin (HP-β-CD);
isopropyl alcohol;
isopropyl myristate;
laurocapram; (*e.g.*, Azone®);
lauroyl macrogol-32 glycerides (e.g. Gelucire® 44/14);
macrogol-15 hydroxystearate (*e.g.*, Solutol® HS15);
medium chain triglycerides (*e.g.*, Miglyol® 810, Miglyol® 840 or Miglyol® 812);
methyl laurate;
N-methyl-2-pyrrolidine (*e.g.*, Pharmasolve®);
mineral oil;
mono diglycerides (*e.g.*, Capmul® MCM);
octyldodecanol;
oleic acid;
oleyl alcohol;
peanut oil;
1,2-pentanediol;
polysorbates (*e.g.*, Tween® 80);
polyethylene glycol (*e.g.*, PEG-8, PEG 400, PEG1000, PEG 3350, PEG 6000, or Lutrol® E 400);
polyoxyl 35 castor oil (*e.g.*, Cremophor® EL);
polyoxyl 40 hydrogenated castor oil (*e.g.*, Cremophor® RH 40);
propylene glycol;
propylene glycol diacetate;
propylene glycol monocaprylate (*e.g.*, Capmul PG-8, Capryol 90);
propylene glycol monolaurate (*e.g.*, Capmul PG-12);
propylene glycol monooleate;
2-pyrrolidone;
soybean oil;

stearyl alcohol;

sulfobutylether-β-cyclodextrin (*e.g.,* Capitsol®);

tocopherols (*e.g.*, Vitamin E acetate);

α-tocopherol polyethylene glycol succinate (TPGS);

water; and

white petrolatum.

Additional pharmaceutically acceptable excipients are disclosed herein.

"Solvents" refer to substances that readily dissolve other substances, such as a spiro-oxindole compound of the invention, in order to form a solution. Suitable solvents for the purposes of this invention include polyethylene glycol (*e.g.,* PEG 400, PEG 100, and PEG 3350), diethylene glycol monoethyl ether (*e.g.,* Transcutol®), Tween 80, alcohols (*e.g.,* oleyl alcohol, and stearyl alcohol), Labrasol®, caprylic/capric triglyceride, fatty acid esters (*e.g.*, isopropyl myristate, and diisopropyl adipate (*e.g.,* Ceraphyl® 230)), diethyl sebacate, propylene glycol monocaprylate (*e.g.*, Capmul® PG-8), propylene glycol laurate (*e.g.,* Capmul® PG-12), mono diglycerides (*e.g.,* Capmul® MCM), glyceryl monocaprylate (*e.g.,* Capmul® MCM C8), medium chain triglycerides, hexylene glycol, glyceryl mono-oleate (*e.g.,* Peceol™), 1,2-pentanediol, octyldodecanol, glyceryl mono-linoleate (*e.g.,* Maisine™ 35-1), isopropyl alcohol, glycerol oleate/propylene glycol (*e.g.,* Arlacel® 186), mineral oil, water, and glycerine.

"Penetration enhancing agents" refer to substances that increase the permeability of the skin or mucosa to a pharmacologically active ingredient, preferably a spiro-oxindole compound of the invention, so as to increase the rate at which the active ingredient permeates through the skin or mucosa of a mammal, preferably a human. Suitable penetration enhancing agents for the purposes of this invention include, but are not limited to, dimethyl sulfoxide (DMSO), decylmethylsulfoxide, laurocapram (*e.g.*, Azone®), pyrrolidones (*e.g.*, 2-pyrrolidone, and *N*-methyl-2-pyrrolidine (Pharmasolve®)), surfactants, alcohols (*e.g.*, oleyl alcohol), oleic acid, polyethylene glycol (*e.g.*, PEG 400), diethylene glycol monoethyl ether (*e.g.,* Transcutol®), and fatty acid esters (*e.g.*, isopropyl myristate, methyl laurate, glycerol monooleate, and propylene glycol monooleate). A penetration enhancing agent may be used independently or more than one may be used in a pharmaceutical composition of the invention.

"Ointment bases" refers to substances that function as a carrier and enhance penetration into the skin in order to deliver a pharmacologically active ingredient, preferably a spiro-oxindole compound of the invention, to the area to be treated in the

mammal, preferably a human. Suitable "ointment bases" for the purposes of this invention include, but are not limited to, polyethylene glycols (*e.g.*, PEG 400 and PEG 3350). An ointment base may be used independently or more than one may be used in a pharmaceutical composition of the invention.

"Stiffening agents" refers to substances which increase the viscosity and/or physical stability of a pharmaceutical composition of the invention. Suitable "stiffening agents" for the purposes of this invention include, but are not limited to, stearyl alcohol, carbopols, dimethicone and polymers. A stiffening agent may be used independently or more than one may be used in a pharmaceutical composition of the invention.

"Antioxidants" refers to substances which are capable of preventing the oxidation of another molecule. Suitable "antioxidants" for the purposes of this invention include, but are not limited to, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherols (*e.g.*, Vitamin E acetate), flavinoid, glutathione, ascorbic acid and its esters, DMSO, and chelating agents (*e.g.*, EDTA and citric acid).

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which

retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

A "pharmaceutical composition" refers to a formulation of a spiro-oxindole compound of the invention and a medium generally accepted in the art for the topical administration of the spiro-oxindole compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable excipients. For purposes of this disclosure, the phrase "pharmaceutical composition" is interchangeable with the phrase "pharmaceutical formulation".

"Sodium channel-mediated disease or condition" refers to a disease or condition which is ameliorated or alleviated upon modulation of the sodium channel and includes, but is not limited to, pain, or post-herpetic neuralgia. Further examples of sodium channel-mediated diseases or conditions are disclosed below.

"Therapeutically effective amount" refers to that amount of a spiro-oxindole compound of the invention or a pharmaceutical composition of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, of the indicated disease or condition in the mammal, preferably a human. The amount of the spiro-oxindole compound or the pharmaceutical composition which constitutes a "therapeutically effective amount" will vary depending on the spiro-oxindole compound, the pharmaceutical composition, the nature of the disease or condition and its severity, other conditions (*e.g.*, age, weight, general

health) affecting the health of the mammal to be treated, and the manner of administration, as well as upon the potency, bioavailability and *in vivo* half-life of the components of the pharmaceutical composition used, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.*, arresting its development;

(iii) relieving the disease or condition, *i.e.*, causing regression of the disease or condition; or

(iv) relieving the symptoms resulting from the disease or condition.

As used herein, the terms "disease" and "condition" may be used interchangeably or may be different in that the particular malady or condition may not have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

"Analgesia" refers to an absence of pain in response to a stimulus that would normally be painful.

"Allodynia" refers to a condition in which a normally innocuous sensation, such as pressure or light touch, is perceived as being extremely painful.

EMBODIMENTS OF THE INVENTION

Of the various aspects of the invention set forth above in the Summary of the Invention, certain embodiments are preferred.

Of the pharmaceutical compositions of the invention, as set forth above in the Summary of the Invention, one embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients selected from the exemplary list of pharmaceutically acceptable

excipients as set forth above in the Definitions.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipients are selected from one or more solvents, optionally from one or more penetration enhancing agents, optionally from one or more stiffening agents, optionally from one or more ointment bases, and optionally from one or more antioxidants.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and two or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipients are selected from one or more solvents, optionally from one or more penetration enhancing agents, optionally from one or more stiffening agents, optionally from one or more ointment bases, and optionally from one or more antioxidants.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and two or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipients are selected from one or more solvents, from one or more penetration enhancing agents, from one or more stiffening agents, from one or more ointment bases, and optionally from one or more antioxidants.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein one of the pharmaceutically acceptable excipients is a solvent selected from polyethylene glycol, diethylene glycol monoethyl ether, polysorbates, alcohols, carpylocaproyl macrogolglycerides, caprylic/capric triglyceride, fatty acid esters, diethyl sebacate, propylene glycol monocaprylate, propylene glycol laurate, mono diglycerides, glyceryl monocaprylate, medium chain triglycerides, hexylene glycol, glyceryl monooleate, 1,2-pentanediol, octyldodecanol, glyceryl mono-linoleate, glycerol oleate/propylene glycol, mineral oil, water, or glycerine.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein one of the pharmaceutically acceptable excipients is a penetration enhancing agent selected from dimethyl sulfoxide, decylmethylsulfoxide, laurocapram, pyrrolidones, surfactants, alcohols, oleic acid, polyethylene glycol, diethylene glycol monoethyl ether, or fatty acid esters.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein one of the pharmaceutically acceptable excipients is a stiffening agent selected from stearyl alcohol, carbopols, dimethicone or polymers.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein one of the pharmaceutically acceptable excipients is an ointment base selected from polyethylene glycols.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein one of the pharmaceutically acceptable excipients is an antioxidant selected from butylated hydroxytoluene, butylated hydroxyanisole, tocopherols, flavinoid, glutathione, ascorbic acid and esters, dimethyl sulfoxide, or chelating agents.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein each pharmaceutically acceptable excipient is present in a concentration of from about 0.01% w/w to about 99% w/w.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a

racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein a first pharmaceutically acceptable excipient is a solvent present at a concentration of from about 30% w/w to about 70% w/w, a second pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 2% w/w to about 25% w/w, a third pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 1% w/w to about 10% w/w, a fourth pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 1% w/w to about 25% w/w, a fifth pharmaceutically acceptable excipient is a stiffening agent present in a concentration of from about 0.1% w/w to about 10% w/w, a sixth pharmaceutically acceptable exicipient is an antioxidant present in a concentration of from about 0.01% w/w to about 2% w/w, and a seventh pharmaceutically acceptable excipient is an ointment base present in a concentration of from about 10% w/w to about 50% w/w.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein a first pharmaceutically acceptable excipient is a solvent present at a concentration of from about 45% w/w to about 55% w/w, a second pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 5% w/w to about 15% w/w, a third pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 2.5% w/w to about 7.5% w/w, a fourth pharmaceutically acceptable excipient is a penetration enhancing agent present in a concentration of from about 2.5% w/w to about 7.5% w/w, a fifth pharmaceutically acceptable excipient is a stiffening agent present in a concentration of from about 0.1% w/w to about 7.5% w/w, a sixth pharmaceutically acceptable exicipient is an antioxidant present in a concentration of from about 0.05% w/w/ to about 1% w/w, and a seventh pharmaceutically acceptable excipient is an ointment base present in a concentration of from about 15% w/w to about 30% w/w.

Another embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients selected from a solvent selected from PEG 400 or PEG 3350; one or more penetration enhancing

agents selected from Transcutol® P, oleyl alcohol or isopropyl myristate; a stiffening agent selected from stearyl alcohol; an ointment base selected from PEG 400 or PEG 3350; and an antioxidant selected from butylated hydroxytoluene.

Of this embodiment, a further embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, wherein PEG 400 is present in a concentration of from about 30% w/w to about 70% w/w, Transcutol® P is present in a concentration of from about 2% w/w to about 25% w/w, oleyl alcohol is present in a concentration of from about 1% w/w to about 10% w/w, isopropyl myristate is present in a concentration of from about 1% w/w to about 25% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 10% w/w, BHT is present in a concentration of from about 0.01% w/w to about 2% w/w, and PEG 3350 is present in a concentration of from about 10% w/w to about 50% w/w.

Of this embodiment, a further embodiment is a pharmaceutical composition comprising a therapeutically effective amount of the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, wherein PEG 400 is present in a concentration of from about 45% w/w to about 55% w/w, Transcutol® P is present in a concentration of from about 5% w/w to about 15% w/w, oleyl alcohol is present in a concentration of from about 2.5% w/w to about 7.5% w/w, isopropyl is myristate present in a concentration of from about 2.5% w/w to about 7.5% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 7.5% w/w, BHT is present in a concentration of from about 0.05% w/w to about 1% w/w, and PEG 3350 is present in a concentration of from about 15% w/w to about 30% w/w.

Of all of the above embodiments, a further embodiment is wherein the spiro-oxindole compound is present in a concentration of from about 0.1% w/w to about 10% w/w.

Of this embodiment, a further embodiment is wherein the spiro-oxindole compound is present in a concentration of from about 2% w/w to about 8% w/w.

Of all of the above embodiments, a further embodiment is wherein the pharmaceutical composition comprises the spiro-oxindole compound at a concentration of 2.0% w/w; PEG 400 at a concentration of 52.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 5% w/w;

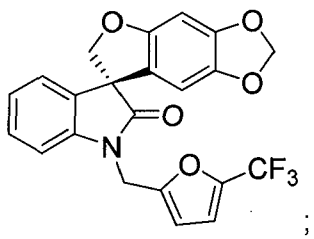
butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

Of all of the above embodiments, another further embodiment is wherein the pharmaceutical composition comprises the spiro-oxindole compound at a concentration of 4% w/w; PEG 400 at a concentration of 50.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 5% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

Of all of the above embodiments, another further embodiment is wherein the pharmaceutical composition comprises the spiro-oxindole compound at a concentration of 4% w/w; PEG 400 at a concentration of 50.9% w/w; Transcutol® P at a concentration of 5% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 10% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

Of all of the above embodiments, another further embodiment is wherein the pharmaceutical composition comprises the spiro-oxindole compound at a concentration of 8% w/w; PEG 400 at a concentration of 46.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 5% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

Of all of the above embodiments, a further embodiment is wherein the spiro-oxindole compound is a compound of the following formula:



;

or a pharmaceutically acceptable salt thereof.

Of the methods of treating, preventing or ameliorating a sodium channel-mediated disease or a condition in a mammal, as set forth above in the Summary of the Invention, one embodiment comprises topically administering to the mammal,

preferably a human, in need thereof a therapeutically effective amount of the pharmaceutical composition of any of the above embodiments of pharmaceutical compositions of the invention.

Of this embodiment, a further embodiment is wherein the wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, post-herpetic neuralgia, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-operative pain, pruritis, osteoarthritis, trigeminal neuralgia, familial erythromelalgia, primary erythromelalgia, familial rectal pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, and combinations thereof.

Specific embodiments of the pharmaceutical compositions of the invention and methods of using the pharmaceutical compositions of the invention are described in more detail below.

UTILITY OF THE PHARMACEUTICAL COMPOSITIONS OF THE INVENTION

This invention is directed to pharmaceutical compositions comprising one or more pharmaceutically acceptable excipients and a therapeutically effective amount of the spiro-oxindole compound, or a pharmaceutically acceptable salt thereof, for use in the treatment of sodium channel-mediated diseases or conditions, preferably diseases or conditions related to pain, such as for example, post-herpetic neuralgia, osteoarthritis, and persistent post-operative pain, in a mammal by topically administering a therapeutically effective amount of the pharmaceutical composition to the mammal, preferably a human, in need thereof.

Sodium channel-mediated diseases or conditions of particular interest to the invention are those disease or conditions which are ameliorated or alleviated by the modulation, preferably the inhibition (or blocking), of the sodium channel. Preferably the sodium channel-mediated diseases or conditions of the invention are those diseases or conditions which are ameliorated or alleviated by the modulation, preferably the inhibition (or blocking) of neuronal voltage-gated sodium channels (Na_V's), including, but not limited to, pain or post-herpetic neuralgia.

Accordingly, the invention provides a method of treating a range of sodium channel-mediated diseases or conditions in a mammal, preferably a human, wherein the diseases or conditions are selected from, but are not limited to, pain, post-herpetic

neuralgia (PHN), post-operative pain, pruritis, pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, familial erythromelalgia, primary erythromelalgia, familial rectal pain, eudynia, heat sensitivity, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), painful diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, tendonitis, bursitis, musculoskeletal sprains, tenosinovitis, chondromalacia patellae, myositis, myotonia (including but not limited to SCN4A-related myotonia), paramyotonia, rhabdomyolysis, paroxysmal dystonia, myasthenia syndromes, malignant hyperthermia, sodium channel toxin related illnesses, cancer pain, restless leg syndrome, fibromyalgia, and neurodegenerative disease, as well as other neurological disorders including multiple sclerosis, by administering to the mammal a therapeutically effective amount of a pharmaceutical composition of the invention.

For purposes of this invention and unless otherwise specifically defined herein, the term "pain" refers to all categories of pain and is recognized to include, but is not limited to, neuropathic pain, inflammatory pain, nociceptive pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, somatic pain, visceral pain, myofacial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, reflex sympathetic dystrophy, brachial plexus avulsion, acute pain (*e.g.*, musculoskeletal and post-operative pain), chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, conditions associated with cephalic pain, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, and combinations thereof.

Pruritis, commonly known as itch and also known as pruritus, is a common dermatological condition. While the exact causes of pruritis are complex and poorly understood, there has long been acknowledged to be mediated by sensory neurons some of which also mediate pain responses. In particular, it is believed that sodium channels likely communicate or propagate along the nerve axon the itch signals along the skin. Transmission of the itch impulses results in the unpleasant sensation that elicits the desire or reflex to scratch.

From a neurobiology level, it is believed that there is a shared complexity of specific mediators, related neuronal pathways and the central processes of itch and pain and recent data suggest that there is a broad overlap between pain- and itch-related peripheral mediators and/or receptors (Ikoma *et al.*, *Nature Reviews Neuroscience*, 7:535-547, 2006). Remarkably, pain and itch have similar mechanisms

of neuronal sensitization in the peripheral nervous system and the central nervous system but exhibits intriguing differences as well.

For example, the mildly painful stimuli from scratching are effective in abolishing the itch sensation. In contrast, analgesics such as opioids can generate severe pruritis. The antagonistic interaction between pain and itch can be exploited in pruritis therapy, and current research concentrates on the identification of common targets for future analgesic and antipruritis therapy. COMPOUND A, or a pharmaceutically acceptable salt thereof, has been shown to have analgesic effects in a number of animal models at oral doses ranging from 1 mg/Kg to 100 mg/Kg. Accordingly, COMPOUND A, as an enantiomer or a pharmaceutically acceptable salt thereof, can also be useful for treating pruritis.

The types of pruritis, include, but are not limited to:

a) psoriatic pruritis, itch due to hemodialysis, and itching caused by skin disorders (*e.g.*, dermatitis), systemic disorders, neuropathy, psychogenic factors or a mixture thereof;

b) itch caused by allergic reactions, insect bites, hypersensitivity (*e.g.*, dry skin, eczema, psoriasis), acne, inflammatory conditions or injury;

c) skin irritation or inflammatory effect from administration of another therapeutic such as, for example, antibiotics, antivirals and antihistamines; and

d) itch caused by viral infections, such as itch associated with post-herpetic neuralgias.

The general utility of the spiro-oxindole compound, or a pharmaceutically acceptable salt thereof, of the invention as a sodium channel blocker is described in PCT Published Patent Application No. WO 06/110917. In particular, the general utility of the spiro-oxindole compound, or a pharmaceutically acceptable salt thereof, used in the pharmaceutical compositions of the invention in mediating, especially inhibiting, the sodium channel ion flux has been determined using the assays described in PCT Published Patent Application No. WO 06/110917. The general utility of COMPOUND A, or a pharmaceutically acceptable salt, used in the pharmaceutical compositions of the invention in treating sodium-channel mediated diseases or conditions may be established in industry standard animal models and in the animal models disclosed in PCT Published Patent Application No. WO 06/110917 for demonstrating the efficacy of the spiro-oxindole compound, or a pharmaceutically acceptable salt thereof, in treating such diseases and conditions.

Accordingly, this invention provides a method of treating a range of sodium

channel-mediated diseases or condition, preferably neuronal voltage-gated sodium channel-mediate diseases or condition, in a mammal, preferably a human, through inhibition of ion flux through a voltage-dependent sodium channel in the mammal, preferably a neuronal voltage-gated sodium channel, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

As noted above, the pharmaceutical compositions of the invention are useful in treating sodium channel-mediated diseases or conditions, preferably neuronal voltage-gated sodium channel-mediated diseases or conditions. In particular, the pharmaceutical compositions of the invention are useful in treating or lessening the severity of a disease or condition where activation or hyperactivity of one or more of neuronal voltage-gated sodium channels selected from $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.5$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, or $Na_V1.9$ is implicated in the disease or condition. Preferably, the pharmaceutical compositions of the invention are useful in treating or lessening the severity of a disease or condition where activation or hyperactivity of $Na_V1.7$ is implicated in the disease or condition, such as pain or post-herpetic neuralgia.

Accordingly, the invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of one or more of neuronal voltage-gated sodium channels selected from $Na_V1.1$, $Na_V1.2$, $Na_V1.3$, $Na_V1.4$, $Na_V1.5$, $Na_V1.6$, $Na_V1.7$, $Na_V1.8$, or $Na_V1.9$ is implicated in the disease, condition or disorder, wherein the methods comprise administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of the invention as set forth above.

Further disclosure of the utility of the pharmaceutical compositions of the invention is set forth below.

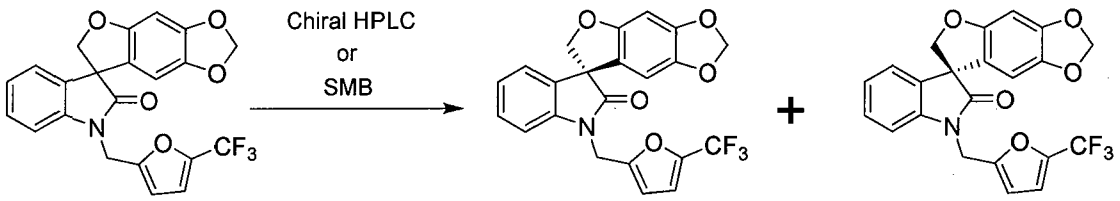
PREPARATION OF THE SPIRO-OXINDOLE COMPOUND OF THE INVENTION

The spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, used in the pharmaceutical compositions of the invention can be prepared by the methods disclosed in PCT Published Patent Application No. WO 06/110917, or by methods known to one skilled in the art. COMPOUND A and its corresponding (*R*)-enantiomer, and their pharmaceutically acceptable salts, can be prepared by the methods disclosed in PCT Published Patent Application No. WO 2011/002708, the relevant disclosure of

which is disclosed herein in its entiretly, or by methods known to one skilled in the art.

COMPOUND A, or a pharmaceutically acceptable salt thereof, and its corresponding (*R*)-enantiomer can be prepared by the resolution of the spiro-oxindole compound using either chiral high pressure liquid chromatography methods or by simulated moving bed chromatography methods, as described below in the following Reaction Scheme wherein "chiral HPLC" refers to chiral high pressure liquid chromatography and "SMB" refers to simulated moving bed chromatography:

REACTION SCHEME



Spiro-oxindole compound COMPOUND A (*R*)-enantiomer

One of ordinary skill in the art would recognize variations in the above Reaction Scheme which are appropriate for the resolution of the individual enantiomers.

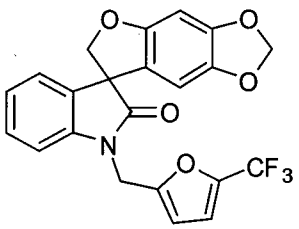
Alternatively, COMPOUND A and its corresponding *(R)*-enantiomer can be synthesized from chiral starting materials which are known or readily prepared using process analogous to those which are known.

Preferably, COMPOUND A obtained by the resolution methods disclosed herein is substantially free of the (*R*)-enantiomer or contains only traces of the (*R*)-enantiomer.

The following Synthetic Examples serve to illustrate the resolution methods disclosed by the above Reaction Scheme and are not intended to limit the scope of the invention.

SYNTHETIC EXAMPLE 1

Synthesis of 1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one (Spiro-oxindole compound)



To a suspension of spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one (1.0 g, 3.6 mmol), which can be prepared according to the methods disclosed in PCT Published Patent Application No. WO 06/110917, and cesium carbonate (3.52 g, 11 mmol) in acetone (50 mL) was added 2-bromomethyl-5-trifluoromethylfuran (1.13 g, 3.9 mmol) in one portion and the reaction mixture was stirred at 55–60 °C for 16 hours. Upon cooling to ambient temperature, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography, eluting with ethyl acetate/hexane (1/9 – 1/1) to afford 1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one, *i.e.*, the Spiro-oxindole compound, (1.17 g, 76%) as a white solid: mp 139–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-6.97 (m, 5H), 6.72 (d, *J* = 3.24 Hz, 1H), 6.66 (s, 1H), 6.07 (s, 1H), 5.90-5.88 (m, 2H), 5.04 (ABq, 2H), 4.74 (ABq, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 155.7, 153.5, 148.8, 142.2, 141.9, 140.8, 140.2, 139.7, 139.1, 132.1, 129.2, 124.7, 124.1, 123.7, 121.1, 120.1, 117.6, 114.5, 114.4, 110.3, 109.7, 103.0, 101.9, 93.8, 80.0, 57.8, 36.9; MS (ES+) m/z 430.2 (M + 1), 452.2 (M + 23); Cal'd for $C_{22}H_{14}F_3NO_5$: C, 61.54%; H, 3.29%; N, 3.26%; Found: C, 61.51%; H, 3.29%; N, 3.26%.

SYNTHETIC EXAMPLE 2

Resolution of the Spiro-oxindole Compound by Chiral HPLC

The spiro-oxindole compound was resolved into COMPOUND A and the corresponding (*R*)-enantiomer by chiral HPLC under the following conditions:

Column:	Chiralcel ® OJ-RH; 20 mm I.D. × 250 mm, 5 mic; Lot: OJRH CJ-EH001 (Daicel Chemical Industries, Ltd)
Eluent:	Acetonitrile/Water (60/40, v/v, isocratic)
Flow rate:	10 mL/min
Run time:	60 min
Loading:	100 mg of compound of formula (I) in 1 mL of acetonitrile
Temperature:	Ambient

Under the above chiral HPLC conditions, the (*R*)-enantiomer, *i.e.*, (*R*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro[furo[2,3-*f*][1,3]-benzodioxole-7,3'-indol]-2'(1'*H*)-one, was isolated as the first fraction as a white solid; ee (enantiomeric excess) >99% (analytical OJRH, 55% acetonitrile in water); mp 103-105 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-6.99 (m, 5H), 6.71 (d, *J* = 3.35 Hz, 1H), 6.67 (s, 1H), 6.05 (s, 1H), 5.89 (ABq, 2H), 5.03 (ABq, 2H), 4.73 (ABq, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2,

155.9, 152.0, 149.0, 142.4, 142.0, 141.3, 132.0, 129.1, 123.9, 120.6, 119.2, 117.0, 112.6, 109.3, 108.9, 103.0, 101.6, 93.5, 80.3, 58.2, 36.9; MS (ES+) *m/z* 430.2 (M + 1), $[\alpha]_D$ −17.46 (*c* 0.99, DMSO). COMPOUND A, *i.e.*, (*S*)-1'-{[5-(trifluoromethyl)furan-2-yl]methyl}spiro-[furo[2,3-*f*][1,3]benzodioxole-7,3'-indol]-2'(1'*H*)-one, was isolated as the second fraction as a white solid; ee > 99% (analytical OJRH, 55% acetonitrile in water); mp 100-102 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32-6.99 (m, 5H), 6.71 (d, *J* = 3.43 Hz, 1H), 6.67 (s, 1H), 6.05 (s, 1H), 5.89 (ABq, 2H), 5.03 (ABq, 2H), 4.73 (ABq, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.9, 152.0, 149.0, 142.4, 142.0, 141.3, 132.0, 129.1, 123.9, 120.6, 119.2, 117.0, 112.6, 109.3, 108.9, 103.0, 101.6, 93.5, 80.3, 58.2, 36.9; MS (ES+) *m/z* 430.2 (M + 1), $[\alpha]_D$ +14.04 (*c* 0.99, DMSO).

SYNTHETIC EXAMPLE 3

Resolution of the Spiro-oxindole Compound by SMB Chromatography

The spiro-oxindole compound was resolved into COMPOUND A and the corresponding (*R*)-enantiomer by SMB chromatography under the following conditions:

Extract:	147.05 mL/min
Raffinate:	76.13 mL/min
Eluent:	183.18 mL/min
Feed:	40 mL/min
Recycling:	407.88 mL/min
Run Time:	0.57 min
Temperature:	25 °C
Pressure:	46 bar

The feed solution (25 g of compound of formula (I) in 1.0 L of mobile phase (25:75:0.1 (v:v:v) mixture of acetonitrile /methanol/trifluoroacetic acid)) was injected continuously into the SMB system (Novasep Licosep Lab Unit), which was equipped with eight identical columns in 2-2-2-2 configuration containing 110 g (per column, 9.6 cm, 4.8 cm I.D.) of chiralpack AD as stationary phase. The first eluting enantiomer (the (*R*)-enantiomer) was contained in the raffinate stream and the second eluting enantiomer (COMPOUND A) was contained in the extract stream. The characterization data of COMPOUND A and the (*R*)-enantiomer obtained from the SMB resolution were identical to those obtained above utilizing chiral HPLC.

PREPARATION OF THE PHARMACEUTICAL COMPOSITIONS OF THE INVENTION

The preparation of the pharmaceutical compositions of the invention employs

conventional techniques of pharmaceutical formulation, medicinal chemistry and the like, which are within the skill of one ordinarily skilled in the art. Such techniques are explained fully in the literature. Preparation of pharmaceutical compositions are described, for example, in *Remington: The Science and Practice of Pharmacy*, 21st edition (Lippincott Williams & Wilkins, (2005) and Ansel *et al.*, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 8th Ed. (Med, PA: Williams & Wilkins, 2005), hereby incorporated by reference.

The pharmaceutical compositions of the invention are preferably in ointment form. Ointments are semisolids that contain little if any water and are typically prepared by mixing the active ingredient with a greasy or non-greasy base with the aid of suitable machinery.

The pharmaceutical compositions of the invention comprise one or more pharmaceutically acceptable excipients.

It is understood that the pharmaceutically acceptable excipients used in any of the topical pharmaceutical compositions of the invention are preferably sterile and/or preferably have been approved by the United States Food and Drug Administration, the European Medicines Agency or Health Canada as being acceptable for use in topical formulations to be administered to humans and animals.

In the preparation of pharmaceutical compositions of the invention, extensive studies, such as solubility and stability, were conducted to provide pharmaceutical compositions which allowed for the desired therapeutically effective amount of the active ingredient, *i.e.*, the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, preferably COMPOUND A, or a pharmaceutically acceptable salt thereof, to be dissolved in one or more pharmaceutically acceptable excipients and which allowed for the active ingredient to be readily solubilized in the pharmaceutical composition, and well-preserved for multiple applications. Furthermore, the pharmaceutical compositions need to be physically and chemically stable at ambient temperature over a suitable period of time, preferably for a period of time from about 1 month to about 5 years, more preferably for a period of time from about 1 year to about 3 years.

The spiro-oxindole compound of the invention, particularly, COMPOUND A, is relatively lipophilic and has poor water solubility. COMPOUND A's water solubility is less than 5µg/mL. Furthermore, COMPOUND A has a calculated Log P of about 3.07, and does not contain functional groups that can be ionised by pH alteration and consequently varying the pH of a solution to 2, 7.4 and 12 does not change the

solubility of COMPOUND A, which remains at < 5 µg/mL.

Attempts to improve the solubility of COMPOUND A for use in a topical pharmaceutical composition, preferably as an ointment, were undertaken using a variety of solubilization techniques. The aim was to conduct a thorough investigation of the use of various pharmaceutically acceptable excipients to maximize the solubility of COMPOUND A. A series of solubility studies, which were performed using standard solubility testing techniques, was therefore carried out to identify proper excipient(s) and/or excipient combinations for achieving the target dosage strength for COMPOUND A. The solubility of COMPOUND A in these studies was determined by UV spectrophotometry using COMPOUND A's UV absorbance wavelength at 312 nm.

In addition to the solubility studies undertaken, a series of stability studies were conducted to determine the physical and chemical stability of the pharmaceutical compositions prepared.

Based on the results obtained from the solubility and stability studies and the results obtain from *in vivo* efficacy studies, the following representative pharmaceutical compositions of the invention were prepared:

TABLE 1

Component	Function	% (w/w)	% (w/w)	% (w/w)	% (w/w)	% (w/w)
COMPOUND A	Active Ingredient	1.0	2.0	4.0	4.0	8.0
PEG 400	Solvent and ointment base	53.9	52.9	50.9	50.9	46.9
Transcutol® P	Penetration enhancer	10.0	10.0	5.0	10.0	10.0
Oleyl alcohol	Penetration enhancer	5.0	5.0	5.0	5.0	5.0
Isopropyl myristate	Penetration enhancer	5.0	5.0	5.0	5.0	5.0
Stearyl alcohol	Stiffening agent	5.0	5.0	10.0	5.0	5.0
Butylated hydroxytoluene (BHT)	Antioxidant	01	0.1	0.1	0.1	0.1
PEG 3350	Ointment base	20.0	20.0	20.0	20.0	20.0
Total		100.0	100.0	100.0	100.0	100.0

In general, each pharmaceutically acceptable excipient may be present in a pharmaceutical composition of the invention in a concentration of from about 0.5% w/w to about 99.0% w/w. More preferred, each pharmaceutically acceptable excipient may be present in a pharmaceutical composition of the invention in a concentration of from about 1% w/w to about 90% w/w. Even more preferred, each pharmaceutically acceptable excipient may be present in a pharmaceutical composition of the invention in a concentration of from about 10% w/w to about 80.0% w/w.

Preferably, in a pharmaceutical composition of the invention, PEG 400 is present in a concentration of from about 30% w/w to about 70% w/w, Transcutol® P is present in a concentration of from about 2% w/w to about 25% w/w, oleyl alcohol is present in a concentration of from about 1% w/w to about 10% w/w, isopropyl myristate is present in a concentration of from about 1% w/w to about 25% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 10% w/w, BHT is present in a concentration of from about 0.01% w/w to about 2% w/w, and PEG 3350 is present in a concentration of from about 10% w/w to about 50% w/w.

More preferably, in a pharmaceutical composition of the invention, PEG 400 is present in a concentration of from about 45% w/w to about 55% w/w, Transcutol® P is present in a concentration of from about 5% w/w to about 15% w/w, oleyl alcohol is present in a concentration of from about 2.5% w/w to about 7.5% w/w, isopropyl myristate is present in a concentration of from about 2.5% w/w to about 7.5% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 7.5% w/w, BHT is present in a concentration of from about 0.05% w/w to about 1% w/w, and PEG 3350 is present in a concentration of from about 15% w/w to about 30% w/w.

Preferably, in a pharmaceutical composition of the invention, the spiro-oxindole compound, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof, is present in a concentration of from about 0.1% w/w to about 10% w/w, and preferably from about 2% w/w to about 8% w/w.

The stability of the pharmaceutical compositions disclosed herein may be tested in conventional manner, *e.g.*, by measurement of COMPOUND A, or a pharmaceutically acceptable salt thereof, and its degradation products, dissolution, friability, disintegration time, microbial content, appearance and/or microscopy, for defined periods of time.

Preferably, the pharmaceutical compositions of this invention will be stable for a time period of between about 1 month and about 5 years when kept at a temperature between about 5 °C and about 50 °C. More preferably, the pharmaceutical

compositions of this invention will be stable for a time period of between about 6 months and about 4 years when kept at a temperature between about 15 °C and about 45 °C. Even more preferably, the pharmaceutical compositions of this invention will be stable for a time period of between about 6 months and about 3 years when kept at a temperature between about 25 °C and about 40 °C. In a more preferred embodiment, the pharmaceutical compositions are stable when kept at a temperature of between about 25 °C and about 40 °C over a period of time such as a year, and preferably 2 years. More preferably, the pharmaceutical compositions are stable for 3 years.

The pharmaceutical compositions of the invention set forth above in Table 1 may be prepared as set forth in the following PREPARATION EXAMPLE 1. It is understood, however, that that one skilled in the art would be able to prepare the pharmaceutical compositions by similar methods or by methods known to one skilled in the art. It is also understood that one skilled in the art would be able to prepare in a similar manner as described below other pharmaceutical compositions of the invention not specifically illustrated below by using the appropriate components and modifying the parameters of the preparation as needed.

PREPARATION EXAMPLE 1

A standard manufacturing vessel with a propeller/shaft is tared and the tare weight recorded. With continuous propeller mixing, oleyl alcohol, isopropyl myristate, Transcutol® P, PEG 3350, stearyl alcohol, PEG 400 and butylated hydroxytoluene (BHT) are added to the vessel in the amounts listed above in Table 1, one excipient at a time until a homogenous solution is obtained before the addition of the next excipient, at preferably 60 °C to 70 °C. To the resultant mixture is added the desired amount of COMPOUND A, or a pharmaceutically acceptable salt thereof, in the amount listed above in Table 1 at preferably 60 °C to 70 °C. The resultant mixture is mixed for a suitable period of time, preferably for a period of time of between about 30 minutes and about 1 hour. Upon completion (when COMPOUND A, or a pharmaceutically acceptable salt thereof, is completely dissolved), the propeller mixer is removed and the homogenization process is started. A Silverson Mixer (Model No. L4RT) is used for the homogenization, where the homogenization is carried out for 10 minutes and the rotor speed is kept at 6000 rpm. During the homogenization process, the temperature of the solution is constantly monitored and is kept at preferably between about 60 °C and about 70 °C. After the homogenization is completed, the heat source is removed to cool the mixture, and quickly switched to propeller mixing

until an ointment is formed and the temperature reaches a suitable temperature, preferably 35 °C or below. The sides of the vessel are continuously scraped down during the cooling and mixing stage to ensure the ointment is homogenous. The resulting ointment is then transferred to an appropriate container.

The process described above can be carried out utilizing conventional equipment and under conventional conditions known to those skilled in the art. All of the raw materials were used as obtained from the various manufactures with the following exception of COMPOUND A, which is obtained as described herein.

ADMINISTRATION OF THE PHARMACEUTICAL COMPOSITIONS OF THE INVENTION

The pharmaceutical compositions of the invention are to be topically administered to a mammal, preferably a human. The pharmaceutical composition is applied topically to a site at or adjacent to a region where the treatment is desired. Typically, one to four applications per day of a pharmaceutical composition of the invention are recommended during the treatment period, or it can be reapplied as often as necessary. Relief is typically obtained within minutes and lasts for periods of variable duration ranging from minutes to hours to even, in some cases, days. Generally, the amount of the pharmaceutical formulation of the invention applied to the affected skin area ranges from about 0.02 g/cm^2 of skin surface area to about 0.5 g/cm^2, preferably, 0.1 g/cm^2 to about 0.30 g/cm^2 of skin surface area.

In some embodiments, the pharmaceutical composition of the invention, when topically administered to the skin of a mammal in need thereof, exerts only a local effect. In other embodiments, the pharmaceutical composition of the invention, when topically administered to the skin of a mammal in need thereof, additionally has a systemic effect.

Application of the pharmaceutical composition of the invention may be performed by a medical professional or by the patient. In certain embodiments, for maximum effectiveness and increased absorption, the area to which the pharmaceutical composition of the invention is to be administered is first cleansed, for example using an astringent, such as a standard commercial antiseptic or alcohol. The area is then allowed to dry, and the pharmaceutical composition of the invention is applied onto the target area and rubbed until all the pharmaceutical composition has been absorbed or no residue remains on the skin.

Typically, a successful therapeutic effective amount of a pharmaceutical

composition of the invention will meet some or all of the following criteria. As will be appreciated by one skilled in the art, the therapeutically effective dosage of a spiro-oxindole compound of the invention, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, preferably as COMPOUND A, or a pharmaceutically acceptable salt thereof, will be such that it is effective for its intended purpose (*e.g.*, prevent, reduce or alleviate pain). In general, a spiro-oxindole compound of the invention, as an enantiomer, a racemate or a non-racemic mixture of enantiomers, preferably as COMPOUND A, or a pharmaceutically acceptable salt thereof, is present in a pharmaceutical composition of the invention in an amount of from about 2% to about 10% of the total weight of the composition, preferably in an amount of from about 4% to about 8% of the total weight of the composition, more preferably, of from about 4% to about 6% of the total weight of the composition.

The potency (as expressed by IC_{50} value) of COMPOUND A, or a pharmaceutically acceptable salt thereof, should be less than 10 μM, preferably below 1 μM and most preferably below 50 nM. The IC_{50} ("Inhibitory Concentration – 50%") is a measure of the amount of compound required to achieve 50% inhibition of ion flux through a sodium channel, over a specific time period, in an assay of the invention. For example, COMPOUND A, or a pharmaceutically acceptable salt thereof, when tested in the guanidine influx assay disclosed in PCT Published Patent Application No. WO 06/110917, demonstrated an IC_{50} of less than 1 μM concentration.

The recipients of administration of the pharmaceutical compositions of the invention can be any vertebrate animal, such as mammals. Among mammals, the preferred recipients are mammals of the Orders Primate (including humans, apes and monkeys), Arteriodactyla (including horses, goats, cows, sheep, and pigs), Rodenta (including mice, rats, rabbits, and hamsters), and Carnivora (including cats, and dogs). Among birds, the preferred recipients are turkeys, chickens and other members of the same order. The most preferred recipients are humans.

COMBINATION THERAPY

The pharmaceutical compositions of the invention may be usefully combined with one or more other therapeutic agent or as any combination thereof, in the treatment of sodium channel-mediated diseases and conditions. For example, the pharmaceutical composition of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents, including, but not limited to:

- opiates analgesics, *e.g.*, morphine, heroin, cocaine, oxymorphine, levorphanol, levallorphan, oxycodone, codeine, dihydrocodeine, propoxyphene, nalmefene, fentanyl, hydrocodone, hydromorphone, meripidine, methadone, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;
- non-opiate analgesics, *e.g.*, acetomeniphen, and salicylates (*e.g.*, aspirin);
- nonsteroidal antiinflammatory drugs (NSAIDs), *e.g.*, ibuprofen (Advil®), naproxen, fenoprofen, ketoprofen, diclofenac, diflusinal, etodolac, fenbufen, flufenisal, flurbiprofen, indomethacin, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin and zomepirac;
- anticonvulsants, *e.g.*, carbamazepine, oxcarbazepine, lamotrigine, gabapentin and pregabalin;
- antidepressants such as tricyclic antidepressants, *e.g.*, amitriptyline, clomipramine, despramine, imipramine, duloxetine and nortriptyline;
- COX-2 selective inhibitors, *e.g.*, celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;
- alpha-adrenergics, *e.g.*, doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, and 4-amino-6,7-dimethoxy-2-(5- methane sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- barbiturate sedatives, *e.g.*, amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal and thiopental;
- tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, *e.g.*, (αR, 9*R*)-7-[3,5-bis(trifluoromethyl)benzyl)]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7*H*-[1,4]diazocino[2,1-*g*][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethylphenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2*S*,3*S*);
- paracetamol;
- metabotropic glutamate receptor (mGluR) antagonists;
- local anaesthetic such as mexiletine and lidocaine;

- corticosteroid such as dexamethasone;
- muscarinic antagonists, *e.g.*, tolterodine, propiverine, tropsium t chloride, darifenacin, solifenacin, temiverine and ipratropium;
- cannabinoids;
- vanilloid receptor agonists (*e.g.*, resinferatoxin) or antagonists (*e.g.*, capsazepine);
- topical agents (*e.g.*, lidocaine, capsacin and resiniferotoxin);
- muscle relaxants such as benzodiazepines, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol and orphrenadine;
- anti-histamines or H1 antagonists;
- NMDA receptor antagonists;
- PDEV inhibitors;
- Tramadol®;
- cholinergic (nicotinc) analgesics;
- alpha-2-delta ligands;
- prostaglandin E2 subtype antagonists;
- leukotriene B4 antagonists; and
- 5-lipoxygenase inhibitors

Sodium channel-mediated diseases and conditions that may be treated and/or prevented using such combinations include but not limited to, pain, post-herpetic neuralgia (PHN), post-operative pain, pruritis, pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, familial erythromelalgia, primary erythromelalgia, familial rectal pain, eudynia, heat sensitivity, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), painful diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, tendonitis, bursitis, musculoskeletal sprains, tenosinovitis, chondromalacia patellae, myositis, myotonia (including but not limited to SCN4A-related myotonia), paramyotonia, rhabdomyolysis, paroxysmal dystonia, myasthenia syndromes, malignant hyperthermia, cystic fibrosis, sodium channel toxin related illnesses, cancer pain, restless leg syndrome, fibromyalgia, and neurodegenerative disease, as well as other neurological disorders including multiple sclerosis.

As used herein "combination" refers to any mixture or permutation of a pharmaceutical composition of the invention with one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include

simultaneous or sequentially delivery of a pharmaceutical composition of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a pharmaceutical composition of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include different routes of administration of a pharmaceutical composition of the invention with another therapeutic agent. For example, the pharmaceutical composition of the invention is administered topically in combination with another therapeutic agent that is administered orally. Unless the context makes clear otherwise, "combination" may include formulations of a pharmaceutical composition of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

ARTICLE OF MANUFACTURE

The present invention also provides kits that contain a pharmaceutical composition of the invention. The kit also includes instructions for the use of the pharmaceutical composition for modulating the activity of sodium channels, for the treatment of pain, as well as other utilities as disclosed herein. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. It will be evident to those of ordinary skill in the art that such compositions which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

The invention may be even better understood by way of the following non-limiting Biological Examples which describe assays which can be performed to demonstrate the utility of the invention.

BIOLOGICAL EXAMPLE 1

Dose Proportionality in CFA Induced Chronic Inflammatory Pain

In this test, mechanical hyperalgesia is assessed with electronic von Frey filament by means of Electrovonfrey anesthesiometer (Model 2290, IITC Life Science, Woodland Hills, CA). Following a full week of acclimatization to the vivarium facility, 150 µL of the "Complete Freund's Adjuvant" (CFA) emulsion (CFA suspended in an oil/saline (1:1) emulsion at a final concentration of 0.5 mg/mL) was injected subcutaneously into the plantar surface of the left hind ankle joint of rats under light

isoflurane anaesthesia. Animals were allowed to recover from the anaesthesia and the baseline mechanical nociceptive thresholds of all animals were assessed one week after the administration of CFA. All animals were habituated to the experimental chambers for 20 minutes on the day of the experiment. The animals were then randomly assigned to 5 different test groups including a vehicle control group and 4 pharmaceutical compositions with COMPOUND A at 1%, 2%, 4% and 8% (w/w) groups. After baseline measurements, animals were anaesthetized under isoflurane, shaved at the site of application, and then dosed by application of 50 mg test compositions on the entire ipsilateral hind ankle and foot. Animals were then placed in Plexiglas tubes for 30 minutes to prevent early removal/ingestion of drug. Test compositions were applied twice a day for 3 days. On the fourth day, immediately after application, animals were placed in tubes for 15 minutes and then removed and placed in Plexiglas enclosures for 15 minutes prior to making paw withdrawal measurements. Von Frey withdrawal thresholds were measured as the mean of several independent determinations made within 1-2 minutes of each other on the affected paw of each animal 30 minutes post-dosing. The time point used was previously determined to show the highest analgesic effect for each test composition.

The response thresholds of animals to tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 15 minutes of accommodation, a von Frey hair was applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals with sufficient force, measured in grams, to elicit a crisp response of the paw. The response indicated a withdrawal from the painful stimulus and constituted the efficacy endpoint.

Results

At baseline, there were no significant differences between the means of the von Frey paw withdrawal measurements for the 5 test groups. On the fourth day of dosing at 30 minutes post-dosing, the groups treated with pharmaceutical compositions of COMPOUND A at 2%, 4%, and 8% (w/w) all showed statistically significant increases in the von Frey mechanical paw withdrawal thresholds as expressed by percent change from baseline (CFB) to indicate an analgesic effect (see Figure 1). The analgesic effect for the compositions with COMPOUND A increased with increasing doses up to the highest dose tested of 8% (w/w), which showed the maximum percent CFB at +45.1%. The 1% (w/w) dosage group, however, did not demonstrate an observable increase in von Frey mechanical paw withdrawal threshold. The results, as

set forth in Figure 1, indicate that compositions of COMPOUND A have analgesic effects in the CFA-induced inflammatory pain model in the range of 2% to 8% (w/v).

BIOLOGICAL EXAMPLE 2

Time Course of Efficacy in the Neuropathic Pain Model; Chronic Constriction Injury

Neuropathic pain is characterized by spontaneous pain and stimulus-evoked allodynia and hyperalgesia. Pharmaceutical compositions of the invention were evaluated in Chronic Constriction Injury model using Sprague-Dawley rats as described below.

An approximately 3 cm incision was made through the skin and the fascia at the mid thigh level of a rat's left hind leg using a no. 10 scalpel blade. The left sciatic nerve was exposed via blunt dissection through the biceps femoris with care to minimize haemorrhagia. Four loose ligatures were tied along the sciatic nerve using four chromic gut sutures at intervals of 1 mm to 2 mm apart. The tension of the loose ligatures was tight enough to induce slight constriction of the sciatic nerve when viewed under a dissection microscope at a magnification of 4 fold. As sham controls, the right sciatic nerve was exposed and manipulated in the same manner as described above, except sutures were not tied onto the nerve. Antibacterial ointment was applied directly into the wound, and the muscle was closed using sterilized sutures. Betadine® was applied onto the muscle and its surroundings, followed by skin closure with surgical clips.

A painful neuropathy was allowed to develop for at least 14 days in the ipsilateral leg as determined by lower paw withdrawal thresholds to a mechanical stimulus. Only those with significant hyperalgesia, as determined by reduced threshold of paw withdrawal to the von Frey filament, measured in grams, were enrolled in the study. All animals enrolled in the study showed paw withdrawal thresholds of <12 g.

The response thresholds of animals to tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglass enclosure set on a mire mesh surface. After 15 minutes of accommodation, a von Frey hair was applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals with sufficient force, measured in grams, to elicit a crisp response of the paw. The response indicated a withdrawal from the painful stimulus and constituted the efficacy endpoint. The force (in grams) required to elicit a crisp withdrawal response was recorded before dosing as a baseline measurement, and at multiple time points post-dosing.

Three days prior to baseline measurement, animals were anaesthetized under isoflurane and the whole of the ipsilateral hind legs, including the upper sciatic notch thigh area, ankle and foot, was shaved. The animals were then randomly assigned to one of 4 different test groups including a vehicle control group, a 5% (w/v) Lidocaine (Xylocaine®), and 2 pharmaceutical compositions of the invention comprising COMPOUND A at 4% (w/w) containing either 5% or 10% Transcutol® P. After baseline measurement, 100 mg of the test composition was applied on the entire shaved area. The animals were then placed in plastic tubes for at least 15 minutes, to prevent early removal/ingestion of drug. Subsequently, animals were placed in the Plexiglas enclosure 15 minutes before von Frey measurement at the respective time points. Von Frey withdrawal thresholds were measured as the mean of several independent determinations made within 1-2 minutes of each other on the affected paw of each animal at 0.5, 1 and 2 hours post dosing.

Results

The percent mean change from baseline (CFB) for each groups' paw withdrawal thresholds is shown in Figure 2. Observations of +23.1%, +26.3%, and +33.8% CFB were made for the 5% (w/v) lidocaine group and 4% (w/w) COMPOUND A in 5% and 10% Transcutol® P test groups at 0.5 hours post-dosing, respectively. At 1 hour post-dosing, +18.1% and +26.7% CFB were observed for 4% (w/w) COMPOUND A in 5% and 10% Transcutol® P treatment groups respectively. No significant changes ($p>.05$) were observed for the 5% (w/v) lidocaine treatment group at any time points later than 0.5 hours post-dosing. The 4% (w/w) COMPOUND A in 10% transcutol group exhibited analgesic effects from 0.5 hour up to 2 hours post-dosing, with improved efficacy and longer duration of analgesia as compared to the 4% (w/w) COMPOUND A in 5% transcutol group. Both groups of 4% (w/w) COMPOUND A exhibited a longer lasting analgesic effect when compared with the 5% lidocaine group, which exhibited analgesic effects only up to 0.5 hours post-dosing in the CCI-induced neuropathic pain model.

BIOLOGICAL EXAMPLE 3

STZ Model of Diabetic Neuropathy

This study evaluates the efficacy of a pharmaceutical composition of the invention in the STZ-induced neuropathic pain model in male Sprague-Dawley rats, following acute dosing, as compared with a 5% (w/v) topical Lidocaine (Xylocaine®) and a 1.16% (w/v) topical Diclofenac (Voltaren®). A rodent model of painful peripheral

diabetic neuropathy (PDN) that mimics human condition was created by inducing a diabetic state in the rat through the ablation of the insulin producing pancreatic beta cells. A single streptozotocin (STZ) injection destroys beta cells in rats and produces a diabetic state that over time progresses to painful Peripheral Diabetic Neuropathy (PDN).

Streptozotocin (STZ) was dissolved in citrate buffer (20 mM, pH 4.5) and administered at a dose of 60 mg/Kg, intraperitoneal, to induce pancreatic beta-cell death. Blood glucose level was measured once a week following injection, using the AccuSoft Blood Glucose Monitoring System. A booster injection was administered two weeks post-initial injection to animals that did not display elevated blood glucose levels following the first injection. Animals with plasma glucose concentrations above 16 mmol/L were considered diabetic and included in the study. Hyperalgesia and allodynia, which are signs of diabetic neuropathic pain, were monitored using the von Frey test as described below. Von Frey measurements were recorded from both left and right paws. Only those with significant hyperalgesia as determined by reduced threshold, measured in grams, of paw withdrawal to the von Frey filament were enrolled in the study. The study was executed during the 8th week following STZ injection. During this time their health status was closely monitored.

The animals were randomly divided into 4 test groups (n = 7 animals/group) including a vehicle control, a 5% (w/v) Lidocaine (Xylocaine®), a 1.16% (w/v) Diclofenac (Voltaren®), and a pharmaceutical composition with 4% (w/w) COMPOUND A. After baseline measurement, 50 mg of the test composition was applied on the entire left foot. Animals were then placed in Plexiglas tubes for 15 minutes to prevent early removal/ingestion of drug, and then moved to the Plexiglas enclosure for von Frey measurement. The paw withdrawal thresholds of animals from mechanical tactile stimuli were measured using the Electrovonfrey anesthesiometer (Model 2290, IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated acrylic enclosure set on a wire mesh surface. After 15 minutes of accommodation, a flexible von Frey hair (tip #15) was applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals, with sufficient force to elicit a crisp response of the paw. The response indicated a withdrawal from the painful stimulus and constitutes the efficacy endpoint. The force (g) required to elicit a crisp withdrawal response was recorded before dosing as a baseline measurement, and at 30 minutes post-dosing.

Withdrawal measurements were recorded from both the treated (left) and un-treated (right) paws. The von Frey paw withdrawal data were analyzed using

GraphPad Prism 5 statistical analysis software. One-way ANOVA was used for multivariate analysis with Bonferroni adjustment. Unpaired t-test was used for univariate analysis. Results are expressed as mean ± SEM. Values that reached a $p<.05$ level of significance were considered statistically significant.

Results

At baseline, there were no significant differences between the four test groups in the von Frey paw withdrawal measurements for treated paws, nor were there differences between the left and right hind paw measurements.

At 30 minutes post-dosing, the percent mean change from baseline (CFB) for each groups' paw withdrawal thresholds (of treated paws) is provided in Figure 3. The change from baseline reached 44.9% for the 4% (w/w) COMPOUND A dosage group ($p< 0.05$), substantially above the 25.9% change from baseline observed in the 5% (w/v) Lidocaine group. No significant CFB was observed in the 1.16% (w/v) Diclofenac group.

Therefore, a local analgesic effect was observed for composition containing 4% (w/w) COMPOUND A in the STZ-induced neuropathic pain model at 30 minutes post-dosing, manifesting as a 44.9% change from baseline, greater than the local efficacy observed with the reference compounds.

BIOLOGICAL EXAMPLE 4

Relationship between Efficacy and Systemic Exposure for Topical and Oral Administration; Chronic Constriction Injury

The Chronic Constriction Injury (CCI) model, an established neuropathic pain model in the rat, is used in this study to compare the levels of efficacy and systemic exposure of COMPOUND A between the topical and oral administration in male rats.

A peripheral neuropathy was induced in rats by placing loose constrictive ligatures around the common sciatic nerve as described by Bennett G J, and Xie Y-K., *Pain*, (1988) 33: pp. 87–107. Eight-week old male Sprague Dawley rats were anaesthetized with 3.5% isoflurane, and a 3 cm incision was made through the skin and fascia at the mid-thigh level of the animal's left hind leg using a no. 10 scalpel blade. The left sciatic nerve was exposed via blunt dissection through the biceps femoris, with care taken to minimize haemorrhagia. Four loose ligatures were tied along the sciatic nerve using four chromic gut sutures at intervals of 1 mm to 2 mm apart. The tension of the loose ligatures was tight enough to induce slight constriction of the sciatic nerve when viewed under a dissection microscope at a magnification of 4

fold. Antibacterial ointment was applied directly into the wound, and the muscle was closed using sterilized sutures. Betadine® was applied onto the muscle and its surroundings, followed by skin closure with surgical clips.

A painful neuropathy was allowed to develop in the ipsilateral leg as determined by lower paw withdrawal thresholds to a mechanical stimulus. Only those with significant hyperalgesia as determined by reduced threshold, measured in grams, to paw withdrawal to the von Frey filament were enrolled in the study. All animals enrolled in the study showed paw withdrawal thresholds of <12 g.

The paw withdrawal thresholds of animals from mechanical tactile stimuli were measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals were placed in an elevated Plexiglass enclosure set on a wire mesh surface. After 15 minutes of accommodation in this enclosure, a von Frey hair was applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals, with sufficient force, measured in grams, to elicit a crisp response of the paw. The response indicated a withdrawal from the painful stimulus and constituted the efficacy endpoint.

Following paw withdrawal baseline measurements, animals were randomly divided into 4 different test groups (N = 8 animals/ group), including a vehicle control group for oral dosage, a vehicle control group for topical dosage, and two treatment groups. For the oral dosage groups, animals were dosed by oral gavages after baseline measurement. Doses of COMPOUND A were chosen based on previous studies indicating that the oral dose of 25 mg/Kg of COMPOUND A produces an approximately half-maximal reversal of pain response and a level of efficacy comparable to that of the pharmaceutical composition of the invention comprising COMPOUND A at 8% (w/w). For the topical dosage groups, 50 mg of the test composition was applied on the ipsilateral ankle and foot. Animals were then placed in plastic tubes for 15 minutes, to prevent early removal/ingestion of drug. Subsequently, animals were placed in the Plexiglass enclosure for 15 minutes prior to paw withdrawal measurement. Von Frey withdrawal thresholds were measured as the mean of several independent determinations made within 1-2 minutes of each other on the affected paw of each animal. Withdrawal measurements were taken 60 minutes post dosing for the oral dosage group and 30 minutes post-dosing for the topical dosage group, representing their respective peak efficacy time points as determined in previous studies.

Blood samples were taken from the same animals immediately after withdrawal

threshold measurements using the following procedure at approximately 10-15 minutes after their respective efficacy time points. The rats were bled by jugular vein puncture while under anaesthesia. The time at which each blood sample was drawn, relative to the time of dosing, was recorded. Each blood sample (~ 150 µL) was collected into a heparin-coated, labelled microvette tube containing 10 µL of heparin (100 Units) and placed on ice immediately. The blood samples were centrifuged at 4 °C to separate the plasma. The plasma was transferred to labelled tubes and snap-frozen in liquid nitrogen for storage at -80 °C. At the time of analysis, the plasma was thawed and extracted using solid phase extraction, and the plasma drug concentration was quantified by HPLC/MS/MS.

The von Frey paw withdrawal data were analyzed using GraphPad Prism 5 statistical analysis software. One-way ANOVA was used for multivariate analysis with Bonferroni adjustment. Unpaired t-test was used for univariate analysis. Results are expressed as mean ± SEM. Values that reached a $p<.05$ level of significance were considered statistically significant.

Results

At baseline, there were no significant differences between the means of the von Frey paw withdrawal measurements for the four test groups.

The percent mean Change From Baseline (CFB) for each groups' paw withdrawal thresholds is shown in Figure 4. At 60 and 30-minute post-dosing, the CFB reached 44.3% for the 25 mg/Kg COMPOUND A oral dosage group and 47.1% for the 8% (w/w) COMPOUND A topical dosage group respectively, which was statistical significance ($p<0.001$) when compared to the vehicle groups and indicated an analgesic effect. No statistical significance was observed between the CFB of the oral and topical dosage groups ($p = .742$).

Plasma samples were collected from the animals immediately after von Frey testing. The systemic plasma concentration of COMPOUND A for the oral and topical dosage groups is shown in Figure 5. The plasma level of COMPOUND A in the topical dosage group was significantly lower (~20x) than the level in the oral dosage group ($p < .0001$).

8% (w/w) COMPOUND A by topical administration exhibited a degree of efficacy (47% CFB) that is comparable to 25 mg/kg COMPOUND A (44% CFB) by oral administration in the CCI neuropathic pain model. Systemic plasma exposure of COMPOUND A was significantly lower (~20x) in the topical dosage group than the oral dosage group. Therefore, COMPOUND A given by topical administration in the CCI

neuropathic pain model provides efficacy comparable to COMPOUND A by oral administration with minimal systemic exposure.

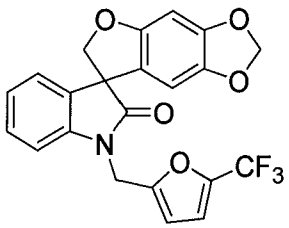
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Unless indicated otherwise, any U.S. patent, U.S. patent application publication, or PCT published patent application referred to in this specification is incorporated herein by reference in its entirety, including U.S. Provisional Patent Application No. 61/308,759.

Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

WHAT IS CLAIMED IS

1. A pharmaceutical composition for topical administration to a mammal comprising one or more pharmaceutically acceptable excipients and a therapeutically effective amount of a spiro-oxindole compound having the following formula:



as an enantiomer, a racemate or a non-racemic mixture of enantiomers, or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition of Claim 1 comprising two or more pharmaceutically acceptable excipients.

3. The pharmaceutical composition of Claim 2, wherein the pharmaceutically acceptable excipients are selected from one or more solvents, one or more penetration enhancing agents, one or more stiffening agents, or one or more ointment bases.

4. The pharmaceutical composition of Claim 3, further comprising one or more antioxidants.

5. The pharmaceutical composition of Claim 3 or 4, wherein each pharmaceutically acceptable excipient is present in a concentration of from about 0.01% w/w to about 99% w/w.

6. The pharmaceutical composition of Claim 5, wherein an solvent is selected from PEG 400 or PEG 3350, a penetration enhancing agent is selected from Transcutol® P, oleyl alcohol, or isopropyl myristate, a stiffening agent is stearyl alcohol, an ointment base is selected from PEG 400 or PEG 3350, and the antioxidant is butylated hydroxytoluene (BHT).

7. The pharmaceutical composition of Claim 6, wherein PEG 400 is

present in a concentration of from about 30% w/w to about 70% w/w, Transcutol® P is present in a concentration of from about 2% w/w to about 25% w/w, oleyl alcohol is present in a concentration of from about 1% w/w to about 10% w/w, isopropyl myristate is present in a concentration of from about 1% w/w to about 25% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 10% w/w, BHT is present in a concentration of from about 0.01% w/w to about 2% w/w, and PEG 3350 is present in a concentration of from about 10% w/w to about 50% w/w.

8. The pharmaceutical composition of Claim 7, wherein PEG 400 is present in a concentration of from about 45% w/w to about 55% w/w, Transcutol® P is present in a concentration of from about 5% w/w to about 15% w/w, oleyl alcohol is present in a concentration of from about 2.5% w/w to about 7.5% w/w, isopropyl myristate is present in a concentration of from about 2.5% w/w to about 7.5% w/w, stearyl alcohol is present in a concentration of from about 0.1% w/w to about 7.5% w/w, BHT is present in a concentration of from about 0.05% w/w to about 1% w/w, and PEG 3350 is present in a concentration of from about 15% w/w to about 30% w/w.

9. The pharmaceutical composition of Claim 8, wherein the spiro-oxindole compound is present in a concentration of from about 0.1% w/w to about 10% w/w.

10. The pharmaceutical composition of Claim 9, wherein the spiro-oxindole compound is present in a concentration of from about 2% w/w to about 8% w/w.

11. The pharmaceutical composition of Claim 1 comprising the spiro-oxindole compound at a concentration of 2.0% w/w; PEG 400 at a concentration of 52.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 5% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

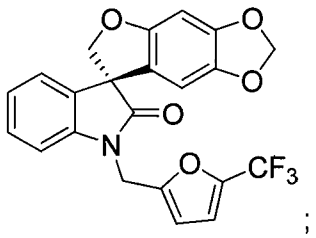
12. The pharmaceutical composition of Claim 1 comprising the spiro-oxindole compound at a concentration of 4% w/w; PEG 400 at a concentration of 50.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl

alcohol at a concentration of 5% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

13. The pharmaceutical composition of Claim 1 comprising the spiro-oxindole compound at a concentration of 4% w/w; PEG 400 at a concentration of 50.9% w/w; Transcutol® P at a concentration of 5% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 10% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

14. The pharmaceutical composition of Claim 1 comprising the spiro-oxindole compound at a concentration of 8% w/w; PEG 400 at a concentration of 46.9% w/w; Transcutol® P at a concentration of 10% w/w; oleyl alcohol at a concentration of 5% w/w; isopropyl myristate at a concentration of 5% w/w; stearyl alcohol at a concentration of 5% w/w; butylated hydroxytoluene at a concentration of 0.1% w/w; and PEG 3350 at a concentration of 20% w/w of the pharmaceutical composition.

15. The pharmaceutical composition of any one of Claims 1-14 wherein the spiro-oxindole compound is a compound of the following formula:



;

or a pharmaceutically acceptable salt thereof.

16. A method of treating, preventing or ameliorating a sodium channel-mediated disease or a condition in a mammal, wherein the method comprises topically administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of any one of Claims 1 to 15.

17. The method of Claim 16, wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, post-herpetic neuralgia, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-operative pain, pruritis, osteoarthritis, trigeminal neuralgia, familial erythromelalgia, primary erythromelalgia, familial rectal pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, and combinations thereof.

18. The method of Claim 16, wherein the mammal is a human.

19. A method of treating pain through inhibition of ion flux through a voltage-dependent sodium channel in a mammal, wherein the method comprises topically administering to the mammal in need thereof a therapeutically effective amount of a pharmaceutical composition of any one of Claims 1 to 15.

20. The method of Claim 19, wherein the mammal is a human.