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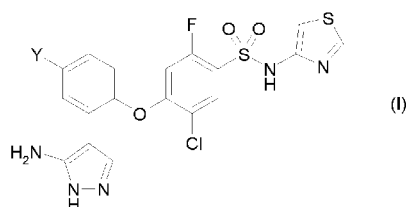
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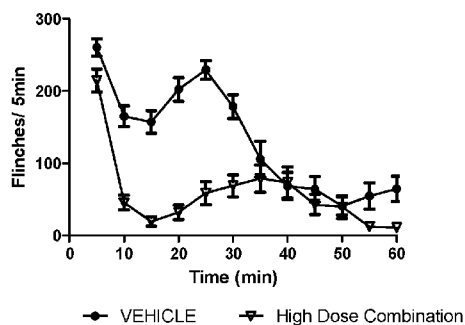
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(54) Title: PHARMACEUTICAL COMBINATIONS COMPRISING GABAPENTIN OR PREGABALIN WITH NAV1.7 INHIBITORS



(57) Abstract: The invention relates to a method of treating pain comprising the separate, sequential or simultaneous administration to an individual in need of such treatment of a therapeutically effective amount of a compound according to formula (I) or pharmaceutically acceptable salt thereof, wherein Y is -Cl or -CF₃; and of a therapeutically effective amount of gabapentin or pregabalin, or a pharmaceutically acceptable salt thereof.

Fig 3





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PHARMACEUTICAL COMBINATIONS COMPRISING GABAPENTIN OR PREGABALIN WITH NAV1.7 INHIBITORS

Field of the Invention

The invention relates to the treatment of pain using combinations of pharmaceutically
5 active agents. More particularly, this invention relates to the use of combinations of an
N-thiazolyl-4-phenoxybenzenesulfonamide derivative and a second pharmaceutically
active agent, and to pharmaceutical compositions containing them.

Background

- 10 The *N*-thiazolyl-4-phenoxybenzenesulfonamide derivatives that are the first component
of the combinations of the present invention are modulators of the Nav1.7 sodium
channel. The compounds are disclosed in International Patent Application
PCT/IB2010/050033, published as WO2010/079443.
- 15 Voltage-gated sodium channels are found in all excitable cells including myocytes of
muscle and neurons of the central and peripheral nervous system. In neuronal cells,
sodium channels are primarily responsible for generating the rapid upstroke of the
action potential. In this manner sodium channels are essential to the initiation and
propagation of electrical signals in the nervous system. Proper and appropriate function
20 of sodium channels is therefore necessary for normal function of the neuron.
Consequently, aberrant sodium channel function is thought to underlie a variety of
medical disorders (see Hubner C.A., Jentsch T.J., *Hum. Mol. Genet.*, **11(20)**: 2435-45
(2002) for a general review of inherited ion channel disorders) including epilepsy
(Yogeeswari *et al.*, *Curr. Drug Targets*, **5(7)**: 589-602 (2004)), arrhythmia (Noble D.,
25 *Proc. Natl. Acad. Sci. USA*, **99(9)**: 5755-6 (2002)), myotonia (Cannon, S.C., *Kidney Int.*
57(3): 772-9 (2000)), and pain (Wood, J.N. *et al.*, *J. Neurobiol.*, **61(1)**: 55-71 (2004)).

There are currently at least nine known members of the family of voltage-gated sodium
channel (VGSC) alpha subunits. Names for this family include SCN_x, SCNA_x, and
30 Nav_{x.x}. The VGSC family has been phylogenetically divided into two subfamilies
Nav1._x (all but SCN6A) and Nav2._x (SCN6A). The Nav1._x subfamily can be functionally
subdivided into two groups, those which are sensitive to blocking by tetrodotoxin (TTX-
sensitive or TTX-S) and those which are resistant to blocking by tetrodotoxin (TTX-
resistant or TTX-R).

An increasing body of evidence suggests that Na_v1.7 may play a key role in various pain states, including acute, inflammatory and/or neuropathic pain. Deletion of the SCN9A gene in nociceptive neurons of mice led to a reduction in mechanical and thermal pain thresholds and reduction or abolition of inflammatory pain responses (Nassar *et al.*, *Proc Natl Acad Sci USA*, **101**(34): 12706-11 (2004)). In humans, Na_v1.7 protein has been shown to accumulate in neuromas, particularly painful neuromas (Kretschmer *et al.*, *Acta. Neurochir. (Wien)*, **144**(8): 803-10 (2002)). Gain of function mutations of Na_v1.7, both familial and sporadic, have been linked to primary erythralgia, a disease characterized by burning pain and inflammation of the extremities (Yang *et al.*, *J. Med. Genet.*, **41**(3): 171-4 (2004), and paroxysmal extreme pain disorder (Waxman, *SG Neurology*, **7**;69(6): 505-7 (2007)). Congruent with this observation is the report that the non-selective sodium channel blockers lidocaine and mexiletine can provide symptomatic relief in cases of familial erythralgia (Legroux-Crepel *et al.*, *Ann. Dermatol Venereol.*, **130**: 429-433) and carbamazepine is effective in reducing the number and severity of attacks in PEPD (Fertleman *et al.*, *Neuron*, **52**(5):767-74 (2006). Further evidence of the role of Nav1.7 in pain is found in the phenotype of loss of function mutations of the SCN9A gene. Cox and colleagues (*Nature*, **444**(7121):894-8 (2006)) were the first to report an association between loss-of-function mutations of SNC9A and congenital indifference to pain (CIP), a rare autosomal recessive disorder characterized by a complete indifference or insensitivity to painful stimuli. Subsequent studies have revealed a number of different mutations that result in a loss of function of the SCN9A gene and and the CIP phenotype (Goldberg *et al.*, *Clin Genet.*; **71**(4): 311-9 (2007), Ahmad *et al.*, *Hum Mol Genet.* **1**;16(17): 2114-21 (2007)).

Na_v1.7 inhibitors are therefore potentially useful in the treatment of a wide range of disorders, particularly pain.

The second component of the combinations of the present invention is a pharmaceutically active agent selected from gabapentin and pregabalin.

Gabapentin (2-[1-(aminomethyl)cyclohexyl]acetic acid) and pregabalin ((S)-3-(aminomethyl)-5-methylhexanoic acid) are ligands for the $\alpha_2\text{-}\delta$ subunit of calcium channels. They have been reported to be effective in the treatment of neuropathic pain.

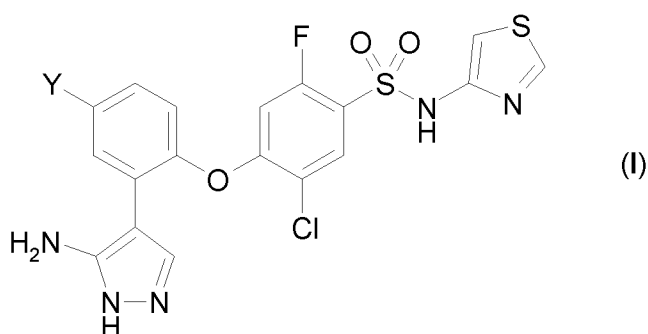
Gabapentin is marketed under the brand name Neurontin and pregabalin is marketed under the brand name Lyrica.

There is an ongoing need to provide improved methods for managing pain. The use as disclosed herein of a combination of a $\text{Na}_v1.7$ modulator and a modulator of activity at the α -2 delta subunit of calcium channels may afford a therapeutic regimen that provides: a greater efficacy; and/or the ability to use lower doses of the combination when compared to the individual agents; and/or an improved tolerability to the use of either agent alone.

Summary of the Invention

In a first aspect **A1**, the present invention provides a method of treating pain.

In a first embodiment **A1E1**, the present invention provides a method of treating pain comprising the administration to an individual in need of such treatment of a therapeutically effective amount of a compound according to formula (I)



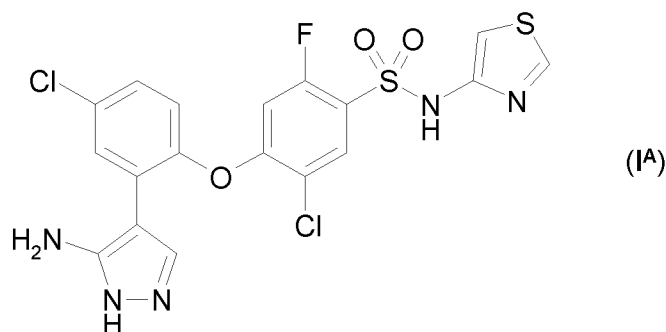
or a pharmaceutically acceptable salt thereof, wherein $-Y$ is $-\text{Cl}$ or $-\text{CF}_3$;

wherein said method further comprises the separate, sequential or simultaneous administration of a therapeutically effective amount of a second pharmaceutically active compound selected from gabapentin and pregabalin, or a pharmaceutically acceptable salt thereof.

In a further embodiment **A1E2**, the present invention provides the method of embodiment **A1E1** which consists essentially of the administration of a compound according to formula (I) and a second pharmaceutically active compound selected from gabapentin and pregabalin, or a pharmaceutically acceptable salt of one or both said compounds.

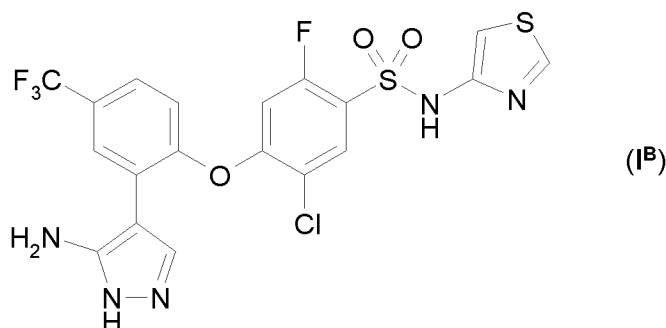
In a further embodiment **A1E3**, the present invention provides the method of embodiments **A1E1** or **A1E2**, wherein the compound according to formula (I) is 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-

5 yl)benzenesulfonamide (**I^A**) or a pharmaceutically acceptable salt thereof.



In a further embodiment **A1E4**, the present invention provides the method of embodiments **A1E1** or **A1E2**, wherein the compound according to formula (I) is 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-

10 yl)benzenesulfonamide (**I^B**) or a pharmaceutically acceptable salt thereof.



In a further embodiment **A1E5**, the present invention provides the method of any one of
15 embodiments **A1E1**, **A1E2**, **A1E3** and **A1E4**, wherein the second pharmaceutically active compound is gabapentin or a pharmaceutically acceptable salt thereof.

In a further embodiment **A1E6**, the present invention provides the method of any one of
20 embodiments **A1E1**, **A1E2**, **A1E3** and **A1E4**, wherein the second pharmaceutically active compound is pregabalin or a pharmaceutically acceptable salt thereof.

In a further embodiment **A1E7**, the present invention provides the method of any one of embodiments **A1E1**, **A1E2**, **A1E3**, **A1E4**, **A1E5** and **A1E6** wherein the compound according to formula (I) and the second pharmaceutically active compound are administered simultaneously.

5

In a further embodiment **A1E8**, the present invention provides the method of embodiment **A1E7**, wherein the compound according to formula (I) and the second pharmaceutically active compound are administered together as a single pharmaceutical dosage form.

10

In a further aspect **A2**, the present invention provides a combination of pharmaceutically active agents.

In a first embodiment **A2E1**, the present invention provides a combination comprising a compound according to formula (I) and a second pharmaceutically active compound, as defined in embodiments **A1E1** or **A1E2**, or a pharmaceutically acceptable salt of one or both said compounds.

15

In a further embodiment **A2E2**, the present invention provides the combination according to embodiment **A2E1** selected from:

20

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin;

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin;

25

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin; and

30

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin;

or a pharmaceutically acceptable salt of one or both said compounds.

In a further aspect **A3**, the present invention provides a pharmaceutical dosage form.

5 In a first embodiment **A3E1**, the present invention provides a pharmaceutical dosage form comprising a compound according to formula (I) and a second pharmaceutically active compound, as defined in any one of embodiments **A1E1**, **A1E2**, **A1E3**, **A1E4**, **A1E5** and **A1E6**, or a pharmaceutically acceptable salt of one or both said compounds; and one or more pharmaceutically acceptable excipients.

10 In a further embodiment **A3E2**, the present invention provides the pharmaceutical dosage form according to embodiment **A3E1** for use as a medicament.

In a further embodiment **A3E3**, the present invention provides the pharmaceutical dosage form according to embodiments **A3E1** or **A3E2** for use in the treatment of pain.

15 In a further aspect **A4**, the present invention provides a compound according to formula (I) as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, wherein the treatment further comprises the separate, sequential or simultaneous administration of a second pharmaceutically active compound as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof.

20 In a further embodiment **A4E1**, the present invention provides the compound according to aspect **A4** for use in the treatment of pain, wherein the treatment further consists essentially of the separate, sequential or simultaneous administration of a second compound as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof.

25 In a further aspect **A5**, the present invention provides a combination as defined in embodiment **A2E1** or **A2E2**, or a pharmaceutically acceptable salt of one or both said compounds, for use in the treatment of pain.

In a further aspect **A6**, the present invention provides the use of a compound according to formula (I) as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt

thereof, for the manufacture of a medicament for the treatment of pain, wherein the treatment further comprises the separate, sequential or simultaneous administration of of a second pharmaceutically active compound as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof.

5

In a further embodiment **A6E1**, the present invention provides the use of a compound according to aspect **A6**, wherein the treatment further consists essentially of the separate, sequential or simultaneous administration of a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof.

10

In a further aspect **A7**, the present invention provides the use of a combination as defined in embodiment **A2E1** or **A2E2**, or a pharmaceutically acceptable salt of one or both said compounds, for the manufacture of a medicament for the treatment of pain.

15 In a further aspect **A8**, the present invention provides a kit comprising:

- (i) a pharmaceutical dosage form comprising a compound according to formula (I) as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient; and

20

- (ii) a pharmaceutical dosage form comprising a second pharmaceutically active compound as defined in embodiment **A1E1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

25 for use in the the treatment of pain.

In a further embodiment **A8E1**, the present invention provides the kit of aspect **A8** for use in pain which consists essentially of pharmaceutical dosage forms (i) and (ii).

30 Brief Description of the Drawings

Fig 1 is a graphical representation of the degree of flinching over time for the high dose of pregabalin (Group 5).

Fig 2 is a graphical representation of the degree of flinching over time for the high dose of the compound of formula (**I^B**) (Group 3).

Fig 3 is a graphical representation of the degree of flinching over time for the high dose combination of the compound of formula (I^B) and pregabalin (Group 7).

Fig 4 is a graphical representation of the degree of flinching over time for the low dose of pregabalin (Group 4).

5 Fig 5 is a graphical representation of the degree of flinching over time for the high dose of the compound of formula (I^B) (Group 2).

Fig 6 is a graphical representation of the degree of flinching over time for the low dose combination of the compound of formula (I^B) and pregabalin (Group 6).

10 Fig 7.1 is a visualisation using posterior distribution plots on the log scale of the high dose combination during phase 2.

Fig 7.2 is a visualisation using posterior distribution plots on the log scale of the high dose combination during phase 2a.

15 Detailed description of the Invention

As used herein, the term “combinations of the invention” refers to a combination of a compound of formula (I) and a second pharmaceutically active compound, including:

20 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin;

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin;

25 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin; and

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin.

30

The terms “treatment”, “treating” and the like refer to palliative, curative and prophylactic treatment. In the context of the treatment of pain resulting from an injury or pathological condition, it will be understood that it is the pain that is being treated rather than the underlying cause of the pain.

“Separate” administration refers to a therapeutic regimen in which the two agents are administered according to independent schedules. It includes the possibility that, where multiple doses of each agent are administered, then some of the doses may be taken together.

“Sequential” administration refers to a therapeutic regimen in which the two agents are administered according to the same schedule.

10 “Simultaneous” administration refers to a therapeutic regimen in which the two agents are administered together in a single action.

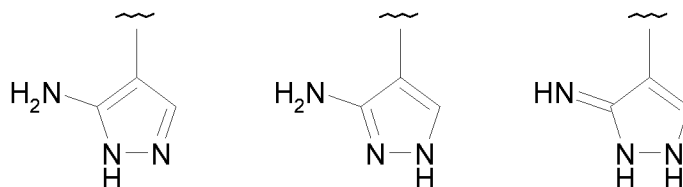
A method of treatment “which consists essentially of the administration of a compound according to formula (I) and a second pharmaceutically active compound selected from gabapentin and pregabalin, or a pharmaceutically acceptable salt of one or both said compounds” refers to a method consisting of the administration of two, and only two, pharmaceutically active agents.

The term “consists essentially of” when used in connection with:

- 20 a combination of a compound according to formula (I) and a second pharmaceutically active compound;
a compound according to formula (I) for use in the treatment of pain wherein the treatment involves a second pharmaceutically active compound;
use of a compound according to formula (I) in the manufacture of a medicament for
25 the treatment of pain wherein the treatment involves a second pharmaceutically active compound; and
a kit of pharmaceutical dosage forms of a compound according to formula (I) and a second pharmaceutically active compound;

has the same meaning as that described just above in connection with a method of
30 treatment.

The compounds of formula (I) may exist in tautomeric forms. Specifically, the aminopyrazole moiety may exist in one or more of the following forms:



All such tautomers and mixtures of tautomers are included within the scope of the present invention. References herein to specific compounds should be understood to refer to the compound and/or its tautomer.

The compounds of formula (I) are capable of forming pharmaceutically acceptable addition salts with acids, and these salts may be used in the invention. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate salts.

Gabapentin and pregabalin have been reported to form salts with both acids and bases. The skilled person will appreciate that the aforementioned salts include ones wherein the counterion is optically active, for example d-lactate or l-lysine, or racemic, for example dl-tartrate or dl-arginine.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (I), gabapentin and pregabalin may be prepared by one or more of three methods:

- i) by reacting the compound of formula (I), gabapentin or pregabalin with the desired acid or base;
 - ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I), gabapentin or pregabalin using the desired acid or base;
 - 5 or
 - iii) by converting one salt of the compound of formula (I), gabapentin or pregabalin to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.
- 10 All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.
- 15 The compounds of formula (I), gabapentin and pregabalin, or pharmaceutically acceptable salts thereof, may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound of formula (I), gabapentin or pregabalin, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable solvent molecules, for example ethanol. The
- 20 term 'hydrate' is employed when said solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone and d₆-DMSO.
- A currently accepted classification system for organic hydrates is one that defines
- 25 isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995), incorporated herein by reference. Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are
- 30 next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly

bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

- 5 The compounds of formula (I), gabapentin and pregabalin may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while
10 exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such
15 materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

- The compounds of formula (I) may be prepared by the methods disclosed in
20 International Patent Application PCT/IB2010/050033, published as WO2010/079443, the disclosure of which is incorporated herein by reference, or by any other method known in the art for the preparation of compounds of analogous structure. Compound (I^A) is Example 788 of WO2010/079443 and compound (I^B) is Example 1029 thereof.

- 25 Gabapentin and pregabalin are well known compounds and may be prepared by methods disclosed in the literature.

- The compounds of formula (I), gabapentin and pregabalin may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation,
30 crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds of formula (I), gabapentin and pregabalin may be administered separately or in combination. Generally, they will be administered as a formulation in

association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compounds of formula (I), gabapentin and pregabalin. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of combinations of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in "Remington's Pharmaceutical Sciences", 19th Edition (Mack Publishing Company, 1995).

Suitable modes of administration include oral, parenteral, topical, inhaled/intranasal, rectal/intravaginal, and ocular/aural administration. When the compounds of formula (I), gabapentin and pregabalin are administered separately they may be administered by different routes.

Formulations suitable for the aforementioned modes of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays, liquid formulations and buccal/mucoadhesive patches..

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or

suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight

%, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

5 Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-
10 granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

15

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma et al (2001). The use of chewing gum to
20 achieve controlled release is described in WO 00/35298.

The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial,
25 intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients
30 such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

- 5 The solubility of compounds of formula (I), gabapentin and pregabalin used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-,
10 controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(dl-lactic-coglycolic)acid (PGLA) microspheres.

15

- The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants,
20 sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

- 25 Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

- The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, can
30 also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using

electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

5

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound of formula (I), gabapentin or pregabalin, or a combination thereof, comprising, for example: ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active; a propellant(s) as
10 solvent; and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be
15 achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters
20 and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose,
25 sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compounds of formula (I), gabapentin or pregabalin per actuation and the actuation volume may vary from 1µl to
30 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

- 5 In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1µg to 100mg of the compounds of formula (I), gabapentin or pregabalin. The overall daily dose will typically be in the range 1µg to 200mg which may be administered in a
10 single dose or, more usually, as divided doses throughout the day.

The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may be administered rectally or vaginally, for example, in the form of a suppository, pessary, microbicide, vaginal ring or enema. Cocoa butter is a traditional suppository base, but
15 various alternatives may be used as appropriate.

The compounds of formula (I), gabapentin and pregabalin, or combinations thereof, may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other
20 formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example,
25 hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

30 The compounds of formula (I), gabapentin and pregabalin may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO91/11172, WO94/02518 and WO98/55148.

For administration to human patients, the total daily dose of the compounds of formula (I) is typically in the range 10mg to 5g, such as 100mg to 3g, for example 250mg to 2g depending, of course, on the mode of administration and efficacy. The total daily dose of gabapentin is typically in the range 200mg to 3g, such as 500mg to 2.5g, for example 900mg to 1.8g. The total daily dose of pregabalin is typically in the range 50mg to 1g, such as 150mg to 750mg, for example 300mg to 600mg. For example, oral administration may require a total daily dose of from 300mg to 2g of a compound of formula (I) and from 750mg to 2g of gabapentin, or from 150mg to 600mg of pregabalin.

The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Disorders for which the combinations of the invention are indicated include pain. Pain may be either acute or chronic and additionally may be of central and/or peripheral origin. Pain may be of a neuropathic and/or nociceptive and/or inflammatory nature, such as pain affecting either the somatic or visceral systems, as well as dysfunctional pain affecting multiple systems.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Meyer et al., 2006, Wall and Melzack's

Textbook of Pain (5th Ed), Chapter1). These sensory fibres are known as nociceptors, and are characteristically small diameter axons with slow conduction velocities, of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually twelve weeks or less). It is usually, although not always, associated with a specific cause such as a defined injury, is often sharp and severe and can result from numerous origins such as surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation may be altered such that there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury or alteration which can be associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768). As such, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy or postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain, but may include any chronic painful condition affecting any system, such as those described by the International Association for the Study of Pain (Classification of Chronic Pain, a publication freely available for download at <http://www.iasp-pain.org>).

The clinical manifestation of pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms can include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia) (Meyer et al., 2006, Wall and Melzack's Textbook of Pain (5th Ed), Chapter1). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Apart from acute or chronic, pain can also be broadly categorized into: nociceptive pain, affecting either the somatic or visceral systems, which can be inflammatory in nature (associated with tissue damage and the infiltration of immune cells); or neuropathic pain.

Nociceptive pain can be defined as the process by which intense thermal, mechanical, or chemical stimuli are detected by a subpopulation of peripheral nerve fibers, called nociceptors, and can be induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 2006, Wall and Melzack's Textbook of Pain (5th Ed), Chapter1). Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, pain associated with gout, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy). Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Nociceptive pain can also be related to inflammatory states. The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (McMahon et al., 2006, Wall and Melzack's Textbook of Pain (5th Ed), Chapter3). A
5 common inflammatory condition associated with pain is arthritis. It has been estimated that almost 27 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease (Lawrence et al., 2008, Arthritis Rheum, 58, 15-35); most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a
10 significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Rheumatoid arthritis is an immune-mediated, chronic, inflammatory polyarthritis disease, mainly affecting peripheral synovial joints. It is one of the commonest chronic inflammatory conditions in developed countries and is a major cause of pain.

15 In regard to nociceptive pain of visceral origin, visceral pain results from the activation of nociceptors of the thoracic, pelvic, or abdominal organs (Bielefeldt and Gebhart, 2006, Wall and Melzack's Textbook of Pain (5th Ed), Chapter48). This includes the reproductive organs, spleen, liver, gastrointestinal and urinary tracts, airway structures, cardiovascular system and other organs contained within the abdominal cavity. As such
20 visceral pain refers to pain associated with conditions of such organs, such as painful bladder syndrome, interstitial cystitis, prostatitis, ulcerative colitis, Crohn's disease, renal colic, irritable bowel syndrome, endometriosis and dysmenorrhea (Classification of Chronic Pain, available at <http://www.iasp-pain.org>). Currently the potential for a neuropathic contribution (either through central changes or nerve injury/damage) to
25 visceral pain states is poorly understood but may play a role in certain conditions (Aziz et al., 2009, Dig Dis 27, Suppl 1, 31-41)

Neuropathic pain is currently defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Nerve damage can be caused by
30 trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia,

multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Dworkin, 2009, Am J Med, 122, S1-S2; Geber et al., 2009, Am J Med, 122, S3-S12; Haanpaa et al., 2009, Am J Med, 122, S13-S21). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Dworkin, 2009, Am J Med, 122, S1-S2; Geber et al., 2009, Am J Med, 122, S3-S12; Haanpaa et al., 2009, Am J Med, 122, S13-S21). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain, cancer pain and even migraine headaches may include both nociceptive and neuropathic components.

Similarly other types of chronic pain, perhaps less well understood, are not easily defined by the simplistic definitions of nociceptive or neuropathic. Such conditions include in particular fibromyalgia and chronic regional pain syndrome, which are often described as dysfunctional pain states e.g. fibromyalgia or complex regional pain syndrome (Woolf, 2010, J Clin Invest, 120, 3742-3744), but which are included in classifications of chronic pain states (Classification of Chronic Pain, available at <http://www.iasp-pain.org>).

The combinations of the invention may optionally be used in combination with one or more further pharmacologically active compounds. Such combinations offer the possibility of further significant advantages, including patient compliance, ease of dosing and synergistic activity.

In the combinations that follow the combination of the invention may be administered simultaneously, sequentially or separately in combination with the other therapeutic agent or agents.

Useful further pharmacologically active agents include one or more agents selected from:

- a selective Nav1.3 channel modulator, such as a compound disclosed in WO2008/118758;
- 5 • a selective Nav1.8 channel modulator, such as a compound disclosed in WO2013/114250;
- a selective Nav1.9 channel modulator;
- a compound which modulates activity at more than one Nav channel, including a non-selective modulator such as bupivacaine, carbamazepine, lamotrigine, lidocaine, mexiletine or phenytoin;
- 10 • any inhibitor of nerve growth factor (NGF) signaling, such as: an agent that binds to NGF and inhibits NGF biological activity and/or downstream pathway(s) mediated by NGF signaling (e.g. tanezumab), a TrkA antagonist or a p75 antagonists, or an agent that inhibits downstream signaling in regard to NGF stimulated TrkA or P75 signalling;
- 15 • an inhibitor of neurotrophic pathways, where such inhibition is achieved by: (a) an agent that binds to nerve growth factor (NGF) (e.g. tanezumab, fasinumab or fulranumab), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) or neurotrophin-4 (NT-4), or to more than one of the aforementioned neurotrophins (e.g. soluble P75); or (b) an agent that inhibits receptor function at one or more of TrkA, TrkB, TrkC or P75, either at the orthosteric site, an allosteric site or by inhibition of the catalytic activity of the receptor(s);
- 20 • a compound which increases the levels of endocannabinoid, such as a compound with fatty acid amid hydrolase inhibitory (FAAH) or monoacylglycerol lipase (MAGL) activity;
- 25 • an analgesic, in particular paracetamol;
- an opioid analgesic, such as: buprenorphine, butorphanol, cocaine, codeine, dihydrocodeine, fentanyl, heroin, hydrocodone, hydromorphone, levallorphan, levorphanol, meperidine, methadone, morphine, nalmefene, nalorphine, naloxone, naltrexone, nalbuphine, oxycodone, oxymorphone, propoxyphene or pentazocine;
- 30 • an opioid analgesic which preferentially stimulates a specific intracellular pathway, for example G-protein as opposed to beta arrestin recruitment, such as TRV130; an opioid analgesic with additional pharmacology, such as: noradrenaline

(norepinephrine) reuptake inhibitory (NRI) activity, e.g. tapentadol; serotonin and norepinephrine reuptake inhibitory (SNRI) activity, e.g. tramadol; or nociceptin receptor (NOP) agonist activity, such as GRT6005;

- a nonsteroidal antiinflammatory drug (NSAID), such as a non-selective cyclooxygenase (COX) inhibitor, e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac; or a COX-2 selective inhibitor, e.g. celecoxib, deracoxib, etoricoxib, mavacoxib or parecoxib;
- a prostaglandin E₂ subtype 4 (EP4) antagonist;
- a microsomal prostaglandin E synthase type 1 (mPGES-1) inhibitor;
- a sedative, such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a GABA_A modulator with broad subtype modulatory effects mediated via the benzodiazepine binding site, such as chlordiazepoxide, alprazolam, diazepam, lorazepam, oxazepam, temazepam, triazolam, clonazepam or clobazam;
- a GABA_A modulator with subtype-selective modulatory effects mediated via the benzodiazepine binding site with reduced adverse effects, for example sedation, such as TPA023, TPA023B, L-838,417, CTP354 or NSD72;
- a GABA_A modulator acting via alternative binding sites on the receptor, such as barbiturates, e.g. amobarbital, aprobarbital, butabital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, or thiopental; neurosteroids such as alphaxalone, alphadolone or ganaxolone; β -subunit ligands, such as etifoxine; or δ -preferring ligands, such as gaboxadol;
- a GlyR3 agonist or positive allosteric modulator;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, metaxolone, methocarbamol or orphenadrine;
- a glutamate receptor antagonist or negative allosteric modulator, such as an NMDA receptor antagonist, e.g. dextromethorphan, dextrophan, ketamine or, memantine; or an mGluR antagonist or modulator;
- an alpha-adrenergic, such as clonidine, guanfacine or dexmetatomidine;
- a beta-adrenergic such as propranolol;

- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- a tachykinin (NK) antagonist, such as aprepitant or maropitant;
- a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- 5 • a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), varenicline or nicotine;
- a Transient Receptor Potential V1 (TRPV1) receptor agonist (e.g. resiniferatoxin or capsaicin) or antagonist (e.g. capsazepine or mavatrap);
- a Transient Receptor Potential A1 (TRPA1) receptor agonist (e.g. cinnamaldehyde or mustard oil) or antagonist (e.g. GRC17536 or CB-625);
- 10 • a Transient Receptor Potential M8 (TRPM8) receptor agonist (e.g. menthol or icilin) or antagonist;
- a Transient Receptor Potential V3 (TRPV3) receptor agonist or antagonist (e.g. GRC-15300);
- 15 • a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist, such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist;
- a PDEV inhibitor, such as sildenafil, tadalafil or vardenafil;
- 20 • an alpha-2-delta ligand such as gabapentin, gabapentin enacarbil or pregabalin ;
- a serotonin reuptake inhibitor (SRI) such as sertraline, demethylsertraline, fluoxetine, norfluoxetine, fluvoxamine, paroxetine, citalopram, desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiopin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- 25 • anNRI, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine, especially a selective noradrenaline reuptake inhibitor such as reboxetine;
- an SNRI, such as venlafaxine, O-desmethylvenlafaxine, clomipramine, desmethylclomipramine, duloxetine, milnacipran and imipramine;
- 30 • an inducible nitric oxide synthase (iNOS) inhibitor;
- a leukotriene B4 antagonist;
- a 5-lipoxygenase inhibitor, such as zileuton;

- a potassium channel opener or positive modulator, such as an opener or positive modulator of KCNQ/Kv7 (e.g. retigabine or flupirtine), a G protein-coupled inwardly-rectifying potassium channel (GIRK), a calcium-activated potassium channel (Kca) or a potassium voltage-gated channel such as a member of subfamily A (e.g. Kv1.1),
5 subfamily B (e.g. Kv2.2) or subfamily K (e.g. TASK, TREK or TRESK);
- a P2X₃ receptor antagonist (e.g. AF219) or an antagonist of a receptor which contains as one of its subunits the P2X₃ subunit, such as a P2X_{2/3} heteromeric receptor;
- a Cav2.2 calcium channel blocker (N-type), such as ziconotide; and
10 • a Cav3.2 calcium channel blocker (T-type), such as ethosuximide.

There is also included within the scope the present invention combinations of the combinations of the invention together with one or more additional therapeutic agents which slow down the rate of metabolism of the compound of the invention, thereby
15 leading to increased exposure in patients. Increasing the exposure in such a manner is known as boosting. This has the benefit of increasing the efficacy of the compound of the invention or reducing the dose required to achieve the same efficacy as an unboosted dose. The metabolism of the compounds of the invention includes oxidative processes carried out by P450 (CYP450) enzymes, particularly CYP 3A4 and
20 conjugation by UDP glucuronosyl transferase and sulphating enzymes. Thus, among the agents that may be used to increase the exposure of a patient to a compound of the present invention are those that can act as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9,
25 CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP 3A4 include ritonavir, saquinavir, ketoconazole, N-(3,4-difluorobenzyl)-N-methyl-2-[[4-methoxypyridin-3-yl)amino]sulfonyl}benzamide and N-(1-(2-(5-(4-fluorobenzyl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetyl)piperidin-4-yl)methanesulfonamide.

30 It is within the scope of the invention that two or more pharmaceutical compositions, at least one of which contains a compound of formula (I) and one of which contains gabapentin or pregabalin, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a

compound of formula (I) and one of which contains gabapentin or pregabalin, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like. The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

Experimental

In vivo evaluation in mice

Animals: Male CD-1 mice (Charles River, Raleigh, NC) weighing 27-36 grams on the day of dosing were housed five per cage. Animals had free access to food and water and were maintained on a 12:12 hour light/dark schedule.

Compounds and dosing solutions: The Compound of formula (I^B) and pregabalin were formulated as solutions in 0.5% methyl cellulose. The high and low dose combinations were formulated together in 0.5% methyl cellulose into a single suspension for oral dosing. Compounds were dosed via oral gavage at 10mL/kg.

Experimental procedure: Animals were tested for paw movement responses to an injection of a 2.5% formalin solution (20 µl in saline) using the Automated Nociception Analyzer (Yaksh *et al.*, 2001). This device uses a magnetic detection system to measure paw movements defined as flinches. Small metal bands were attached to the left hind paw of mice just before placement into individual circular test chambers (4 mice per session) 60 minutes prior to formalin injection. Mice were orally administered test compounds 2 hours prior to formalin injection. To initiate the experiment mice were injected with 20 µl of 2.5% formalin subcutaneously on the dorsal surface of the left hind paw and placed in the test chambers. The instrument then recorded rapid foot movements counted in one minute bins continuously for 60 minutes.

Treatment groups were assigned to balance treatments across days and across test chambers.

Immediately following the 60 minute flinching observation, the mice were euthanized and blood and brain tissue were removed for bioanalysis of the compound of formula (I^B) and pregabalin levels.

Experimental groups: Table 1 summarizes the groups tested in the study.

Group	Pregabalin dose (mg/kg – 'mpk')	Compound (I ^B) dose (mg/kg – 'mpk')	Vehicle	Dose volume mL/kg	No. of mice
1	0	0	0.5% methyl cellulose	10	14
2	0	30	0.5% methyl cellulose	10	15
3	0	100	0.5% methyl cellulose	10	15
4	10	0	0.5% methyl cellulose	10	16
5	30	0	0.5% methyl cellulose	10	15
6	10	30	0.5% methyl cellulose	10	16
7	30	100	0.5% methyl cellulose	10	16

Group 6 low dose combination
Group 7 high dose combination

Excluded animals: One mouse was excluded from both the vehicle group and from the compound of formula (I^B) 30 mg/kg group because of an incomplete formalin injection. One mouse was excluded from the compound of formula (I^B) 100 mg/kg group because the metal paw band fell off during the course of the flinching study. One mouse was excluded from the pregabalin 30mg/kg group because it only received a partial dose of test compound.

Data analysis: The total flinches were counted over particular time intervals or phases.

The phases summarized in this study were:

Phase 1: 0-9 minutes

Phase 2: 10-60 minutes

5 Phase 2a: 10-40 minutes

Flinching events were automatically recorded by the Automated Nociception Analyzer (Yaksh *et al.*, 2001) and the total number of flinches for each phase was calculated automatically. The results for each experimental group are set out in tables 2.1 to 2.7
10 below.

Table 2.1: Vehicle (Group 1)

Animal #	Total number of flinches counted at 5 minute intervals											
	5	10	15	20	25	30	35	40	45	50	55	60
1	178	121	97	97	218	195	210	203	102	61	163	93
2	266	149	77	150	213	71	15	61	11	0	0	0
3	302	187	240	267	229	256	32	16	14	97	52	5
4	317	204	210	220	273	275	247	226	227	132	80	96
5	283	105	71	234	240	175	27	30	48	7	18	0
6	290	196	208	293	293	215	68	15	3	0	0	30
7	310	241	198	288	230	188	86	31	26	78	124	206
8	270	217	180	233	228	173	137	79	125	106	103	93
9	225	157	172	190	189	154	149	49	76	2	1	3
10	263	138	116	96	313	210	283	29	15	14	9	136
11	195	51	92	197	149	163	145	137	16	2	4	123
12	201	140	139	178	153	123	6	34	10	33	202	103
13	268	168	238	208	210	235	69	44	96	4	0	0
14	279	237	160	183	273	66	5	4	129	31	7	18
mean	261	165	157	202	229	179	106	68	64	41	55	65
SEM	12	14	16	16	13	16	25	19	17	12	18	18

Table 2.2: Compound (I^B) 30 mg/kg (Group 2)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	293	172	194	197	242	282	210	208	134	167	248	200
2	340	260	239	291	242	298	182	125	72	61	60	25
3	302	61	192	209	252	239	119	49	29	30	15	14
4	278	68	51	219	210	164	258	174	56	39	20	16
5	266	126	128	173	188	26	32	23	14	10	3	4
6	316	239	202	293	299	309	213	141	232	58	57	204
7	294	289	247	221	293	270	134	123	9	10	0	23
8	216	190	161	269	184	102	62	48	17	10	4	7
9	229	150	98	63	186	177	155	110	82	22	58	24
10	203	96	183	298	227	174	154	103	18	96	25	103
11	285	69	208	155	297	299	230	224	147	126	10	5
12	253	184	85	150	248	114	81	9	11	9	146	48
13	332	202	200	243	221	178	125	190	185	210	7	54
14	332	179	135	290	310	100	160	35	6	4	4	63
15	291	133	236	238	293	174	260	119	46	147	103	157
mean	282	161	171	221	246	194	158	112	71	67	51	63
SEM	11	18	15	17	11	22	18	18	19	17	18	18

Table 2.3: Compound (I^B) 100 mg/kg (Group 3)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	318	191	56	32	16	14	117	145	133	225	161	116
2	280	106	219	41	74	76	28	20	7	30	7	9
3	210	63	1	0	36	75	62	56	66	37	42	11
4	296	147	137	215	265	154	199	189	68	67	155	239
5	285	203	138	181	169	130	127	82	60	26	23	6
6	178	91	22	96	144	68	46	17	15	33	12	24
7	289	111	63	123	189	173	72	45	42	39	11	5
8	214	314	335	84	35	1	12	13	14	0	0	0
9	208	128	175	61	44	114	138	9	0	0	0	74

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
10	207	154	94	65	123	85	46	56	75	26	30	9
11	317	205	134	213	210	136	24	23	21	11	9	6
12	300	255	166	60	88	288	143	49	29	35	21	89
13	276	222	185	124	57	171	144	44	51	28	17	132
14	258	183	134	169	142	175	172	124	67	35	3	35
15	286	94	89	108	133	263	112	116	258	105	24	17
mean	261	164	130	105	115	128	96	66	60	46	34	51
SEM	12	18	22	17	19	21	15	14	17	14	13	17

Table 2.4: Pregabalin 10 mg/kg (Group 4)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	322	65	5	186	182	202	34	28	56	152	12	8
2	258	109	170	313	318	173	75	328	226	186	107	96
3	291	106	144	197	217	157	163	33	5	6	6	3
4	198	95	7	61	172	110	144	88	29	60	2	0
5	321	217	209	224	210	112	73	170	10	1	4	0
6	239	43	28	283	235	235	158	87	32	5	2	4
7	294	149	163	281	244	198	191	51	8	76	127	34
8	154	49	6	0	32	123	67	96	61	22	13	5
9	259	186	2	74	11	165	144	22	109	114	140	159
10	280	105	71	286	258	24	12	5	8	6	0	0
11	223	63	8	134	177	134	42	12	9	2	12	0
12	192	62	36	154	166	139	54	5	0	2	0	1
13	249	112	84	148	248	154	122	98	12	13	10	10
14	287	209	159	219	285	260	198	293	219	229	35	11
15	202	52	83	211	181	129	168	35	78	7	2	40
16	176	91	83	21	78	103	114	58	7	2	0	0
mean	247	107	79	175	188	151	110	88	54	55	30	23
SEM	13	14	18	24	21	14	15	24	18	19	12	11

Table 2.5: Pregabalin 30 mg/kg (Group 5)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	199	63	66	103	126	30	6	5	4	2	113	0
2	243	173	23	118	192	202	251	124	32	79	11	4
3	174	11	27	139	221	95	174	42	28	6	9	7
4	137	7	0	76	112	125	27	7	6	6	16	71
5	103	28	25	162	79	94	57	82	16	8	14	32
6	197	194	111	145	231	150	35	12	200	155	0	5
7	243	74	76	125	297	248	173	58	22	17	43	1
8	245	86	41	33	195	121	64	0	0	0	0	24
9	78	0	91	157	131	67	1	1	0	0	26	41
10	241	125	4	135	162	199	88	128	41	26	22	148
11	282	153	118	294	316	213	102	145	1	2	1	0
12	163	5	0	0	67	101	29	0	0	0	0	0
13	229	187	37	102	175	170	72	154	8	10	17	73
14	172	56	0	186	154	173	80	3	4	6	94	22
15	213	164	103	213	171	43	32	13	1	0	99	91
mean	195	88	48	133	175	135	79	52	24	21	31	35
SEM	15	19	11	18	18	17	18	15	13	11	10	11

Table 2.6: Low Dose Combination (Group 6)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	295	100	48	143	234	156	59	130	18	17	20	11
2	288	75	122	250	198	122	14	44	18	11	5	40
3	199	56	16	88	86	86	84	30	28	64	11	7
4	239	106	69	131	192	56	6	28	6	5	0	0
5	270	119	126	231	181	73	287	134	17	10	6	8
6	258	93	205	322	337	284	168	66	31	0	0	208
7	119	71	165	140	52	224	95	68	66	42	41	114
8	193	23	71	146	264	167	65	53	10	6	1	0
9	281	51	28	32	233	263	111	23	152	91	3	12

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
10	245	158	161	89	233	223	107	127	51	75	22	14
11	242	108	49	203	180	199	115	12	6	10	5	158
12	135	11	1	1	23	42	49	22	18	10	0	1
13	273	121	27	175	188	191	43	16	11	11	3	43
14	230	142	109	256	178	99	86	5	3	1	3	100
15	184	56	8	132	171	113	80	27	31	1	0	0
16	133	45	35	86	29	58	25	0	0	0	0	22
mean	224	83	78	152	174	147	87	49	29	22	8	46
SEM	14	10	16	21	22	19	17	11	9	7	3	16

Table 2.7: High Dose Combination (Group 7)

	Total number of flinches counted at 5 minute intervals											
Animal #	5	10	15	20	25	30	35	40	45	50	55	60
1	130	10	11	25	0	61	20	12	1	0	0	0
2	179	2	2	1	2	40	101	101	63	53	20	11
3	247	44	1	2	4	0	1	25	58	15	10	4
4	274	22	4	99	168	105	44	17	7	0	0	2
5	162	14	8	9	0	5	109	23	10	1	0	0
6	257	106	11	14	6	6	98	58	38	52	25	38
7	265	69	24	17	153	73	274	275	236	140	24	13
8	120	5	14	0	0	20	4	42	34	50	31	21
9	75	76	12	69	18	19	0	2	51	46	33	20
10	292	56	2	8	94	147	174	245	76	25	23	28
11	264	58	96	32	35	53	148	100	38	2	7	5
12	239	15	0	38	119	154	35	5	4	2	1	8
13	259	84	14	63	145	180	99	11	20	8	0	0
14	225	19	42	0	53	90	106	165	19	233	17	2
15	243	135	64	136	126	142	11	2	1	2	3	10
16	201	11	2	1	13	6	37	91	29	0	1	10
mean	215	45	19	32	59	69	79	73	43	39	12	11
SEM	16	10	7	10	16	15	19	22	14	16	3	3

Graphical representation of the time course of flinching for both the high dose and low dose combinations are shown in, respectively Figs 1 to 3 and 4 to 6.

- 5 The total numbers of flinches within each phase were analyzed separately on the log scale using a linear model accounting for experimental day. Individual treatment comparisons were performed and summarized using means, differences, 95% confidence intervals and p-values. Results for the high dose Phase 2 and Phase 2a total flinches, where a statistically significant additive effect was seen, are visualized in
10 Figs 7.1 and 7.2 using posterior distribution plots of the treatment means on the log scale.

Results:

- The high dose combination resulted in a significant additive effect in Phase 2 and Phase
15 2a ($p < 0.01$). In Phase 2 flinching was decreased by 30%, 40% and 69% by the compound of formula (I^B) 100 mg/kg, pregabalin 30 mg/kg and the combination dose, respectively. In Phase 2a flinching was decreased by 36%, 38% and 74% by the compound of formula (I^B) 100 mg/kg, pregabalin 30 mg/kg and the combination dose, respectively.

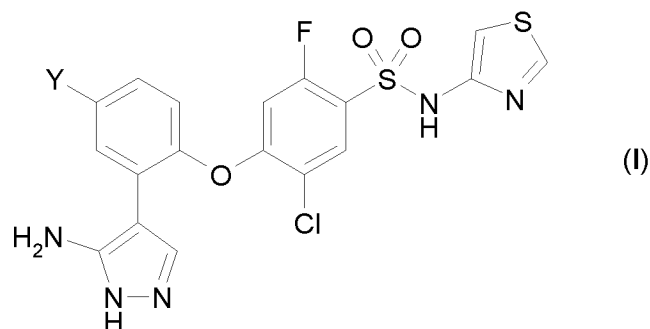
20

In vivo evaluation in a man

- The combined effects of pregabalin and Nav 1.7 blockade may also be examined in clinical pain studies. Clinical studies can examine single or multiple doses of either or both agents in exploratory pain endpoints in healthy volunteers or patients. Clinical
25 studies can also be carried out in pain patient populations employing, for example, parallel group, cross-over or randomised withdrawal study designs.

Claims

1. A method of treating pain comprising the administration to an individual in need of such treatment of a therapeutically effective amount of a compound of formula (I)



- or a pharmaceutically acceptable salt thereof, wherein $-\text{Y}$ is $-\text{Cl}$ or $-\text{CF}_3$; wherein said method further comprises the separate, sequential or simultaneous administration of a therapeutically effective amount of a second pharmaceutically active compound selected from gabapentin and pregabalin, or a pharmaceutically acceptable salt thereof.
2. The method according to claim 1 which consists essentially of the administration of a compound according to formula (I) and a second pharmaceutically active compound selected from gabapentin and pregabalin, or a pharmaceutically acceptable salt of one or both said compounds.
 3. The method according to either claim 1 or claim 2 wherein the compound according to formula (I) is 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide or a pharmaceutically acceptable salt thereof.
 4. The method according to either claim 1 or claim 2 wherein the compound according to formula (I) is 4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide or a pharmaceutically acceptable salt thereof.

5. The method according to any one of claims 1 to 4 wherein the second compound is gabapentin or a pharmaceutically acceptable salt thereof.
6. The method according to any one of claims 1 to 4 wherein the second compound is pregabalin or a pharmaceutically acceptable salt thereof.
7. The method according to any one of claims 1 to 6 wherein the compound according to formula (I) and the second compound are administered simultaneously.
8. The method according to claim 7 wherein the compound according to formula (I) and the second compound are administered together as a single pharmaceutical dosage form.
9. A combination comprising a compound according to formula (I) and a second pharmaceutically active compound, as defined in claim 1 or claim 2, or a pharmaceutically acceptable salt of one or both said compounds.
10. The combination according to claim 9 selected from:

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin;

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin;

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with gabapentin; and

4-[2-(5-amino-1*H*-pyrazol-4-yl)-4-(trifluoromethyl)-phenoxy]-5-chloro-2-fluoro-*N*-(1,3-thiazol-4-yl)benzenesulfonamide in combination with pregabalin;

or a pharmaceutically acceptable salt of one or both said compounds.

11. A pharmaceutical dosage form comprising a compound according to formula (I) and a second pharmaceutically active compound, as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt of one or both said compounds, and one or more pharmaceutically acceptable excipients.
12. The pharmaceutical dosage form according to claim 11 for use as a medicament.
13. The pharmaceutical dosage form according to either claim 11 or 12 for use in the treatment of pain.
14. A compound according to formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of pain, wherein the treatment further comprises the separate, sequential or simultaneous administration of a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof.
15. The compound according to claim 14 for use in the treatment of pain, wherein the treatment further consists essentially of the separate, sequential or simultaneous administration of a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof.
16. The use of a compound according to formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of pain, wherein the treatment further comprises the separate, sequential or simultaneous administration of a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof.
17. The use of a compound according to claim 16, wherein the treatment further consists essentially of the separate, sequential or simultaneous administration of a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof.

18. A kit comprising:

- (i) a pharmaceutical dosage form comprising a compound according to formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient; and
- (ii) a pharmaceutical dosage form comprising a second compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

for use in the the treatment of pain.

19. The kit of claim 18 for use in pain which consists essentially of pharmaceutical dosage forms (i) and (ii).

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Fig 1

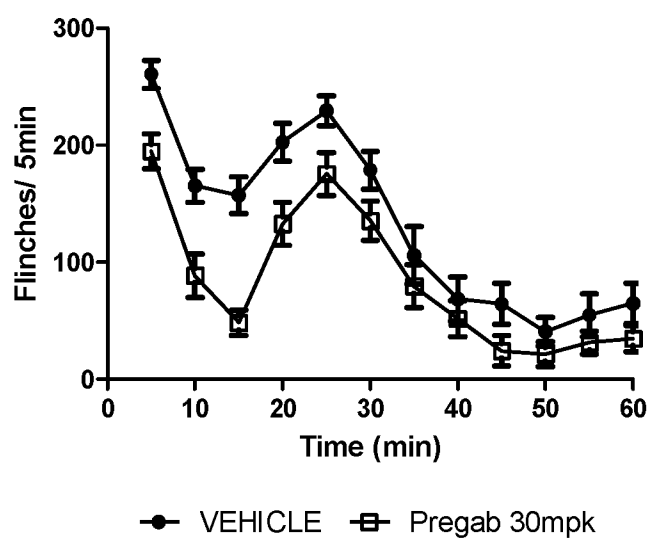
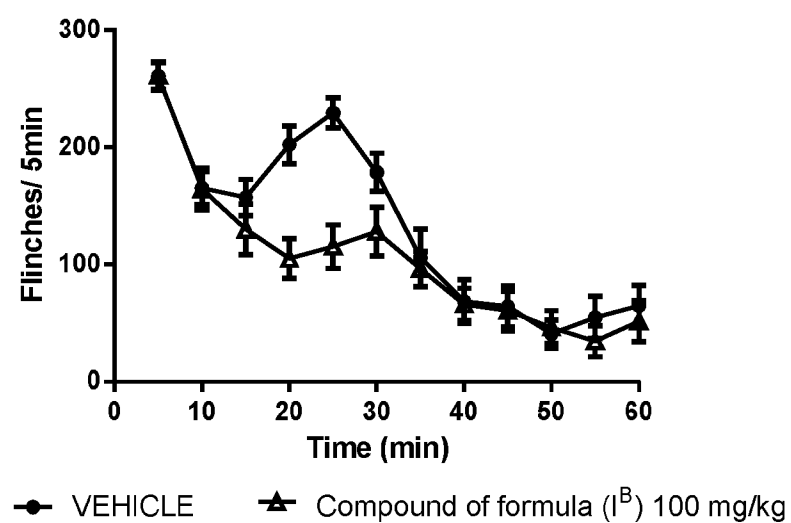


Fig 2



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Fig 3

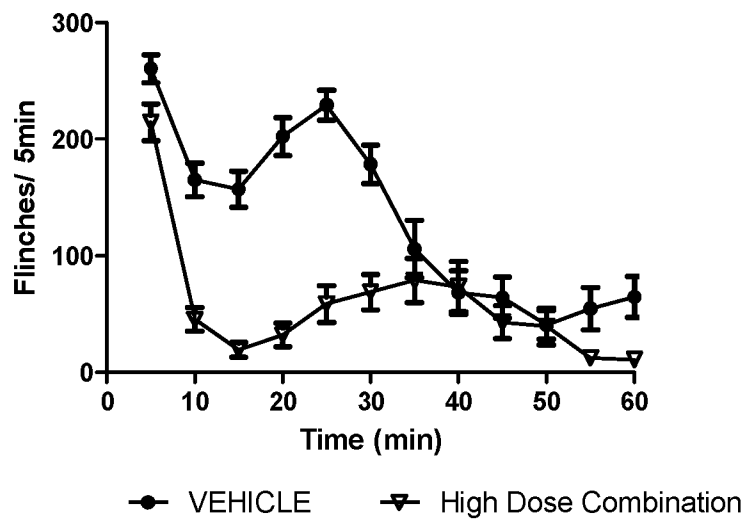
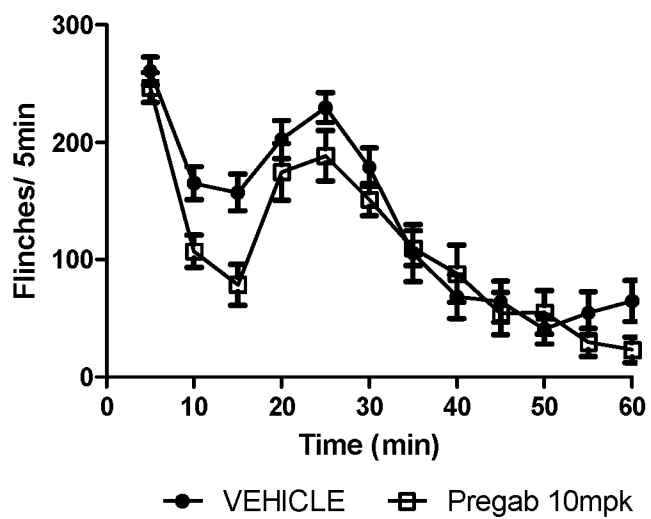


Fig 4



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Fig 5

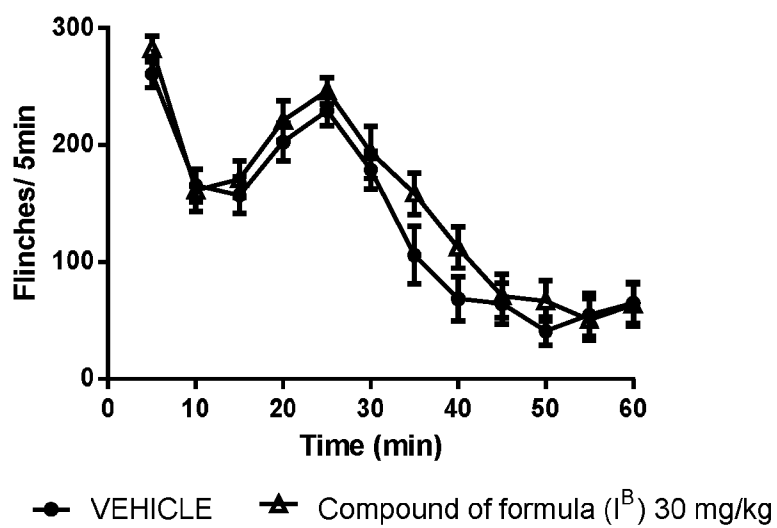
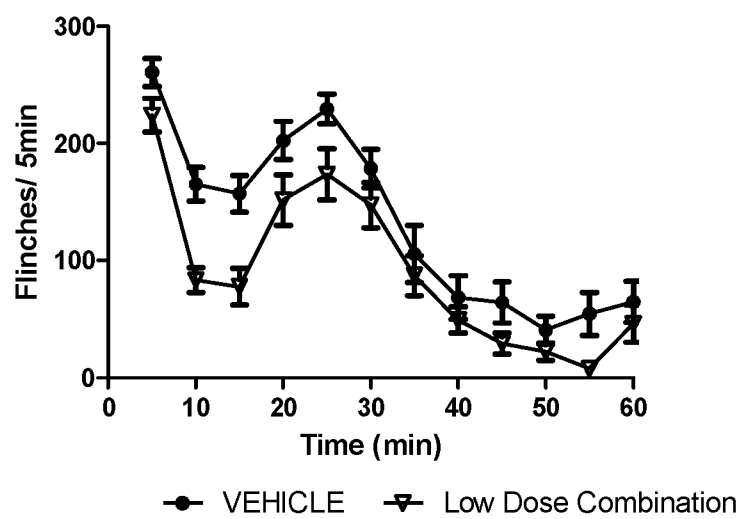


Fig 6



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Fig 7.1

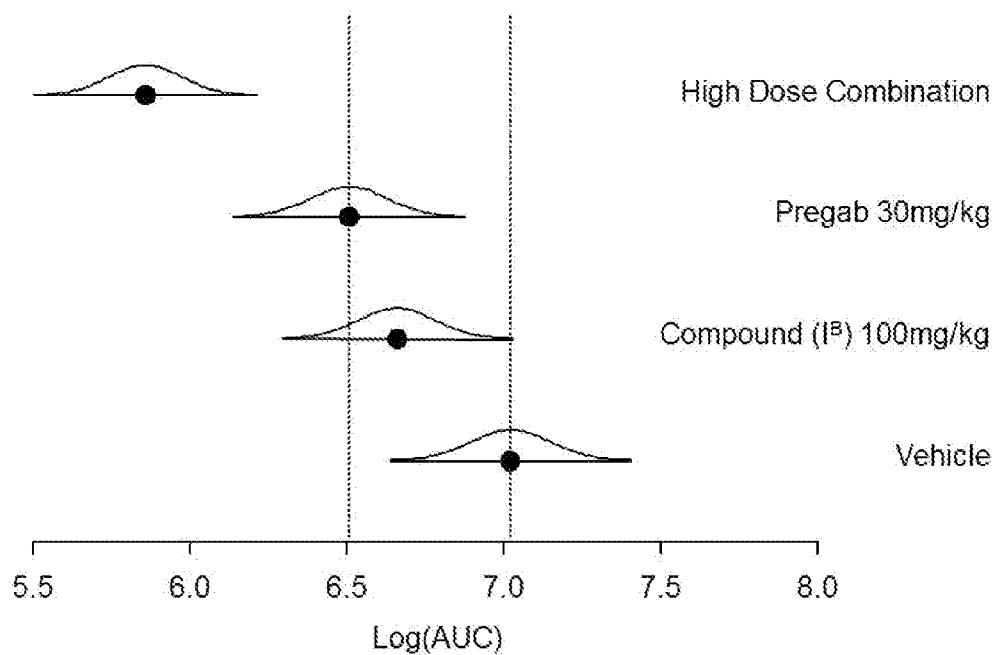
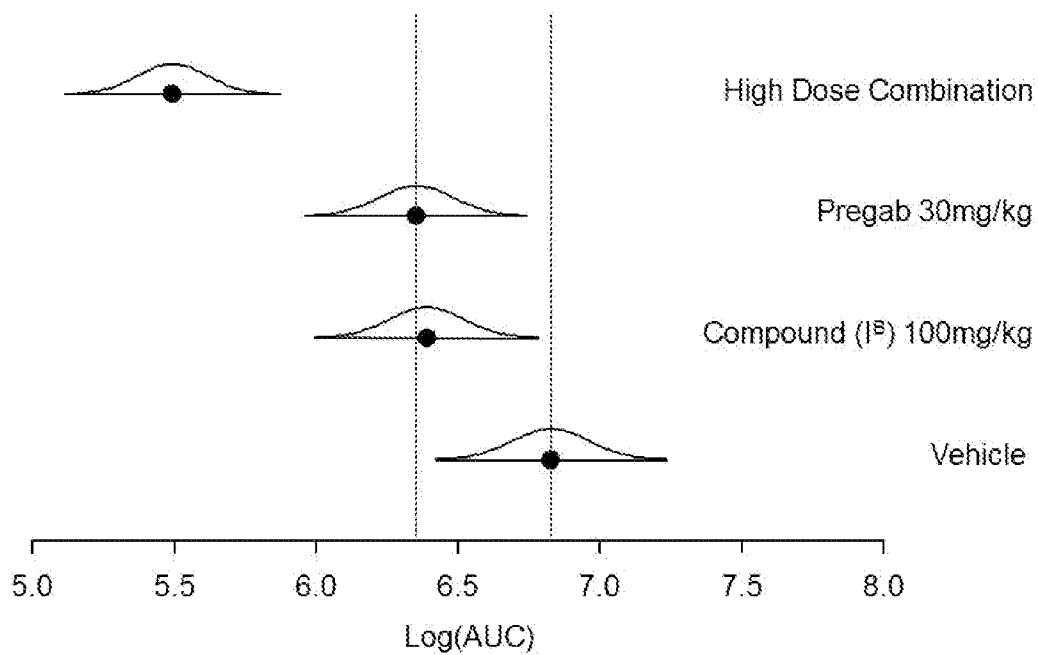


Fig 7.2



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055100

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/195 A61K31/197 A61K31/427 A61P29/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/079443 A1 (PFIZER LTD [GB]; ICAGEN INC [US]; BEAUDOIN SERGE [US]; LAUFERSWEILER M) 15 July 2010 (2010-07-15) cited in the application the whole document examples 788,1028 page 65, line 32 page 67, line 29 - line 30 -----	1-19
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
16 October 2015	09/11/2015	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Economou, Dimitrios	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/055100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010079443	A1	15-07-2010	
		AP 2811 A	31-12-2013
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