

COMPOUND FOR USE IN THE TREATMENT OF PAIN AND ENANTIOPURE COMPOSITIONS THEREOF

Technical field

The present disclosure relates to the use of the monoamine reuptake inhibitor IP2016 (formula (I)) for the treatment of pain. The present disclosure relates to an enantiopure composition of the enantiomers of IP2016 and their use as a medicament.

Background

Treatment of central nervous system conditions (CNS) with active ingredients is challenging due to numerous complex biological factors influencing the outcome of effect and potential negative side effects.

In treating pain, particularly neuropathic pain, occurring after a lesion or injury to the somatosensory system the quality of life of subjects is severely impacted. Evoked pain may spread to neighbouring areas and involve peripheral and central sensitization. The prevalence of neuropathic pain is 6.9 to 10%, often affecting people with diabetes. Currently, 200 million people worldwide suffer from neuropathic pain, also known as diabetic polyneuropathy.

While different treatment regimes exist, like anticonvulsants, tri- and tetracyclic antidepressants; serotonin- and noradrenaline-reuptake inhibitors e.g. duloxetine; and local treatments, a risk-benefit assessment must consider different drawbacks. Side effects may occur, including nausea, fatigue, dizziness, increased sweating, dry mouth, constipation, reduced appetite, insomnia, diarrhea, disturbed consciousness and trembling, and increased intraocular pressure and high blood pressure (BP). Moreover, current treatments present with negative drug interactions.

In short, inadequate response to drug treatments constitutes a substantial unmet need in patients with neuropathic pain, and currently, less than one-third of painful diabetic neuropathy patients derive sufficient pain relief with existing pharmacotherapies. In the field of amine reuptake inhibitors, the specific receptor activity profile of the active ingredient may strongly influence the pharmacological profile, efficacy, and side effects of the active ingredient.

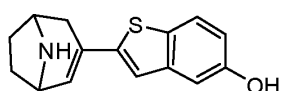
Thus, active ingredients are strongly needed to display a specific, selective profile of amine reuptake inhibition to achieve better treatment for CNS conditions,

particularly pain, thereby improving inadequate response to existing treatments.

Summary

As outlined above, new compounds and compositions to treat CNS conditions, particularly pain, are highly desired. The present disclosure provides a compound
5 useful in the treatment of pain, such as neuropathic pain.

In one main aspect, the present disclosure provides for a compound according to formula (I),



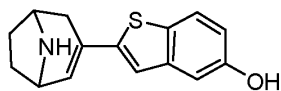
(I), or a pharmaceutically acceptable salt thereof,
for use in a method of treatment, prevention or alleviation of pain in a subject.

10 The inventors have shown that the compound of formula (I) has antinociceptive effects in different models of pain in animals.

After a process of separation and isolation of the enantiomers of the compound of formula (I), the inventors have found that one of the enantiomers, (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, has increased
15 potency and improved receptor activity profile in monoamine transporters compared to the other enantiomer. In addition to providing an improved inhibition profile in monoamine transporters, the (-) enantiomer has also been observed to exert a higher effect on opioid μ receptors compared to the (+) enantiomer.

Acting on opioid μ receptors and also on the monoamine transporters for serotonin
20 (5-HTT), norepinephrine (NET) and dopamine (DAT) is advantageous in treatment of pain. Thus, it is here demonstrated (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol has unexpected advantageous properties in the treatment of pain.

In one aspect, the present disclosure provides for a composition comprising a
25 compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of

(-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%.

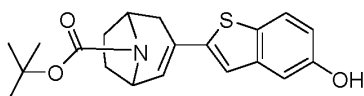
The compounds, compositions, and medical uses thereof of the present invention may provide additional pharmacodynamic advantages compared to other medicaments, such as medicaments for pain. For example the compounds may provide a lower toxicity, reduced incidence of treatment-emergent adverse events (TEAEs), improved safety of the treatment, reduced tendency to cause addiction, or any combination of the foregoing.

In addition, the compounds and compositions described herein may provide improved pharmacokinetic properties such as administration, distribution, metabolism and excretion properties (ADME), improved systemic exposure, serum half-life, clearance, or any combination of the foregoing.

The inventors also demonstrate a method for preparing compositions comprising isolated enantiomers of IP2016 in high purity and larger amounts.

In yet another aspect, the present disclosure provides for a method of manufacturing of (+)- or (-)- 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol with chiral purity of 51% or more, the method comprising:

- a. providing a mixture of
 (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol and
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol;
- b. treating said mixture with (Boc)₂O in order to obtain a mixture of enantiomers of:

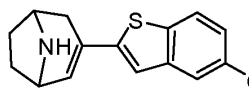


tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

- c. separating said mixture using chiral liquid chromatography to provide isolated enantiomer(s) of
 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate; and
- d. deprotecting the isolated enantiomer(s) in step c. under acidic conditions to obtain enantiopure
 (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

Definitions

As used herein, IP2016, or compound of formula (I) refers to compounds according to the below formula:

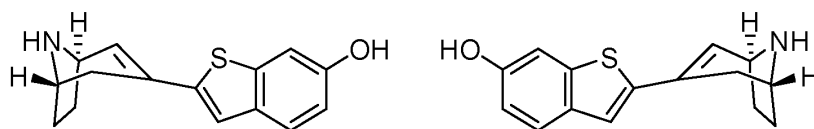


, formula (I) or a pharmaceutically acceptable salt thereof.

- 5 The compound of formula (I) may also be referred to as:
2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

“Enantiomer” as used herein refers to one of a pair of molecular entities that are mirror images of each other and non-superposable. Superposable means the ability to bring particular molecular entities into coincidence (for the corresponding
10 molecular entities to become exact replicas of each other) by no more than translation and rigid rotation.

The compound of formula (I) may exist as two enantiomers as shown in Scheme 1.



Scheme 1. Enantiomers of IP2016.

- 15 These enantiomers are optically active, meaning that they are able to rotate the plane of polarization of a beam of transmitted plane-polarized light. Said optical rotation is the classical distinguishing characteristic of systems containing unequal amounts of corresponding enantiomers. An enantiomer causing rotation in a clockwise direction (when viewed in the direction facing the oncoming light beam)
20 under specified conditions is called dextrorotatory and its chemical name or formula is designated by the prefix (+)-; an enantiomer causing rotation in the opposite sense is levorotatory and designated by the prefix (-)-.

Hence the enantiomers of IP2016 are herein referred to as:

- (+)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, and
25 (-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, respectively.

“Chiral purity”, also abbreviated “cp”, “c.p” or “%cp” as defined herein is a measurement of the purity of chiral substances. It reflects the amount of one enantiomer of a pair of enantiomers relative to the total amount of the two enantiomers. Chiral purity may be calculated as follows:

5
$$\%cp = \frac{(amount\ enantiomer\ 1)}{(amount\ enantiomer\ 1 + amount\ enantiomer\ 2)} \times 100$$

“Enantiomeric excess”, also abbreviated “ee”, or “e.e.” or “%ee” as defined herein is a measurement of purity of chiral substances. It reflects the degree to which a sample contains one enantiomer of a pair of enantiomers in a greater amount than
10 the other enantiomer of the pair. Enantiomeric excess may be calculated as follows:

$$\%ee = \frac{(amount\ enantiomer\ 1 - amount\ enantiomer\ 2)}{(amount\ enantiomer\ 1 + amount\ enantiomer\ 2)} \times 100$$

Enantiomeric excess or chiral purity may be measured or determined using optical techniques such as optical rotation, or using chiral chromatography, to determine
15 the amount of each enantiomer or their relative amounts among each other.

The use of the term “enantiopure” herein refers to compositions where a particular enantiomer has been enriched to above 51% chiral purity. It englobes and may be used to refer to compositions comprising only one specific enantiomer in chiral purities of e.g. 51% or above, 60% or above, 80% or above, 90% or above,
20 95% or above, or 98% or above.

The compound of the invention may exist in a tautomeric form. Any such tautomer is considered to be within the scope of the invention.

Also, in the compound of formula I as defined herein, any hydrogen atom may be replaced by a deuterium (^2H), and any such deuterated compound of formula I,
25 comprising one or more deuterium atoms in place of the corresponding number of hydrogen atoms, is considered to be within the scope of the invention.

It is known in the art that prodrugs can be produced. The person skilled in the art will know which types of molecular moieties can be introduced to a drug to produce a prodrug. It is considered that prodrugs relating to the compound of formula I are within the scope of the invention.

- 5 "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary and human pharmaceutical use.

- 10 The term "pharmaceutically acceptable salt" of a compound refers to a salt that is pharmaceutically acceptable, as defined herein, and preferably possesses the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids, e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; or formed with organic acids, e.g. acetic acid, benzenesulfonic acid, benzoic acid, 15 camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphtoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, 20 trimethylacetic acid; or salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminium ion; or coordinates with an organic or inorganic base. Acceptable organic bases include e.g. diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, morpholine, and tromethamine. Acceptable 25 inorganic bases include e.g. ammonia, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

- 30 As used herein, the terms "treatment" or "treating" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of disease or disorder, stabilized (i.e., not worsening) state of disease or disorder, prevention of the disease or disorder, delay or slowing of disease or disorder progression, amelioration or

palliation of the disease state, and remission (whether partial or total) whether detectable or undetectable.

As used herein, "neuropathic pain" includes reference to a neuropathic component of nociceptive pain.

5 As used herein, "nociceptive" means relating to the perception or sensation of pain.

"Allodynia" refers to pain resulting from stimulus which would not normally provoke pain, such as a light touch of the skin.

"Hyperalgesia" refers to excessive sensitivity to painful stimuli.

10 The term "about" as used herein to refer to an amount or percentage is to be interpreted as a variation of $\pm 10\%$ with respect to the value of the amount or percentage it refers to, such as $\pm 5\%$.

Description of Drawings

15 Figure 1. (A) time course of flinching behaviour after formalin injection, and (B) total flinches are shown for the interphase (Int=6-15 min), the second phase (P2=16-40 min) of the test after administration of formalin. (C) hind paw withdrawal threshold (g) to low threshold von Frey stimulation; pre- vs. post-CCI baseline = 17.3 vs 1.4 g (D) hind paw withdrawal duration (s) to high threshold pinprick stimulation; pre- vs. post-CCI baseline = 0 vs 14.9 s. All groups n=8 rats. Data are presented as mean $\pm$ S.E.M. *P<0.05, ***P<0.001 vs corresponding Vehicle, +P<0.05, ++++P<0.001 vs. pre-CCI baseline; One Way ANOVA followed by Dunnett's. Further experimental details are given in Example 1.

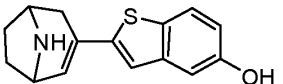
Figure 2. Chromatogram of analytical chiral HPLC analysis of purified isomer 1. Further experimental details are given in Example 4.

25 Figure 3. Chromatogram of analytical chiral HPLC analysis of purified isomer 2. Further experimental details are given in Example 4.

Figure 4. Chiral stability of isomer 1 at pH1. Further experimental details are given in Example 6.

Detailed description*A compound for use in treatment of pain*

In one main aspect, the present disclosure provides for a compound according to formula (I),

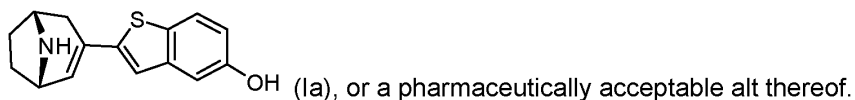
5  (I), or a pharmaceutically acceptable salt thereof, for use in a method of treatment, prevention or alleviation of pain in a subject.

In one embodiment, the compound of formula (I) is 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or a pharmaceutically acceptable salt thereof.

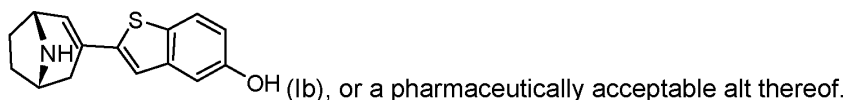
10 In one embodiment, the compound of formula (I) is (-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound of formula (I) is compound is (+)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or a
15 pharmaceutically acceptable salt thereof.

In one embodiment, the compound is according to formula (Ia)



In one embodiment, the compound is according to formula (Ib)



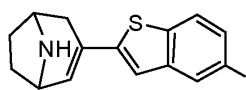
20 The inventors have shown that the compound of formula (I) has antinociceptive effects in different models of pain in animals.

In some embodiments, the pain, the method of treatment and/or or the subject are as described elsewhere herein.

Enantiopure composition(s)

After a process of separation and isolation of the enantiomers of the compound of formula (I), the inventors have found that one of the enantiomers has increased potency and improved receptor activity profile compared to the other enantiomer, and as such confers an unexpected advantage in treatment of pain.

Thus, in one aspect, the present disclosure provides for a composition comprising a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%.

In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.

In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 90%. In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 95%. In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 98%.

In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is from 90% to 100%, such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100%.

In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is from 95% to 100%.

In one embodiment, the chiral purity of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is from 98% to 100%.

In one embodiment, the enantiomeric excess of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%, or at

least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.

In one embodiment, the enantiomeric excess of

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is from 90% to 100%,
 5 such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% enantiomeric excess of (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

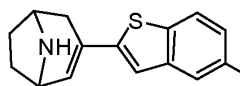
In one embodiment, the enantiomeric excess of
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 50%. In one
 embodiment, the enantiomeric excess of
 10 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 80%. In one
 embodiment, the enantiomeric excess of
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 90%. In one
 embodiment, the enantiomeric excess of
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 95%.

15 The examples further elaborate on how to measure chiral purity.

The examples show that the (-) isomer of IP2016 as determined by optical activity has increased potency and improved receptor activity profile compared to the other enantiomer, and as such confers an unexpected advantage in treatment of pain. In addition to providing an improved inhibition profile in monoamine transporters, the (-)
 20) enantiomer has also been observed to exert a higher effect on opioid μ receptors compared to the (+) enantiomer.

Acting on opioid μ receptors and also on the monoamine transporters for serotonin (5-HTT), norepinephrine (NET) and dopamine (DAT) is advantageous in treatment of pain. Thus, it is here demonstrated
 25 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol has unexpected advantageous properties in the treatment of pain.

In one aspect, the present disclosure provides for a composition comprising a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of

(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%.

In one embodiment, the chiral purity of

(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 60%.

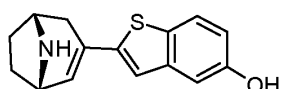
5 In one embodiment, the chiral purity of

(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 90%.

In one embodiment, the chiral purity of

(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 95%,
such as at least of 98%.

10 In one aspect, the present disclosure provides a composition comprising a
compound of formula (Ia):



(Ia), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of the compound of formula (Ia) is at least 51%.

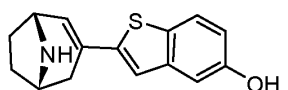
In one embodiment, the chiral purity of the compound of formula (Ia) is at least

15 60%.

In one embodiment, the chiral purity of the compound of formula (Ia) is at least of
90%.

In one embodiment, wherein the chiral purity of the compound of formula (Ia) is at
least of 95%, such as at least of 98%.

20 In one aspect, the present disclosure provides a composition comprising a
compound of formula (Ib):



(Ib), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of the compound of formula (Ib) is at least 51%.

In one embodiment, the chiral purity of the compound of formula (Ib) is at least 60%.

25 In one embodiment, the chiral purity of the compound of formula (Ib) is at least of
90%.

In one embodiment, the chiral purity of the compound of formula (Ib) is at least of 95%, such as at least of 98%.

5 In one embodiment, the enantiomeric excess of (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or the compound of formula (Ia), or the compound of formula (Ib) is respectively at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.

10 In one embodiment, the enantiomeric excess of (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or the compound of formula (Ia), or the compound of formula (Ib) is respectively from 90% to 100%, such as 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% enantiomeric excess.

In one embodiment, the enantiomeric excess of (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 50%.

15 In one embodiment, the enantiomeric excess of (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 80%. In one embodiment, the enantiomeric excess of (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 90%. In one embodiment, the enantiomeric excess of
20 (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 95%.

In one embodiment, the enantiomeric excess of formula (Ia) is at least 50%.

In one embodiment, the enantiomeric excess of formula (Ia) is at least 80%. In one embodiment, the enantiomeric excess of formula (Ia) is at least 90%. In one embodiment, the enantiomeric excess of formula (Ia) is at least 95%.

25 In one embodiment, the enantiomeric excess of formula (Ib) is at least 50%.

In one embodiment, the enantiomeric excess of formula (Ib) is at least 80%. In one embodiment, the enantiomeric excess of formula (Ib) is at least 90%. In one embodiment, the enantiomeric excess of formula (Ib) is at least 95%.

30 In one embodiment, the composition(s) as described herein comprises one or more pharmaceutically acceptable excipients or diluents. The excipient or diluent may be any pharmaceutically acceptable excipient or diluent known in the art. The excipient or diluent must be "acceptable", in the sense of being compatible with the compound

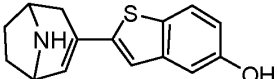
of formula (I), or enantiomers thereof, with other ingredients of the formulation and not harmful to the subject. The excipient or diluent may be solid or liquid without limitation.

5 The composition(s) described herein may be administered and formulated in a wide variety of oral and parenteral dosage form. The preparation of said dosage form may be done as known in the art.

In one embodiment, the composition(s) as described herein may comprises a further therapeutic agent effective for the treatment of pain. Said further therapeutic agent effective for treatment of pain may be any known compound suitable for treatment, or alleviation of pain.

In one aspect, the present disclosure provides a composition as described herein, for use in a method of treatment, prevention, or alleviation of pain in a subject.

In one embodiment, the present disclosure provides a composition comprising a compound of formula (I):

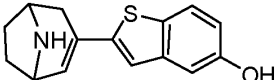
15  (I), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of

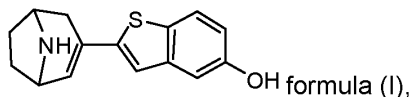
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%, for use in a method of treatment, prevention, or alleviation of pain in a subject.

In one embodiment, the chiral purity of
20 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is from 90% to 100%, such as from 95% to 100%, such as from 98% to 100%. In some embodiments, the pain, the method of treatment and/or or the subject are as described elsewhere herein.

Use of a compound of formula (I),

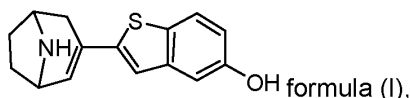
25  formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment, prevention or alleviation of pain, in a subject in need thereof, as described herein.

A method of treatment, prevention or alleviation of pain in a subject in need thereof as described herein, said method comprising administering to the subject a therapeutically effective amount of a compound of formula (I),



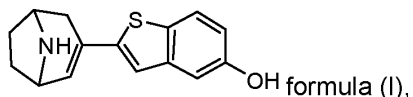
5 or a pharmaceutically acceptable salt thereof.

A method of inducing reduction of pain in a subject in need thereof said method comprising administering to the subject a therapeutically effective amount of a compound of formula (I),



10 or a pharmaceutically acceptable salt thereof, as described herein.

A method of improving the functionality in a subject having pain, said method comprising administering to the subject a therapeutically effective amount of a compound of formula (I),



15 or a pharmaceutically acceptable salt thereof, as described herein.

In one embodiment, the compound of formula (I) is

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or a pharmaceutically acceptable salt thereof.

Any of the embodiments of compositions comprising a compound of formula (I) described herein, particularly
 20 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol, or formula (Ib), may be combined with the methods of treatment, prevention and alleviation of pain, the methods of inducing reduction of pain, or the methods of improving functionality of pain as described herein.

25

Treatment of pain

In one embodiment, the pain is selected from the group consisting of:

- (i) chronic or acute primary pain,
- (ii) chronic or acute cancer-related pain,
- 5 (iii) chronic or acute postsurgical pain,
- (iv) chronic or acute post-traumatic pain,
- (v) chronic or acute secondary musculoskeletal pain,
- (vi) chronic or acute secondary visceral pain,
- (vii) chronic or acute neuropathic pain, and
- 10 (viii) chronic or acute secondary headache or orofacial pain.

In one embodiment, the chronic or acute primary pain is chronic or acute primary visceral pain, chronic or acute widespread pain, fibromyalgia syndrome, chronic or acute primary musculoskeletal pain, chronic or acute primary headache or orofacial pain, such as migraine, burning mouth syndrome, tension-type headache, cluster
15 headache or hemicranias continua; complex regional pain syndrome (CRPS) or painful bruising syndrome.

In one embodiment, chronic or acute cancer-related pain is related to visceral cancer pain, bone cancer pain or neuropathic cancer pain.

In one embodiment, the chronic or acute cancer-related pain is post-cancer
20 treatment pain, such as post-cancer medicine pain, such as painful chemotherapy-induced polyneuropathy, such as post-radiotherapy pain, such as painful radiation-induced neuropathy.

In one embodiment, the chronic or acute postsurgical pain is postsurgical pain after spinal surgery, after herniotomy, after hysterectomy, after amputation, after
25 thoracotomy, after breast surgery, or after arthroplasty.

In one embodiment, the chronic or acute post-traumatic pain is pain after burns injury, pain associated with whiplash injury, pain after musculoskeletal injury.

In one embodiment, the chronic or acute secondary musculoskeletal pain is pain from persistent inflammation, such as inflammation due to infection, inflammation due to crystal deposition, or inflammation due to autoimmune and auto-inflammatory disorders; pain associated with structural changes, such as pain associated to osteoarthritis or associated with spondylosis; pain due to disease of the nervous system such as pain associated to Parkinson's disease, such as pain associated to multiple sclerosis or pain associated to peripheral neurologic disease.

In one embodiment, the chronic or acute secondary visceral pain is pain from mechanical factors, vascular mechanism, or persistent inflammation, such as mechanical factor, vascular mechanism or persistent inflammation in the head, neck, thoracic, abdominal or pelvic regions.

In one embodiment, the chronic or acute neuropathic pain is central neuropathic pain, such as central neuropathic pain associated with spinal cord injury, brain injury, post-stroke pain or associated with multiple sclerosis; peripheral neuropathic pain, peripheral neuropathic pain after nerve injury, painful polyneuropathy or painful radiculopathy; or neuropathic orofacial pain.

In one embodiment, the chronic or acute secondary headache or orofacial pain is chronic dental pain, chronic neuropathic orofacial pain, headache or orofacial pain associated with temporomandibular disorders, associated with disorders in homeostasis or their nonpharmacological treatment, associated with cranial or cervical vascular disorder, associated with non-vascular intracranial disorder, associated with a substance or its withdrawal, or associated with traumatic injury to the head.

In one embodiment, the pain is neuropathic pain. "Neuropathic pain" is caused by a lesion or disease of the somatosensory nervous system. It can be described as electric, burning, or shock like. The pain may occur spontaneously, without provocation, or be provoked by noxious or nonnoxious stimuli. The pain may be constant or intermittent, and may be described as searing, burning, or icy cold. Neuropathic pain can originate from several different sources.

In one embodiment, the neuropathic pain is acute neuropathic pain. In one embodiment, the neuropathic pain is chronic neuropathic pain.

In one embodiment, the neuropathic pain is due to alcoholism, diabetes, multiple sclerosis, multiple myeloma, stroke, cancer, cytomegalovirus, trigeminal neuralgia, spinal cord injury, or amputation.

5 In one embodiment, the neuropathic pain is due to chronic progressive nerve disease.

In one embodiment, the neuropathic pain is due to infection.

In one embodiment, the neuropathic pain is due to injury. In one embodiment, the neuropathic pain is ongoing pain after neuropathic injury.

In one embodiment, the neuropathic pain is due to a side effect of a medication.

10 In one embodiment, the neuropathic pain is due to a medical procedure, such as surgery.

In one embodiment, the neuropathic pain is idiopathic.

In one embodiment, the neuropathic pain is a neuropathic component of nociceptive pain.

15 In one embodiment, the neuropathic pain is due to diabetic neuropathy. In one embodiment, the diabetes is chronic diabetes.

In one embodiment, the neuropathic pain is neuropathic cancer pain.

In one embodiment, the neuropathic pain is due to treatment-emergent neuropathy.

20 In one embodiment, the treatment-emergent neuropathy is due to chemotherapy. In one embodiment, the treatment-emergent neuropathy is due to radiotherapy. In one embodiment, the treatment-emergent neuropathy is due to surgery.

In one embodiment, the pain is trigeminal neuralgia, allodynia or hyperalgesia.

In one embodiment, the pain is trigeminal neuralgia.

25 In one embodiment, the pain is selected from classical trigeminal neuralgia; secondary trigeminal neuralgia, such as attributed to multiple sclerosis, such as attributed to a space-occupying lesion; and idiopathic trigeminal neuralgia.

In one embodiment, the pain is painful trigeminal neuropathy, such as attributed to herpes zoster, such as post-herpetic neuralgia, such as post-traumatic trigeminal neuropathy, such as idiopathic painful trigeminal neuropathy.

In one embodiment, the pain post-herpetic neuralgia.

In one embodiment, the pain is pain in Parkinson's disease.

In one embodiment, the pain is sexual pain disorder. In one embodiment, the pain is vulvar pain. In one embodiment, the pain is vulvodynia or progressive vulvodynia.

5 In one embodiment, the pain is pain associated with associated with genitourinary syndrome of menopause (GSM), or pain associated with vaginal atrophy, vulvovaginal atrophy, urogenital atrophy, or atrophic vaginitis.

In one embodiment, the compound is capable of inducing a pain reduction in a subject of at least 5%, such as at least 10%, such as at least 15%, such as 20%
10 pain reduction.

In one embodiment, the pain reduction is a subjective measure of pain.

In one embodiment, the pain reduction is a measurement of a pain threshold.

The pain response or reduction can be assessed by subjective pain measurements, such as subjective measurements performed on a visual analogue scale (VAS). For
15 example, having a 100 mm line with 0 representing "no pain" and 100 representing "worst pain imaginable". Subjects can be asked to mark the VAS using a single vertical stroke at the point they consider to reflect their level of pain appropriately.

A numeric rating scale (NRS) can also assess the pain response or reduction. For example, by using an 11-point numeric rating scale ranging from 0 ("no pain") to 10
20 ("worst possible pain") and asking the subject to rate their pain.

Pain response or reduction may also be measured through other subjective measurements, such as by rating responses to a questionnaire with a numeric scale. For example, sexual pain may be evaluated with patient-reported outcome (PRO) questionnaires, with questions related to different aspects of pain and evaluating the
25 response before, after and/or during treatment.

In one embodiment, the measurement of pain is performed on a Visual Analogue Scale (VAS) or a numeric rating scale (NRS) or a patient-reported outcome (PRO).

In one embodiment, the pain occurs at least for 1 minute, such as at least for 5 minutes, such as at least for 10 minutes, such as at least for 30 minutes, such as
30 least for 1 hour, such as at least for 2 hours, such as for more than 2 hours.

In one embodiment, the pain occurs for at least one day, such as for at least 3 days or for at least a week.

5 In one embodiment, the pain occurs during more than a week, such as during more than two weeks, such as during more than three weeks, such as during more than a month, such as during more than two months, such as during more than three months at least 20% of the days, such as at least 30%, such as at least 40% or at least 50% of the days.

10 In one embodiment, the subject is administered with a further therapeutic agent effective for the treatment of pain.

In one embodiment, the compound is administered in an amount from about 0.01 to 100 mg per individual dose.

In one embodiment, the subject is a mammal. In one embodiment, the subject is a human.

15 In one embodiment, the administration of the compound is an oral administration.

In one embodiment, the administration of the compound is parenteral administration, such as cutaneous, mucosal, subcutaneous, intramuscular, intraperitoneal, intravenous or intra-arterial injection.

20 In one embodiment, the compound is formulated in a pharmaceutical composition further comprising a pharmaceutically acceptable diluent, carrier and/or excipient.

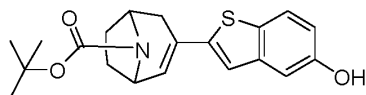
In one embodiment, the compound is formulated as a solid dosage form, such as a tablet, a capsule, a pill, granules or a powder.

A method of manufacturing

The inventors also demonstrate a method for preparing compositions comprising isolated enantiomers of IP2016 in high purity and larger amounts.

In yet another aspect, the present disclosure provides for a method of manufacturing of (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol with chiral purity of 51% or more, the method comprising:

- a. providing a mixture of
(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol and
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol;
- b. treating said mixture with (Boc)₂O in order to obtain a mixture of enantiomers of:



tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

- c. separating said mixture using chiral liquid chromatography to provide isolated enantiomer(s) of
tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate; and
- d. deprotecting the isolated enantiomer(s) in step c. under acidic conditions to obtain enantiopure
(+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

In one embodiment, step b. is performed using dichloromethane (DCM) as solvent and in the presence of diisopropylethylamine (DIPEA).

In one embodiment, step b. is performed between 0 °C to 30 °C.

In one embodiment, a liquid-liquid extraction between an organic and aqueous phase is performed on the mixture in step b. prior to step c.

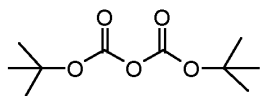
In one embodiment, the liquid chromatography in step c. comprises a stationary phase comprising a chiral selector. In one embodiment, the chiral selector comprises or consists of amylose tris(3-chloro-5-methylphenylcarbamate). Other stationary

phases comprising suitable chiral selectors for the separation in step c. will be known to the skilled person.

In one embodiment, the chiral purity of

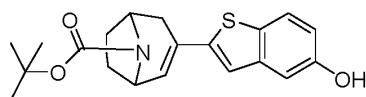
(+)- or (-)- 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is of at least
 5 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.

(Boc)₂O is di-tert-butyl dicarbonate (CAS: 24424-99-5) shown below:



The skilled person will be aware of suitable conditions for deprotecting the tert-butyl
 10 carboxylate (BOC) protecting group as described in step d. In one embodiment, the acidic conditions in step d. are provided by an organic or inorganic acid, such as hydrochloric acid (HCl), trifluoroacetic acid (TFA), or sulphuric acid (H₂SO₄). In one embodiment, the deprotecting in step d. is performed in an organic solvent, such as dioxane; or in an aqueous solution. The acid may be dissolved in a suitable
 15 concentration for deprotecting the tert-butyl carboxylate e.g. 4 M, but other lower or higher concentration may be used.

In one aspect, the present disclosure provides for a compound according to formula (II):



(II), or a pharmaceutically acceptable salt thereof,
 20 or an stereoisomer thereof.

In one embodiment, the compound of formula (II) is

tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

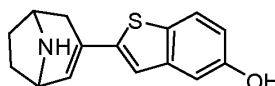
In one embodiment, the compound of formula (II) is

25 (+)-tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

In one embodiment, the compound of formula (II) is
 (-)-tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate.

Items

- 5 1. A compound according to formula (I),



OH formula (I), or a pharmaceutically acceptable salt thereof, for use in a method of treatment, prevention, or alleviation of pain in a subject.

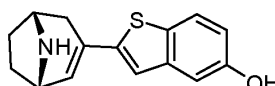
- 10 2. The compound for use according to item 1, wherein the compound is 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

3. The compound for use according to item 1, wherein the compound is (-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

4. The compound for use according to item 1, wherein the compound is (+)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

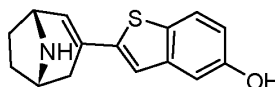
15

5. The compound for use according to item 1, wherein the compound is according to formula (Ia)



OH (Ia), or a pharmaceutically acceptable alt thereof.

- 20 6. The compound for use according to item 1, wherein the compound is according to formula (Ib)



OH (Ib), or a pharmaceutically acceptable alt thereof.

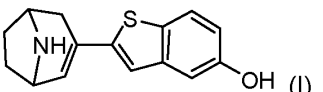
7. The compound for use according to any one of the preceding items, wherein the pain is selected from the group consisting of:
- (i) chronic or acute primary pain,
 - (ii) chronic or acute cancer-related pain,
 - 5 (iii) chronic or acute postsurgical pain,
 - (iv) chronic or acute post-traumatic pain,
 - (v) chronic or acute secondary musculoskeletal pain,
 - (vi) chronic or acute secondary visceral pain,
 - (vii) chronic or acute neuropathic pain, and
 - 10 (viii) chronic or acute secondary headache or orofacial pain.
8. The compound for use according to item 7, wherein the chronic or acute primary pain is chronic or acute primary visceral pain, chronic or acute widespread pain, fibromyalgia syndrome, chronic or acute primary musculoskeletal pain, chronic or acute primary headache or orofacial pain, such as migraine, burning mouth syndrome, tension-type headache, cluster headache or hemicranias continua; complex regional pain syndrome (CRPS) or painful bruising syndrome.
- 15
9. The compound for use according to item 7, wherein the chronic or acute cancer-related pain is related to visceral cancer pain, bone cancer pain or neuropathic cancer pain.
- 20
10. The compound for use according to item 7, wherein the chronic or acute cancer-related pain is post-cancer treatment pain, such as post-cancer medicine pain, such as painful chemotherapy-induced polyneuropathy, such as post-radiotherapy pain, such as painful radiation-induced neuropathy.
- 25
11. The compound for use according to item 7, wherein the chronic or acute postsurgical pain is postsurgical pain after spinal surgery, after herniotomy, after hysterectomy, after amputation, after thoracotomy, after breast surgery, or after arthroplasty.
- 30
12. The compound for use according to item 7, wherein the chronic or acute post-traumatic pain is pain after burns injury, pain associated with whiplash injury, pain after musculoskeletal injury.

13. The compound for use according to item 7, wherein the chronic or acute secondary musculoskeletal pain is pain from persistent inflammation, such as inflammation due to infection, inflammation due to crystal deposition, or inflammation due to autoimmune and auto-inflammatory disorders; pain associated with structural changes, such as pain associated to osteoarthritis or associated with spondylosis; pain due to disease of the nervous system such as pain associated to Parkinson's disease, such as pain associated to multiple sclerosis or pain associated to peripheral neurologic disease.
14. The compound for use according to item 7, wherein the chronic or acute secondary visceral pain is pain from mechanical factors, vascular mechanism, or persistent inflammation, such as mechanical factor, vascular mechanism or persistent inflammation in the head, neck, thoracic, abdominal or pelvic regions.
15. The compound for use according to item 7, wherein the chronic or acute neuropathic pain is central neuropathic pain, such as central neuropathic pain associated with spinal cord injury, brain injury, post-stroke pain or associated with multiple sclerosis; peripheral neuropathic pain, peripheral neuropathic pain after nerve injury, painful polyneuropathy or painful radiculopathy; or neuropathic orofacial pain.
16. The compound for use according to item 7, wherein the chronic or acute secondary headache or orofacial pain is chronic dental pain, chronic neuropathic orofacial pain, headache or orofacial pain associated with temporomandibular disorders, associated with disorders in homeostasis or their nonpharmacological treatment, associated with cranial or cervical vascular disorder, associated with non-vascular intracranial disorder, associated with a substance or its withdrawal, or associated with traumatic injury to the head.
17. The compound for use according to any one of items 1 to 7 or 15 to 16, wherein the pain is neuropathic pain.
18. The compound for use according to any one of items 1 to 7 or any one of items 15 to 17, wherein the neuropathic pain is acute neuropathic pain.
19. The compound for use according to any one of items 1 to 7 or any one of items 15-17, wherein the neuropathic pain is chronic neuropathic pain.

20. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to alcoholism, diabetes, multiple sclerosis, multiple myeloma, stroke, cancer, cytomegalovirus, trigeminal neuralgia, spinal cord injury, or amputation.
- 5 21. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to chronic progressive nerve disease.
22. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to infection.
- 10 23. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to injury.
24. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is ongoing pain after neuropathic injury.
25. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to a side effect of a medication.
- 15 26. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to a medical procedure, such as surgery.
27. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is idiopathic.
- 20 28. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is a neuropathic component of nociceptive pain.
29. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to diabetic neuropathy.
30. The compound for use according to item 29, wherein the diabetes is chronic diabetes.
- 25 31. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is neuropathic cancer pain.
32. The compound for use according to any one of items 17 to 19, wherein the neuropathic pain is due to treatment-emergent neuropathy.

33. The compound for use according to item 32, wherein the treatment-emergent neuropathy is due to chemotherapy.
34. The compound for use according to item 32, wherein the treatment-emergent neuropathy is due to radiotherapy.
- 5 35. The compound for use according to item 32, wherein the treatment-emergent neuropathy is due to surgery.
36. The compound for use according to any one of the preceding items wherein the pain is trigeminal neuralgia, allodynia or hyperalgesia.
- 10 37. The compound for use according to any one of the preceding items, wherein the pain is trigeminal neuralgia.
38. The compound for use according to item 37, wherein the pain is selected from classical trigeminal neuralgia; secondary trigeminal neuralgia, such as attributed to multiple sclerosis, such as attributed to a space-occupying lesion; and idiopathic trigeminal neuralgia.
- 15 39. The compound for use according to any one of items 37 to 38, wherein the pain is painful trigeminal neuropathy, such as attributed to herpes zoster, such as post-herpetic neuralgia, such as post-traumatic trigeminal neuropathy, such as idiopathic painful trigeminal neuropathy.
- 20 40. The compound for use according to any one of the preceding items, wherein the pain post-herpetic neuralgia.
41. The compound for use according to any one of the preceding items, wherein the pain is pain in Parkinson's disease.
42. The compound for use according to any one of the preceding items, wherein the pain is sexual pain disorder.
- 25 43. The compound for use according to any one of the preceding items, wherein the pain is vulvar pain.
44. The compound for use according to any one of the preceding items, wherein the pain is vulvodynia or progressive vulvodynia.

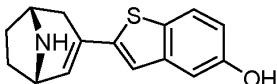
45. The compound for use according to any one of the preceding items, wherein the pain is pain associated with associated with genitourinary syndrome of menopause (GSM), or pain associated with vaginal atrophy, vulvovaginal atrophy, urogenital atrophy, or atrophic vaginitis.
- 5 46. The compound for use according to any one of the preceding items, wherein the compound is capable of inducing a pain reduction in a subject of at least 5%, such as at least 10%, such as at least 15%, such as 20% pain reduction.
47. The compound for use according to item 46, wherein the pain reduction is a subjective measure of pain.
- 10 48. The compound for use according to item 46, wherein the pain reduction is a measurement of a pain threshold.
49. The compound for use according to any one of items 46 to 48, wherein the measurement of pain is performed on a Visual Analogue Scale (VAS) or a numeric rating scale (NRS) or a patient-reported outcome (PRO).
- 15 50. The compound for use according to any one of the preceding items, wherein the pain occurs at least for 1 minute, such as at least for 5 minutes, such as at least for 10 minutes, such as at least for 30 minutes, such at least for 1 hour, such as at least for 2 hours, such as for more than 2 hours.
51. The compound for use according to any one of the preceding items, wherein
- 20 the pain occurs for at least one day, such as for at least 3 days, such as for at least a week.
52. The compound for use according to any one of the preceding items, wherein the pain occurs during more than a week, such as during more than two weeks, such as during more than three weeks, such as during more than a month, such
- 25 as during more than two months, such as during more than three months at least 20% of the days, such as at least 30%, such as at least 40% or at least 50% of the days.
53. The compound for use according to any one of the preceding items, wherein the subject is administered with a further therapeutic agent effective for the
- 30 treatment of pain.

54. The compound for use according to any one of the preceding items, wherein the compound is administered in an amount from about 0.01 to 100 mg per individual dose.
55. The compound for use according to any one of the preceding items wherein the subject is a mammal.
56. The compound for use according to any one of the preceding items, wherein the subject is a human.
57. The compound for use according to any one of the preceding items, wherein the administration of the compound is an oral administration.
58. The compound for use according to any one of items 1 to 56, wherein the administration of the compound is parenteral administration, such as cutaneous, mucosal, subcutaneous, intramuscular, intraperitoneal, intravenous or intra-arterial injection.
59. The compound for use according to any one of the preceding items, wherein the compound is formulated in a pharmaceutical composition further comprising a pharmaceutically acceptable diluent, carrier and/or excipient.
60. The compound for use according to item 59, wherein the compound is formulated as a solid dosage form, such as a tablet, a capsule, a pill, granules or a powder.
61. A composition comprising a compound of formula (I):
- 
- (I), or a pharmaceutically acceptable salt thereof wherein the chiral purity of
- (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%.
62. The composition according to item 61, wherein the chiral purity of
- (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 60%.
63. The composition according to item 61, wherein the chiral purity of
- (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 90%.

64. The composition according to item 61, wherein the chiral purity of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 95%,
such as at least of 98%.

5 65. The composition according to item 61, wherein the the enantiomeric excess of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 10%, or
at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%,
or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least
80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.

66. A composition comprising a compound of formula (Ia):

10  (Ia), or a pharmaceutically acceptable salt thereof
wherein the chiral purity of the compound of formula (Ia) is at least 51%.

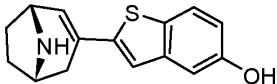
67. The composition according to item 66, wherein the chiral purity of the
compound of formula (Ia) is at least 60%.

15 68. The composition according to item 66, wherein the chiral purity of the
compound of formula (Ia) is at least of 90%.

69. The composition according to item 66, wherein the chiral purity of the
compound of formula (Ia) is at least of 95%, such as at least of 98%.

20 70. The composition according to item 66, wherein the the enantiomeric excess of
the compound of formula (Ia) is at least 10%, or at least 20%, or at least 30%,
or at least 40%, or at least 50%, or at least 55%, or at least 60%, or at least
65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at
least 90%, or at least 95%, or at least 98%.

71. A composition comprising a compound of formula (Ib):

25  (Ib), or a pharmaceutically acceptable salt thereof
wherein the chiral purity of the compound of formula (Ib) is at least 51%.

72. The composition according to item 71, wherein the chiral purity of the
compound of formula (Ib) is at least 60%.

73. The composition according to item 71, wherein the chiral purity of the compound of formula (Ib) is at least of 90%.
74. The composition according to item 71, wherein the chiral purity of the compound of formula (Ib) is at least of 95%, such as at least of 98%.
- 5 75. The composition according to item 71, wherein the the enantiomeric excess of the compound of formula (Ib) is at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.
- 10 76. The composition according to any one of items 61 to 75, further comprising one or more pharmaceutically acceptable excipients or diluents.
77. A composition according to any one of items 61 to 76, for use in a method of treatment, prevention, or alleviation of pain in a subject.
- 15 78. The composition for use according to item 77, wherein the pain is according to any one of items 7 to 52.
79. The composition for use according to any one of items 77 to 78, wherein the composition comprises a further therapeutic agent effective for the treatment of pain.
- 20 80. The composition for use according to any one of items 77 to 79, wherein the composition comprises one or more pharmaceutically acceptable excipients or diluents.

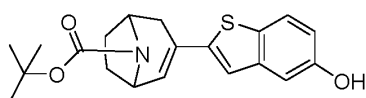
81. A method of manufacturing of

(+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol with chiral purity of 51% or more, the method comprising:

a. providing a mixture of

5 (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol and
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol;

b. treating said mixture with (Boc)₂O in order to obtain a mixture of enantiomers of:



10 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

c. separating said mixture using chiral liquid chromatography to provide isolated enantiomer(s) of

15 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate; and

d. deprotecting the isolated enantiomer(s) in step c. under acidic conditions to obtain enantiopure

(+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

20 82. The method according to item 81, wherein step b. is performed using DCM as solvent and in the presence of diisopropylethylamine (DIPEA).

83. The method according to any one of items 81 to 82, wherein step b. is performed between 0 °C to 30 °C.

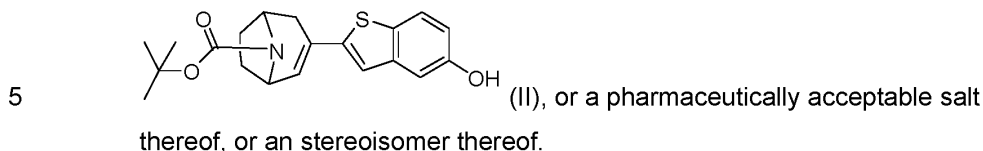
25 84. The method to any one of items 81 to 8376, wherein a liquid-liquid extraction between an organic and aqueous phase is performed on the mixture in step b. prior to step c.

85. The method according to any one of items 81 to 84, wherein the liquid chromatography in step c. comprises a stationary phase comprising a chiral selector.

30 86. The method according to any one of items 81 to 85, wherein the chiral selector is amylose tris(3-chloro-5-methylphenylcarbamate) as chiral selector

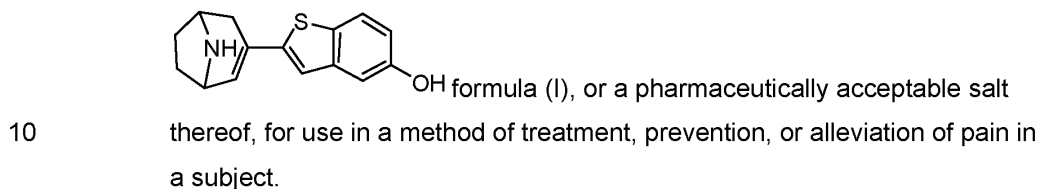
87. The method according to any one of items 81 to 86, wherein the chiral purity of (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol of more than 60%, such as more than 90%, such as more than 95%.

88. A compound according to formula (II):



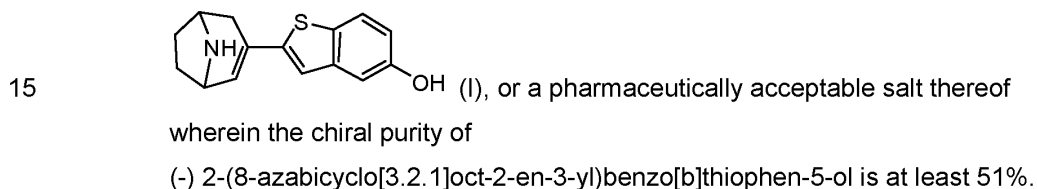
Items A

A1. A compound according to formula (I),



A2. The compound for use according to item A1, wherein the compound is (-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

A3. A composition comprising a compound of formula (I):



A4. The composition according to item A3, wherein the chiral purity of (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 90%.

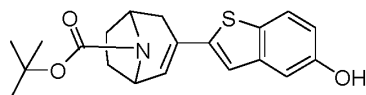
20

A5. The composition according any one of items A3 to A4, wherein the chiral purity of (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 98%.

A6. The composition according to any one of items A3 to A5, further comprising one or more pharmaceutically acceptable excipients or diluents.

25

- A7. A composition according to any one of items A3 to A6, for use in a method of treatment, prevention, or alleviation of pain in a subject.
- A8. The compound for use according to any one of items A1 to A2, or the composition for use according to item A7, wherein the pain is selected from the group consisting of:
- (i) chronic or acute primary pain,
 - (ii) chronic or acute cancer related pain,
 - (iii) chronic or acute postsurgical pain,
 - (iv) chronic or acute post-traumatic pain,
 - (v) chronic or acute secondary musculoskeletal pain,
 - (vi) chronic or acute secondary visceral pain,
 - (vii) chronic or acute neuropathic pain, and
 - (viii) chronic or acute secondary headache or orofacial pain.
- A9. The compound, or the composition, for use according to item A8, wherein the pain is neuropathic pain in a subject.
- A10. The compound, or the composition, for use according to any one of items A8 to A9, wherein the subject is administered with a further therapeutic agent for treatment of pain.
- A11. The compound, or the composition, for use according to any one of items A8 to A10, wherein the subject is a human.
- A12. A method of manufacturing of
 (+)- or (-)- 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol with
 chiral purity of 51% or more, the method comprising:
- a. providing a mixture of
 (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol and
 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol;
 - b. treating said mixture with (Boc)₂O in order to obtain a mixture of enantiomers
- of:



tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

- c. separating said mixture using chiral liquid chromatography to provide isolated enantiomer(s) of
- 5 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate; and
- d. deprotecting the isolated enantiomer(s) in step c. under acidic conditions to obtain enantiopure
- (+)- or (-)- 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

10

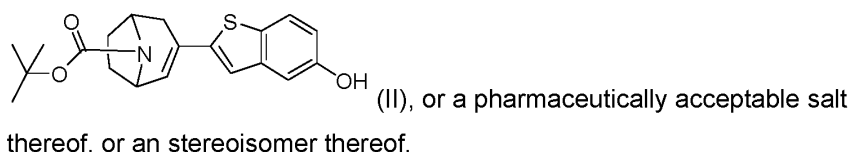
A13. The method according to item A12, wherein the liquid chromatography in step c. comprises a stationary phase comprising a chiral selector.

A14. The method according to item A12, wherein the chiral purity of (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol of more than 60%,

15 such as more than 90%, such as more than 95%.

15

A15. A compound according to formula (II):



20 Examples

Example 1: In vivo efficacy

Materials and Methods

The effects of IP2016 racemate in different animal pain models was studied.

Formalin-induced flinching behavior in rats

25 Formalin injection into the rat's hind paw is associated with spontaneous nociceptive behaviours consisting of flinching, licking, and biting the injected paw, reflecting various facets of sensory and emotional pain processing. Accordingly, formalin-induced flinching behaviour was assessed in normal, uninjured rats (body weight

180–300 g) in a non-biased manner using an Automated Nociception Analyser (Yaksh *et al.*, 2001). Briefly, this involved placing a small C-shaped metal band (10 mm wide × 27 mm long) around the hind paw of the rat, which should be tested. Each rat (four rats were included in each testing session) was randomized for the administration of either IP2016 (3, 10, 30 mg/kg) or a vehicle and then placed in a cylindrical acrylic observation chamber (diameter 15 cm and height 30.5 cm). The experimental observer was blinded for the treatments. After 60 mins, individual rats were gently restrained, and formalin (5% in saline, 50 µl, s.c.) was injected into the dorsal surface of the hind paw using a 27 G needle. They were then returned to their separate observation chambers, each of which was situated upon an enclosed detection device consisting of two electromagnetic coils designed to produce an electromagnetic field in which movement of the metal band could be detected. The analogue signal was then digitized, and a software algorithm was applied to enable discrimination of flinching behaviour from other paw movements before binning into 1-minute sampling intervals. Based on the resulting response patterns, three phases of nociceptive behaviour were identified (Munro *et al.*, 2008). A first phase (0–5 min) can be attributed to the direct chemical stimulation of nociceptors, and the interphase (6–15 min) is linked to the modulation of monoamine-containing pathways which descend from brainstem structures to inhibit nociceptive signaling in the spinal dorsal horn, and the second phase (16–40 min) can be attributed to peripheral inflammatory processes and subsequent sensitization of nociceptive spinal neurons (Coderre and Bennett, 2010). Raw data from the 1-minute sampling intervals were summed for each phase to obtain the total number of flinches occurring during that period. This value was then expressed as a % of the vehicle response for statistical analysis according to the equation, % Vehicle = (post-treatment value) / (Vehicle value) × 100.

Chronic constriction injury procedure

A chronic constriction injury (CCI) was performed in rats (body weight 180-220 g at the time of surgery) under isoflurane anesthesia as described previously (25). The sciatic nerve was exposed at the mid-thigh level proximal to the sciatic trifurcation. Four chromic gut ligatures (4/0) (Ethicon, New Brunswick, NJ) were tied loosely around the nerve, 1-2 mm apart, so the vascular supply was not compromised. The

overlying muscle was closed in layers with 4/0 synthetic absorbable surgical suture. The skin was closed and sutured with 4/0 silk thread.

- 5 Nerve-injured rats were routinely tested for the presence of neuropathic hypersensitivity for up to 5 weeks after surgery, according to previously described methods (26). For low threshold mechanical hypersensitivity (allodynia) testing, individual rats were removed from their home cage and allowed to habituate for 15 min in a 15 x 20 cm white Plexiglass testing cage, placed upon an elevated metal grid allowing access to the plantar surface of the injured hind paw. A series of calibrated von Frey filaments (lower limit=0.065 and upper limit=19.3 g, Stoelting
- 10 Co, Wood Dale IL) were then applied to the hind paw with the increasing force for a period of 1-2 s until an individual filament used just started to bend. The filament was applied 5 times at 1-2 s intervals. The filament that induced a reflex paw withdrawal in 3 out of 5 applications was considered to represent the threshold level for a response to occur. The presence of high threshold mechanical hypersensitivity
- 15 (hyperalgesia) was determined by pressing the plantar surface of the injured hind paw with the point of a safety pin at an intensity sufficient to produce a reflex withdrawal response in normal unoperated animals but at an intensity that was insufficient to penetrate the skin. A cut-off time of 15 s was applied to long withdrawals often seen for the nerve-injured paw.
- 20 On the day of drug testing, baseline responses to von Frey and pinprick stimulation were measured in CCI rats. Subsequently, CCI rats were randomized to injection with IP2016 (mixture of enantiomers, 3, 10, and 30 mg/kg) or vehicle prior to being returned to the von Frey testing chambers. The observer was blinded for the treatments. After 60 minutes, this sequence of behavioral testing was repeated,
- 25 enabling the post-treatment efficacy response to be measured.

Results

The results show that IP2016 produced positive results in pain-associated responses in the animal models (Figure 1). The number of flinches in the formalin model was reduced in the groups treated with IP2016.

Conclusion

The compound of formula (I) shows positive effects in the treatment of pain in animals.

Example 2: Purification of IP2016 enantiomers as HCl salt or salt-free form.

Materials and Methods

Sample material. IP2016 racemate of two isomers as HCl salt (7 g).

5 **Initial tests.** Separation of the racemic mixture as HCl salt was attempted using different analytical chiral columns under variation of solvents and additives.

Salt-free testing. The racemic mixture of HCl salt was treated with 7M NH₃ in methanol and prepared as free amine; during this process 100 mg of HCl salt was taken into 25 mL of RB flask and treated with 10.0 mL of methanolic NH₃ at 0°C and stirred for 3 hours. After addition of methanolic NH₃ clear solution within 10 minutes
10 was observed, after 3 hours precipitation occurred. The obtained precipitated free amine was filtered and used for separation of individual isomers.

Results

At first the separation of the racemic mix was attempted using different analytical chiral columns under variation of solvents and additives. No satisfying separation
15 could be achieved due to the very poor solubility of the components, or nature the hydrochloride salt mixture. The peak shape was wide and inseparable.

For the salt-free tests, no separation could be detected. There was no positive result in either normal or reverse phase chromatography.

Conclusion

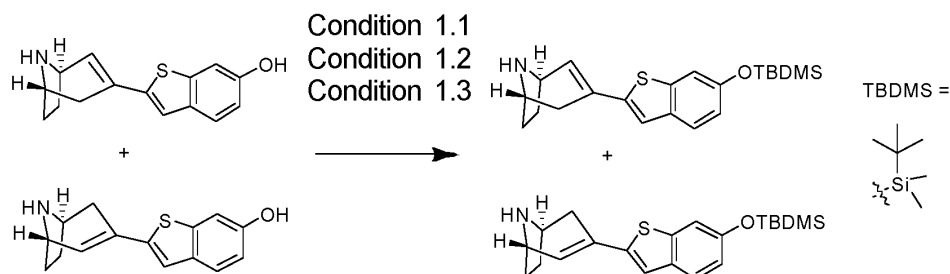
20 Separation of IP2016 enantiomers as hydrochloride salt or as free base was unsuccessful under different conditions due to the properties of the mixture.

Example 3: Testing of protection methods of IP2016

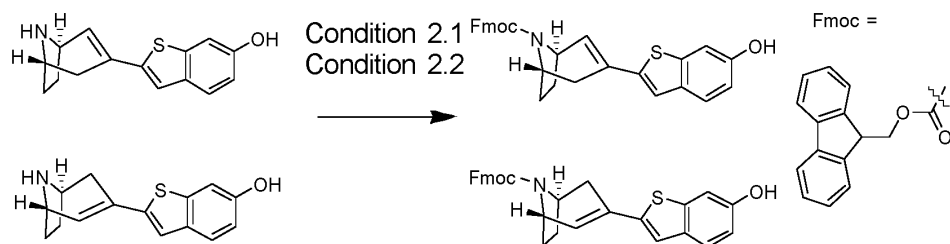
Materials and Methods

25 **Abbreviations.** DMAP: 4-dimethylaminopyridine, DCM: dicloromethane, THF: tetrahydrofuran, DIPEA: diisopropylethylamine.

Preparation of salts of IP2016 racemate for separation was attempted as follows:

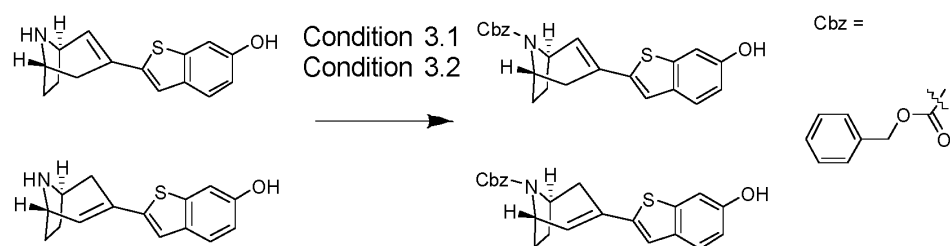
Protection with tert-butyl dimethyl silyl chloride (TBDMS-Cl).

Condition 1.1	TBDMS-Cl, DCM, Et ₃ N, 0 °C to room temperature, 16h
Condition 1.2	TBDMS-Cl, DCM, DMAP, 0 °C to room temperature, 16h
Condition 1.3	TBDMS-Cl, DCM, THF, 0 °C to room temperature, 24h

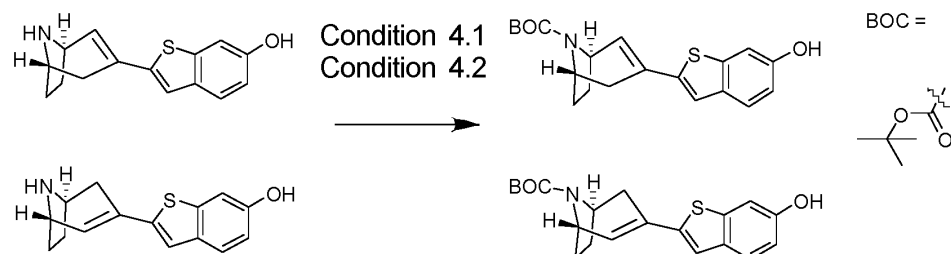
Protection with fluorenylmethyloxycarbonyl chloride (Fmoc-Cl).

5

Condition 2.1	FMoc-Cl, DCM, Et ₃ N, 0 °C to room temperature, 24h
Condition 2.2	FMoc-Cl, THF, Et ₃ N, 0 °C to room temperature, 24h

Protection with benzyl chloroformate (Cbz-Cl).

Condition 3.1	Cbz-Cl, DCM, Et ₃ N, 0 °C to room temperature, 24h
Condition 3.2	Cbz-Cl, K ₂ CO ₃ , KOH, THF, H ₂ O, 0 °C, 1h, room temperature 10h

Protection with tert-butyloxycarbonyl anhydride (Boc₂O).

Condition 4.1	(Boc) ₂ O, 1.0 eq, DCM, Et ₃ N 3.0 eq., 0 °C to rt, 3h
Condition 4.2	(Boc) ₂ O, 1.0 eq, DCM, DIPEA 3.0 eq., 0 °C to rt, 3h

Results

- 5 The protections with TBDMS-Cl, Fmoc-Cl and Cbz-Cl were unsuccessful. Very low yields of conversion were observed with these reagents or lack of formation of the desired product was observed with these reagents.

With (Boc)₂O, under condition 4.1 the major product formed was protected with Boc on both the free amine (-NH) and free hydroxyl (-OH) of IP2016, despite the use of only 1 equivalent of (Boc)₂O. The reaction of this doubly protected product under aqueous NaHCO₃ followed by LiOH to achieve selective deprotection at the -OH was unsuccessful.

15 With (Boc)₂O, under condition 4.2 the mono-protected compound with protection at the -NH was achieved in good yields. The product was washed with water, then extracted with DCM. The separated organics layer was washed with Brine, dried over Na₂SO₄ and concentrated in vacuum. Then purification over silica column was performed to obtain an isolated mixture of IP2016 enantiomers. The product was solid, good soluble in majority of solvents and suitable for successive purification.

Conclusion

- 20 Formation of -NH protected derivatives of IP2016 racemate is not successful with several common protecting reagents under common conditions for protection of amine groups. Specific conditions for protection with (Boc)₂O were identified.

Example 4: Chiral separation of IP2016 isomers

Materials and Methods

The Boc-protected racemate (Boc-IP2016) was separated using liquid chromatography in a column having amylose tris(3-chloro-5-methylphenylcarbamate) as chiral selector in the stationary phase (Chiralpak® IG 5µm 250 x 20mm HPLC-Column). The mobile phase was MeOH with 0.1% diethylamine in isocratic mode and a flow of 15.0 mL/min. For every injection, 50 mg of protected isomer mixture was loaded.

After preparative chiral separation, the isolated individual isomers were treated with 4 M HCl in Dioxane at 0 °C to 20 °C for 12 h. A precipitate was obtained which was filtered and washed with diethylether and pentane and dried before further characterization.

Analytical chiral HPLC. Column CHIRALPAK IG (250 x 4.6 mm), 5 µm. Mobile phase: MeOH/Diethylamine (100/0.1%). Flow rate: 1.0 mL/min. Detection: UV 260 nm.

Analytical LC-MS. Mobile phase A: 0.1% Formic acid in water. Mobile phase B: Acetonitrile:MeOH (50:50). Column: X-BRIDGE C18 (50 x 4.6mm), 3.5 µm. Time/%B: 0/30, 4/100, 5/100, 6/30. Flow: 1.0 mL/min.

Optical rotation measurements. Specific angle of rotation was measured in a MCP 200 apparatus at a wavelength of 589 nm, using an optical path length of 1.00 decimeters (dm) temperature of 20 °C and methanol as solvent.

Results

Isomer 1 was isolated in 577 mg and obtained with chiral purity of 98.11% as determined by the percentage of the area under the peak of isomer 1 compared to the total area under the peak of isomer 1 and isomer 2 in the chromatogram of the sample obtained after the chiral analytical HPLC. Figure 2 shows the chromatogram of Isomer 1. Retention time 12.73 min.

Parameters of chromatogram in Figure 2.

Peak	Ret. Time (min)	Height	Area	Area %
Isomer 1	12.732	159006	7317207	98.11
Isomer 2	19.713	2368	141045	1.89
Total		161374	7458252	100.00

Isomer 2 was isolated in 718 mg and obtained with chiral purity of 97.15% as determined by the percentage of the area under the peak of isomer 2 compared to the total area under the peak of isomer 1 and isomer 2 in the chromatogram of the sample obtained after the chiral analytical HPLC. Figure 3 shows the chromatogram of Isomer 2. Retention time 19.654 min.

Parameters of chromatogram in Figure 3.

Peak	Ret. Time (min)	Height	Area	Area %
Isomer 1	12.786	1345	50233	2.85
Isomer 2	19.654	24601	1713945	97.15
Total		25946	1764177	100.00

Table 1. Optical rotation of separated enantiomers.

	Isomer 1	Isomer 2
Concentration (mg/ 2 mL)	9.5	8.3
Angle of rotation in degrees (°)	-0.026	+0.020
Specific Angle of Rotation (°·mL·dm ⁻¹ ·g ⁻¹)	-5.458	+4.699

	Name
Isomer 1	(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol
Isomer 2	(+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol

Conclusion

Separation of IP2016 different enantiomers in high enantiomeric purity was achieved.

Example 5: Receptor screening assays

Materials and Methods

Effect on monoamine transporters. Two independent experiments were performed in human embryonic kidney (HEK293, ATCC-CRL-1573) cells stably expressing the 5-hydroxytryptamine transporter (hSERT) and noradrenaline transporter (hNAT), respectively. The dopamine transporter (hDAT) was overexpressed in Chinese hamster ovary cells (ATCC-CCL-61). A Neurotransmitter Transporter Assay was used following the providers' instructions (Molecular Devices, San Jose, California, U.S.A.). The cells were seeded in 96-well plates, and the uptake of fluorescence uptake in each cell line was measured in the presence of specific inhibitors of SERT, NAT, and DAT, respectively, citalopram hydrobromide, nisoxetine, and benzoethiophenylcyclohexylpiperidine (BTCP) each 1 μ M and 4-fold serial dilutions, 10 points in duplicate. To measure the effect of a racemic IP2016 sample, Isomer 1 and Isomer 2, the plated cells were exposed to 10 μ M of the compounds or vehicle in 4-fold serial dilution with 10 points in duplicate.

Affinity on opioid μ receptor. The affinity was determined by the measurement of specific radio ligands with affinity for the opioid receptor as they were displaced by the IP2016 samples, as measured by liquid scintillation counting. The opioid agonist DAMGO (CAS number: 78123-71-4) was included as a positive control.

Results

The results of each isomer on monoamine transporters is shown in Table 2. The racemic compound IP2016 inhibited the monoaminergic transporters with the largest effect on 5-HTT>NAT=DAT suggesting most considerable effect on serotonin uptake. In contrast, isomer 1 exhibits a more balanced effect on the three monoamine transporters with 5-HTT>NAT>DAT with less selectivity for the 5-HTT compared to the racemic IP2016. The isomer 2 has less potency for the 5-HTT compared to the racemic IP2016 and isomer 1, and even less selectivity comparing the 5-HTT versus NAT and DAT suggesting it is a more general monoamine reuptake inhibitor. From Table 2, it can be appreciated that Isomer 1 is the most potent of the two stereoisomers on all three monoaminergic transporters.

Table 2. IC₅₀ (nM) of compounds at the 5-hydroxytryptamine transporter (5-HTT), norepinephrine (NAT), and dopamine transporter (DAT).

	5-HTT	NAT	DAT
IP2016 racemate	0.25	51.97	57.33
IP2016 isomer 1	0.75	23.4	49.7
IP2016 isomer 2	6.0	47.09	140.60

In addition, isomer 1 shows an affinity for opioid μ receptors with IC₅₀ 240 nM, thus also indicating further potential effects in the treatment of pain through this receptor. Isomer 1 was seen to exert larger effects on opioid μ compared to isomer 2 at the when tested at the same concentration.

Conclusion

Isomer 1, corresponding to (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol displays higher potency of monoamine reuptake inhibition compared to Isomer 2.

Isomer 1 shows a significant affinity for opioid μ receptors and a higher effect compared to isomer 2, indicative of further improved properties for use in pain management via this receptor in addition to monoamine transporters.

Furthermore, the receptor binding profile of Isomer 1 regarding binding to the monoaminergic transporters and binding to off-targets is different from the racemate.

Example 6: Chiral stability of enantiomers of IP2016

Aim

To assess the stability of IP2016 enantiomers in aqueous medium.

Materials and Methods

Isomer 1 with isomeric purity of 98.11 % as described above was used. Isomer 2 with isomeric purity of 97.15% as describe above was used.

The stability was assessed at a total of 5 pH values: 1, 2, 3, 5 and 7.

On Day 1 of the total stability study the different test samples were prepared. The deprotected isomers were dissolved in pure water, pH Value adjusted to the certain

value using diluted HCl Solution. Racemic mixtures were also measured, because the mixture is also suitable to monitor the retention time differences in the chirality stability measurement. Afterwards the solutions were transferred in hermetically closed HPLC Vials. The measurements started instantly.

- 5 Then incubation took place in the HPLC vials during the total time of the study (18 days). One set was kept at room temperature, another set of the same HPLC Vials were kept cool at 4°C and measured after 4h. Additionally, freshly weighed Standards were prepared: The individual isomers as well as the racemate were freshly weighed immediately before the first measurements on Day 1 in order to
- 10 detect possible changes in the samples already in solution in comparison to the pH-adjusted test samples. On Day 1 of the total stability study the following samples were prepared each:

Test Samples:

- Isomer 1 (dissolved in pure water, adjusted to pH1, pH2, pH3, pH5 and
- 15 pH7 respectively)
- Isomer 2 (dissolved in pure water, adjusted to pH1, pH2, pH3, pH5 and pH7 respectively)
- Original Racemic Material

- 20 **Standards:** Freshly weighed immediately before the measurements:

- Isomer 1 (dissolved in pure water, no pH adjustment)
- Isomer 2 (dissolved in pure water, no pH adjustment)
- Mixture of Isomer 1 and Isomer 2 (dissolved in pure water, no pH adjustment
- 25 • Original Racemic Material (adjusted to pH1, pH2, pH3, pH5 and pH7 respectively)

- On each measurement day each test sample and standard was measured by LC in MeOH/Water (95/5%), 10 mM Ammonium Bicarbonate. Additionally, measurements using the 0.1% DIEA (diisopropylethylamine) method were performed. The stability
- 30 studies were performed over a period of 18 Days.

During the projects with the compounds their chiral stability was monitored continuously by applying stress conditions like temperature, solvent and acidic pH.

Analytical Chiral LC method.

Method 1: Column CHIRALPAK IG-3, 5 μ m RP, 150 x 4.6 mm. Mobile phase: MeOH/water (95/5%), 10 mM ammonium bicarbonate. Flow: 1.0 mL/min. UV: 295 nm.

- 5 Method 2: Column CHIRALPAK IG, 5 μ m, 250 x 4.6 mm. Mobile phase: MeOH/DIEA (100/0.1%). Flow 1.0 mL/min. UV: 295 nm.

Results

- 10 The results showed that the isomers are stable for a minimum of 2 weeks at room temperature in water at pH 1, 2, 3, 5 and 7 without significant modification of chirality, even under stress conditions. Figure 4 shows isomeric purity of Isomer 1 as calculated using the area of the corresponding chiral analytical HPLC peaks at pH 1.

- 15 The results showed that the isomers are stable for a minimum of 1 week at room temperature organic solvent (Dioxane) without significant modification of chirality, even under stress conditions (30 °C).

Conclusion

- 20 The separated an isolated enantiomers of IP2016 have good chiral stability in different conditions, including stress conditions.

Example 7: Stereochemistry configuration studies**Aim**

To perform structural studies on the absolute configuration of IP2016 enantiomers.

Materials and Methods

- 25 Enantiomers of IP2016 were separated as described in Example 4 yielding Isomer 1 and Isomer 2. Each of the separated enantiomers was derivitized using Mosher's reagent (3,3,3-trifluoro-2-methoxy-2-phenyl-propanoic acid, MTPA) in its (R) and (S) configuration respectively.

Hence the following 4 forms were generated:

- Isomer 1 (R)-MTPA
- Isomer 1 (S)-MTPA
- Isomer 2 (R)-MTPA
- 5 • Isomer 2 (S)-MTPA

Additionally, a portion of about 7 mg of the reaction product between IP2016 racemate mixture derivatized with MTPA, was also studied.

All NMR spectra were recorded on a JEOL ECZ spectrometer operating at 400 MHz (9.4 T) at 300 K.

- 10 A broadband probe with ^1H decoupling coil was used for all spectra. The ^1H NMR spectrum was recorded by adding 8 scans with an excitation pulse of 45° . The spectral width was 15 ppm (7.5 kHz clipped to 6.0 kHz) with a digital resolution of 0.22 Hz.

- 15 The hetero-nuclear correlation spectrum (^{13}C -hsqc) was recorded by a matrix of 1k complex data points (f2, ^1H dimension) and 1024 increments (1024 data points) in f1 ^{13}C dimension. The spectral width was 10 ppm in f2 (5 kHz clipped to 4 kHz) and 140 ppm (14.1 kHz) in f1. 8 scans were added with a repetition time of 0.95 s for each increment, resulting in a total of 16192 scans. The experimental time was 4 h.

- 20 The homonuclear correlation spectrum (cosy) was recorded by a matrix of 2k complex data points (f2, ^1H dimension) and 1024 increments (512 complex data points in f1). The spectral width was 10 ppm in f2 (5 kHz clipped to 4 kHz) and f1 (4 kHz). 8 scans were added with a repetition time of 2 s for each increment, resulting in a total of 8096 scans. The experimental time was 4.5 h.

- 25 The homonuclear NOE spectrum (noesy) was recorded by a matrix of 2k complex data points (f2, ^1H dimension) and 1024 increments (512 complex data points in f1). The spectral width was 10 ppm in f2 (5 kHz clipped to 4 kHz) and f1 (4 kHz). 8 scans were added with a repetition time of 3.5 s for each increment, resulting in a total of 8096 scans. The experimental time was 8 h.

- 30 After processing and correcting the baseline using a polynomial of degree 5 with automated detection of the signal threshold a total of 184 integral regions were manually defined and numerically integrated using the Bruker Topspin 4.3.0

software. The limit of sensitivity was evaluated from 12 integration regions in a signal-free part of the spectrum and the variance (in units of the digital resolution) set to 1. The five-fold variance was then added to and subtracted from all the integrals of assigned correlations used for the upper and lower distance. The distance calibration for each of the 4 species was obtained from three (or two in case of the cis-amide of MCC13997) geminal proton pairs which are 1.8 Å apart. (4 or 6 integrals) All distances were calculated assuming the theoretical R^{-6} dependency. Only non-trivial distances are listed in Table 3.

The heteronuclear long-range correlation spectrum (hmbc) was recorded by a matrix of 4k complex data points (f2, ^1H dimension) and 1024 increments (512 complex data points in f1). The spectral width was 8 ppm in f2 (4 kHz clipped to 3.2 kHz) and 110 ppm in f1 (11 kHz, optimized folding at 125 ppm). 24 scans were added with a repetition time of 3.5 s for each increment, resulting in a total of 24576 scans. The experimental time was 15 h.

Different conformational combinations of each of the isomers of IP2016 together with the (R)-isomer of Mosher's salt were modelled using the free software AVOGADRO (Hanwell et al.) and the force field MFF94 (Halgren et al.).

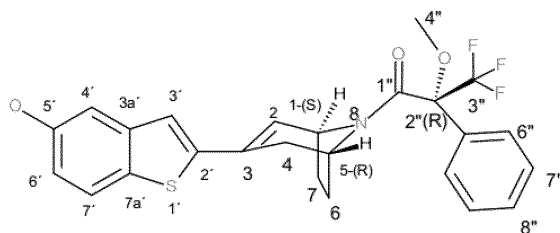
Results

The use of Mosher's salt (MTPA, 3,3,3-trifluoro-2-methoxy-2-phenyl-propanoic acid) derivatives of amines and alcohols in the determination of absolute configuration due to induction of ^1H -NMR chemical shift differences is well documented (Latypov et al.; Seco et al.; Hoyer et al.) and has been validated based on X-ray crystal structures (Ichikawa et al.).

The NMR analysis was carried out on the mixture of diastereomers obtained from derivatization of the IP2016 racemate with (R)-MTPA and the resulting assignment was compared to spectra of the optically pure diastereomers obtained from derivatization of the separated enantiomers of IP2016 with (R)-MTPA or (S)-MTPA.

The diastereomers formed by reaction of the IP2016 enantiomers with (R)-MTPA are described below:

- 2-((1S,5R)-8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol Mosher's salt derivative:



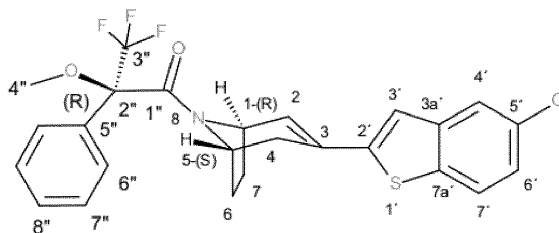
5

Name: (2R)-3,3,3-trifluoro-1-[(1S,5R)-3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl]-2-methoxy-2-phenyl-propan-1-one

Abbreviated: (1S,5R)-(R)MTPA

- 2-((1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol Mosher's salt derivative:

10



Name: (2R)-3,3,3-trifluoro-1-[(1R,5S)-3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl]-2-methoxy-2-phenyl-propan-1-one

Abbreviated: (1R,5S)-(R)MTPA

15

The resulting secondary MTPA amides of each of the IP2016 isomers adopts two stable conformations, resulting in a major (higher populated) and minor (lower populated) rotamer for each diastereoisomer. These rotamers can be assigned based on chemical shift differences in the ^{13}C -NMR and correlations of signals in the NOESY spectra, similarly to well-established rules for the -Pro amide bonds in peptides (London et al.; Dorman et al.; Grathwohl et al.; Siemion et al.).

20

The 4 combinations:

- (1R,5S)-(R)MTPA, major rotamer,
- (1R,5S)-(R)MTPA, minor rotamer,
- (1S,5R)-(R)MTPA, major rotamer, and
- 5 • (1S,5R)-(R)MTPA, minor rotamer;

were modelled using the free software AVOGADRO and the forcefield MMFF94. First, optimal conformations were searched by random orientation of the rotation bonds and the results were further optimized by a force field calculation. Next, the two major conformations of the amide bond for each rotamer were fixed by a
10 constraint of the torsion angle and the procedure was repeated (conformational search and optimization using the MMFF94 force field repeated).

The results were well in accordance with the preference of amide-bond rotamers. Based on the models for the MTPA-derivatives of IP2016 isomers, the orientation of the phenyl ring of the MTPA residue should induce a characteristic decrease in
15 chemical shift of protons located within the anisotropy-cone (Günther et al.). The anisotropy cone of a phenyl ring scales with the inverse square of the distance and, depending on the motional averaging of the phenyl-ring, an induced shielding larger than 0.2 ppm (chemical shift difference between protons) can be observed for distances up to 8 Å.

20 For the major rotamers, the cone of anisotropy points to H2 protons in (1R,5S)-(R)MTPA, and to H7 proton in (1S,5R)-(R)MTPA. For the minor rotamers, the cone of anisotropy points to H6 protons in (1R,5S)-(R)MTPA and to H4 protons in (1S,5R)-(R)MTPA. Thus, said protons are expected to have lower chemical shifts in each of the respective conformations.

25 As can be seen in Table 3, for the major rotamers, protons in the H2 position have a lower chemical shift in Isomer 1 (R)-MTPA (bolded), while protons in the H7 position have a lower chemical shift in Isomer 2 (R)-MTPA (underlined).

For the minor rotamers, protons in the H6 position have a lower chemical shift in Isomer 1 (R)-MTPA (*), while protons in the H4 position have a lower chemical shift
30 in Isomer 2 (R)-MTPA (**).

Table 3. ¹H-NMR shifts of selected protons in Isomer 1 (R)-MTPA and Isomer 2 (R)-MTPA.

Proton	Rotamer	Isomer 2 (R)-MTPA ¹ H chemical shift (δ)	Isomer 1 (R)-MTPA ¹ H chemical shift (δ)	$\Delta\delta$ (Isomer 2-Isomer 1)
H2	Major	6.29	5.17	1.12
	Minor	6.35	6.38	-0.03
H4-a	Major	2.97	3.04	-0.07
	Minor	1.04**	2.99**	-1.95**
H6-a	Major	1.90	2.08	-0.18
	Minor	2.20*	1.05*	1.15*
H7-b	Major	0.94	1.81	-0.87
	Minor	1.86	1.60	0.26
H1	Major	4.23	4.40	-0.17
	Minor	4.91	5.04	-0.13
H5	Major	4.94	4.76	0.18
	Minor	4.55	4.11	0.44

5 Thus, the experimentally measured chemical shift differences based on the expected anisotropic shielding effects of the phenyl group in MTPA provides the following assignment of the following stereochemistry to each of the IP2016 enantiomers:

Isomer 1	2-((1R,5S)-8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol
Isomer 2	2-((1S,5R)-8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol

Conclusion

10 Absolute configuration of IP2016 enantiomers has been assigned based on the interpretation of the chemical shift differences induced by the anisotropy of the phenyl residue in the MTPA derivatives.

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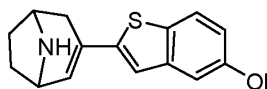
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Claims

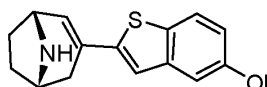
1. A composition comprising a compound of formula (I):



(I), or a pharmaceutically acceptable salt thereof

wherein the chiral purity of

- 5 (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 51%.
2. The composition according to claim 1, wherein the chiral purity of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 60%.
3. The composition according to claim 1, wherein the chiral purity of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 90%.
- 10 4. The composition according to claim 1, wherein the chiral purity of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least of 95%,
such as at least of 98%.
5. The composition according to claim 1, wherein the the enantiomeric excess of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 10%, or
15 at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%,
or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least
80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.
6. The composition according to claim 1, wherein the the enantiomeric excess of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 50 %.
- 20 7. The composition according to claim 1, wherein the the enantiomeric excess of
(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is at least 90 %.
8. The composition according to claim 1, wherein the compound of formula (I) is
a compound of formula (Ib):



(Ib), or a pharmaceutically acceptable salt thereof

25 wherein the chiral purity of the compound of formula (Ib) is at least 51%.

9. The composition according to claim 6, wherein the chiral purity of the
compound of formula (Ib) is at least 60%.

10. The composition according to claim 6, wherein the chiral purity of the compound of formula (Ib) is at least of 90%.
11. The composition according to claim 6, wherein the chiral purity of the compound of formula (Ib) is at least of 95%, such as at least of 98%.
- 5 12. The composition according to claim 6, wherein the enantiomeric excess of the compound of formula (Ib) is at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 55%, or at least 60%, or at least 65%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%.
- 10 13. The composition according to claim 1, wherein the enantiomeric excess of the compound of formula (Ib) is at least 50 %.
14. The composition according to claim 1, wherein the enantiomeric excess of the compound of formula (Ib) is at least 90 %.
- 15 15. The composition according to any one of claims 1 to 14, further comprising one or more pharmaceutically acceptable excipients or diluents.
16. The composition according to any one of claims 1 to 15, comprising a further therapeutic agent effective for the treatment of pain.
17. A composition according to any one of claims 1 to 16, for use in a method of treatment, prevention or alleviation of pain in a subject.
- 20 18. A compound for use in a method of treatment, prevention, or alleviation of pain in a subject, wherein said compound is
(-)-2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.
19. The composition according to claim 17, or the compound for use according to claim 18 wherein the pain is selected from the group consisting of:
25 (i) chronic or acute primary pain,
(ii) chronic or acute cancer-related pain,
(iii) chronic or acute postsurgical pain,
(iv) chronic or acute post-traumatic pain,
(v) chronic or acute secondary musculoskeletal pain,

- (vi) chronic or acute secondary visceral pain,
- (vii) chronic or acute neuropathic pain, and
- (viii) chronic or acute secondary headache or orofacial pain.

- 5 20. The composition or the compound for use according to claim 19, wherein the chronic or acute primary pain is chronic or acute primary visceral pain, chronic or acute widespread pain, fibromyalgia syndrome, chronic or acute primary musculoskeletal pain, chronic or acute primary headache or orofacial pain, such as migraine, burning mouth syndrome, tension-type headache, cluster
- 10 headache or hemicranias continua; complex regional pain syndrome (CRPS) or painful bruising syndrome.
21. The composition or the compound for use according to claim 19, wherein the chronic or acute cancer-related pain is related to visceral cancer pain, bone cancer pain or neuropathic cancer pain.
- 15 22. The composition or the compound for use according to claim 19, wherein the chronic or acute cancer-related pain is post-cancer treatment pain, such as post-cancer medicine pain, such as painful chemotherapy-induced polyneuropathy, such as post-radiotherapy pain, such as painful radiation-induced neuropathy.
- 20 23. The composition or the compound for use according to claim 19, wherein the chronic or acute postsurgical pain is postsurgical pain after spinal surgery, after herniotomy, after hysterectomy, after amputation, after thoracotomy, after breast surgery, or after arthroplasty.
- 25 24. The composition or the compound for use according to claim 19, wherein the chronic or acute post-traumatic pain is pain after burns injury, pain associated with whiplash injury, pain after musculoskeletal injury.
- 30 25. The composition or the compound for use according to claim 19, wherein the chronic or acute secondary musculoskeletal pain is pain from persistent inflammation, such as inflammation due to infection, inflammation due to crystal deposition, or inflammation due to autoimmune and auto-inflammatory disorders; pain associated with structural changes, such as pain associated to

osteoarthritis or associated with spondylosis; pain due to disease of the nervous system such as pain associated to Parkinson's disease, such as pain associated to multiple sclerosis or pain associated to peripheral neurologic disease.

- 5 26. The composition or the compound for use according to claim 19, wherein the chronic or acute secondary visceral pain is pain from mechanical factors, vascular mechanism, or persistent inflammation, such as mechanical factor, vascular mechanism or persistent inflammation in the head, neck, thoracic, abdominal or pelvic regions.
- 10 27. The composition or the compound for use according to claim 19, wherein the chronic or acute neuropathic pain is central neuropathic pain, such as central neuropathic pain associated with spinal cord injury, brain injury, post-stroke pain or associated with multiple sclerosis; peripheral neuropathic pain, peripheral neuropathic pain after nerve injury, painful polyneuropathy or painful
- 15 radiculopathy; or neuropathic orofacial pain.
28. The composition or the compound for use according to claim 19, wherein the chronic or acute secondary headache or orofacial pain is chronic dental pain, chronic neuropathic orofacial pain, headache or orofacial pain associated with temporomandibular disorders, associated with disorders in homeostasis or their
- 20 nonpharmacological treatment, associated with cranial or cervical vascular disorder, associated with non-vascular intracranial disorder, associated with a substance or its withdrawal, or associated with traumatic injury to the head.
29. The composition or the compound for use according to any one of claims 19 and 27 to 28, wherein the pain is neuropathic pain.
- 25 30. The composition or the compound for use according to any one of claims 19 and 27 to 29, wherein the neuropathic pain is acute neuropathic pain.
31. The composition or the compound for use according to any one of claims 19 and 27 to 29, wherein the neuropathic pain is chronic neuropathic pain.
32. The composition or the compound for use according to any one of claims 29 to
- 30 31, wherein the neuropathic pain is due to alcoholism, diabetes, multiple

sclerosis, multiple myeloma, stroke, cancer, cytomegalovirus, trigeminal neuralgia, spinal cord injury, or amputation.

33. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to chronic progressive nerve disease.
- 5 34. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to infection.
35. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to injury.
- 10 36. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is ongoing pain after neuropathic injury.
37. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to a side effect of a medication.
38. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to a medical procedure, such as surgery.
- 15 39. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is idiopathic.
40. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is a neuropathic component of nociceptive pain.
- 20 41. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to diabetic neuropathy.
42. The composition or the compound for use according to claim 41, wherein the diabetes is chronic diabetes.
- 25 43. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is neuropathic cancer pain.
44. The composition or the compound for use according to any one of claims 29 to 31, wherein the neuropathic pain is due to treatment-emergent neuropathy.

45. The composition or the compound for use according to claim 44, wherein the treatment-emergent neuropathy is due to chemotherapy.
- 5 46. The composition or the compound for use according to claim 44, wherein the treatment-emergent neuropathy is due to radiotherapy.
47. The composition or the compound for use according to claim 44, wherein the treatment-emergent neuropathy is due to surgery.
48. The composition or the compound for use according to any one of claims 19 to 47, wherein the pain is trigeminal neuralgia, allodynia or hyperalgesia.
- 10 49. The composition or the compound for use according to any one of claims 19 to 48, wherein the pain is trigeminal neuralgia.
50. The composition or the compound for use according to claim 49, wherein the pain is selected from classical trigeminal neuralgia; secondary trigeminal neuralgia, such as attributed to multiple sclerosis, such as attributed to a space-
15 occupying lesion; and idiopathic trigeminal neuralgia.
51. The composition or the compound for use according to any one of claims 49 to 50, wherein the pain is painful trigeminal neuropathy, such as attributed to herpes zoster, such as post-herpetic neuralgia, such as post-traumatic trigeminal neuropathy, such as idiopathic painful trigeminal neuropathy.
- 20 52. The composition or the compound for use according to any one of claims 19 to 51, wherein the pain post-herpetic neuralgia.
53. The composition or the compound for use according to any one of claims 19 to 52, wherein the pain is pain in Parkinson's disease.
54. The composition or the compound for use according to any one of claims 19 to
25 53, wherein the pain is sexual pain disorder.
55. The composition or the compound for use according to any one of claims 19 to 54, wherein the pain is vulvar pain.

56. The composition or the compound for use according to any one of claims 19 to 55, wherein the pain is vulvodynia or progressive vulvodynia.
57. The composition or the compound for use according to any one of claims 19 to 56, wherein the pain is pain associated with associated with genitourinary syndrome of menopause (GSM), or pain associated with vaginal atrophy, vulvovaginal atrophy, urogenital atrophy, or atrophic vaginitis.
58. The composition or the compound for use according to any one of claims 19 to 57, wherein the composition or the compound is capable of inducing a pain reduction in a subject of at least 5%, such as at least 10%, such as at least 15%, such as 20% pain reduction.
59. The composition or the compound for use according to claim 58, wherein the pain reduction is a subjective measure of pain.
60. The composition or the compound for use according to claim 58, wherein the pain reduction is a measurement of a pain threshold.
61. The composition or the compound for use according to any one of claims 58 to 54, wherein the measurement of pain is performed on a Visual Analogue Scale (VAS) or a numeric rating scale (NRS) or a patient-reported outcome (PRO).
62. The composition or the compound for use according to any one of claims 19 to 61, wherein the pain occurs at least for 1 minute, such as at least for 5 minutes, such as at least for 10 minutes, such as at least for 30 minutes, such at least for 1 hour, such as at least for 2 hours, such as for more than 2 hours.
63. The composition or the compound for use according to any one of claims 19 to 62, wherein the pain occurs for at least one day, such as for at least 3 days, such as for at least a week.
64. The composition or the compound for use according to any one of claims 19 to 63, wherein the pain occurs during more than a week, such as during more than two weeks, such as during more than three weeks, such as during more than a month, such as during more than two months, such as during more than three months at least 20% of the days, such as at least 30%, such as at least 40% or at least 50% of the days.

65. The composition or the compound for use according to any one of claims 19 to 64, wherein the subject is administered with a further therapeutic agent effective for the treatment of pain.
- 5 66. The composition or the compound for use according to any one of claims 19 to 65, wherein the compound is administered in an amount from about 0.01 to 100 mg per individual dose.
67. The composition or the compound for use according to any one of claims 19 to 66 wherein the subject is a mammal.
- 10 68. The composition or the compound for use according to any one of claims 19 to 67, wherein the subject is a human.
69. The composition or the compound for use according to any one of claims 19 to 68, wherein the administration of the composition or the compound is an oral administration.
- 15 70. The composition or the compound for use according to any one of claims 19 to 68, wherein the administration of the composition or the compound is parenteral administration, such as cutaneous, mucosal, subcutaneous, intramuscular, intraperitoneal, intravenous or intra-arterial injection.
- 20 71. The composition or the compound for use according to any one of claims 19 to 70, further comprising a pharmaceutically acceptable diluent, carrier and/or excipient.
72. The composition or the compound for use according to claim 71, wherein the composition or the compound is formulated as a solid dosage form, such as a tablet, a capsule, a pill, granules or a powder.
- 25 73. The composition or the compound for use according to any one of claims 19 to 72, wherein the composition comprises a further therapeutic agent effective for the treatment of pain.

74. A method of manufacturing of

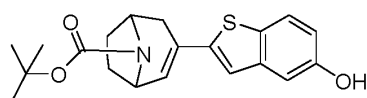
(+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol with chiral purity of 51% or more, the method comprising:

a. providing a mixture of

5 (+) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol and

(-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol;

b. treating said mixture with (Boc)₂O in order to obtain a mixture of enantiomers of:



10 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate

c. separating said mixture using chiral liquid chromatography to provide isolated enantiomer(s) of

15 tert-butyl 3-(5-hydroxybenzo[b]thiophen-2-yl)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate; and

d. deprotecting the isolated enantiomer(s) in step c. under acidic conditions to obtain enantiopure

(+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol.

20 75. The method according to claim 74, wherein step b. is performed using DCM as solvent and in the presence of diisopropylethylamine (DIPEA).

76. The method according to any one of claims 74 to 75, wherein step b. is performed between 0 °C to 30 °C.

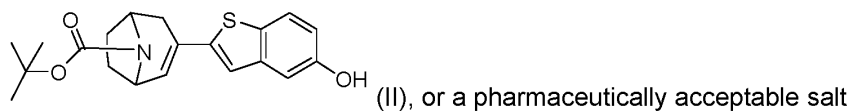
25 77. The method according to any one of claims 74 to 76, wherein a liquid-liquid extraction between an organic and aqueous phase is performed on the mixture in step b. prior to step c.

78. The method according to any one of claims 74 to 77, wherein the liquid chromatography in step c. comprises a stationary phase comprising a chiral selector.

30 79. The method according to any one of claims 74 to 78, wherein the chiral selector is amylose tris(3-chloro-5-methylphenylcarbamate) as chiral selector.

80. The method according to any one of claims 74 to 79, wherein the acidic conditions in step d. are provided by an organic or inorganic acid, such as hydrochloric acid (HCl), trifluoroacetic acid (TFA), or sulphuric acid (H₂SO₄).
81. The method according to any one of claims 74 to 80, wherein the deprotecting
5 in step d. is performed in an organic solvent, such as dioxane; or in an aqueous solution.
82. The method according to any one of claims 74 to 81, wherein the chiral purity of (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is of more than 60%, such as more than 90%, such as more than 95%.
- 10 83. The method according to any one of claims 74 to 82, wherein the chiral purity of (+) or (-) 2-(8-azabicyclo[3.2.1]oct-2-en-3-yl)benzo[b]thiophen-5-ol is of more than 90%.

84. A compound according to formula (II):



15 thereof, or an stereoisomer thereof.