International Patent Specification Nos. WO2007/093880A2 and WO2007/093880A3. The entire contents of the above-mentioned patents and literature references are incorporated herein by reference.

SUMMARY

[0013] The present disclosure provides in one example, use of at least one pyrone-indole compound selected from compounds described in U.S. Patent Nos. 7,635,710, 8,242,163 and 8,569,355 and International Patent Specification Nos. WO2007/093880A2 and WO2007/093880A3, the entire contents of these references are incorporated herein by reference, in an effective amount, in the manufacture of a medicament, for treating itch and /or pruritus, in a patient suffering from dermatological and non-dermatological conditions leading to such symptoms, wherein the medicament additionally comprises at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifier, adjuvant or carrier.

[0013a] In one aspect, the present disclosure refers to the use of a compound having the formula Ar—B—Ar′ (I) in the manufacture of a medicament for treating a subject suffering from itch or pruritus, wherein:

—B— represents:

—X—Y—Z—,

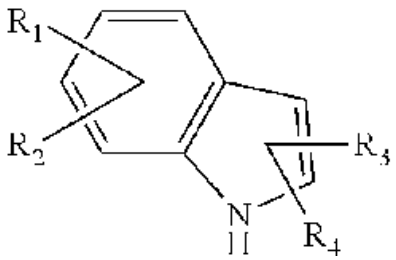
wherein:

X represents —(CH2)n (wherein n is 0-6);

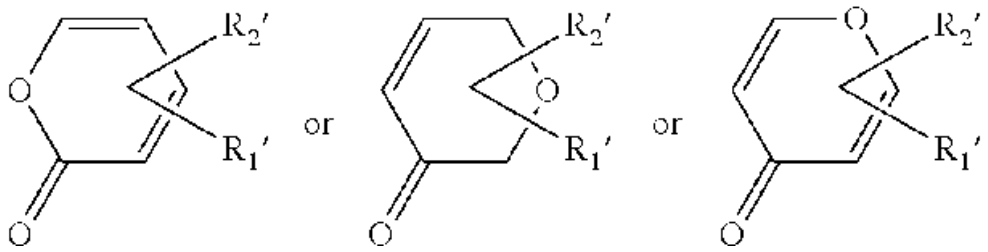
Y represents oxygen, sulphur, >NH or is absent;

Z represents >C=O, >O or >COO or is absent; and wherein at least one of X, Y and Z must be present;

Ar represents an indole nucleus ring system:



Ar′ represents an alpha-, beta- or gamma-pyrone nucleus ring system:



wherein each of R1-4 substitutes the ring system Ar at any available position (includingthe N-position) and each of R1′-R2′ substitutes the ring system Ar′ at any available position and wherein each of R1-4 and R1′-2′ independently represents hydrogen,oxygen, halo, halo-C1-5 alkyl, aryl, acyl, a C5-7 heterocyclic group containing 1-3 hetero atoms independently selected from nitrogen, oxygen or sulphur; a C6-8 heteroaryl group containing 1-3 hetero atoms independently selected from nitrogen, oxygen or sulphur, C1-5 alkyl, C2-5 alkenyl, C2-5 alkynyl, aryl-C1-5 alkyl, aryl- C2-5 alkenyl, aryl-C2-5 alkynyl, hydroxy-C1-5 alkyl, nitro, amino, cyano, cyanamide, guanidino, amidino, acylamido, C1-5 alkylamine, C1-5 alkylamido, hydroxy, thiol, acyloxy, azido, C1-5 alkoxy, carboxy, carbonylamido or styryl; wherein said arylalkyl, arylalkenyl, aralalkynyl, or styryl group optionally can be ring-substituted by one to four substituents independently selected from the group consisting of hydrogen, halo, halo-C1-5 alkyl, aryl, a C5-7 heterocyclic group containing 1-3 hetero atoms independently selected from nitrogen, oxygen and sulphur; a heteroaryl group containing 1-3 hetero atoms independently selected from nitrogen, oxygen and sulphur; C1-5 alkyl, C2-5 alkenyl, C2-5 alkynyl, aryl-C1-5 alkyl, aryl-C2-5 alkenyl, aryl-C2-5alkynyl, hydroxy-C1-5 alkyl, nitro, amino, cyano, cyanamido, guanidino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, S-alkyl or alkylthiol;

and either of R3 or R4 further can include or represent a bond to B; wherein Ar is bonded to B at position 3 on the five-membered ring portion of the Ar ring and Ar′ can be bonded to B at any carbon on the Ar′ ring not substituted by R1′ and R2′; or a salt, stereoisomer, or racemic mixture thereof, and

at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifier, gelling agent, adjuvant or carrier.

[0014] In another example, the present disclosure provides a method for treating a subject suffering from itch and/or pruritus by administering an effective amount of at least one compound of this disclosure to the subject.

[0015] In still another example, the present disclosure provides a medicament for use in a patient suffering from dermatological and non-dermatological conditions leading to itch and/or pruritus. The medicament composition contains an effective amount of at least one compound of this disclosure and at least one additional therapeutic agent selected from UV protectants, hypnotics, sedatives, analgesics, minor tranquilizers, and anti-inflammatory drugs, in addition to at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifiers adjuvant or carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 shows a stimulus voltage pattern used for determining blocking effects on hNav1.x channels.

DETAILED DESCRIPTION OF THE INVENTION

[0017] In one aspect, the present disclosure includes a method for treating a patient suffering from itch and/or pruritus by administering an effective amount of a pharmaceutical composition containing a compound having the formula (I):

Ar-B-Ar' (I)

I claim:

1. Use of a compound having the formula:

Ar—B—Ar′ (I)

in the manufacture of a medicament for treating a subject suffering from itch or pruritus, wherein:

—B— represents:

—X—Y—Z—,

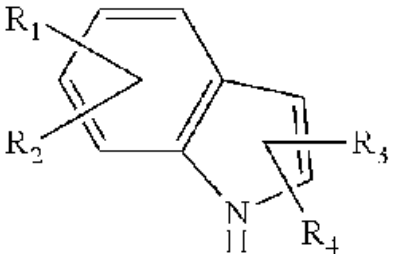
wherein:

X represents —$(CH_2)_n$ (wherein n is 0-6);

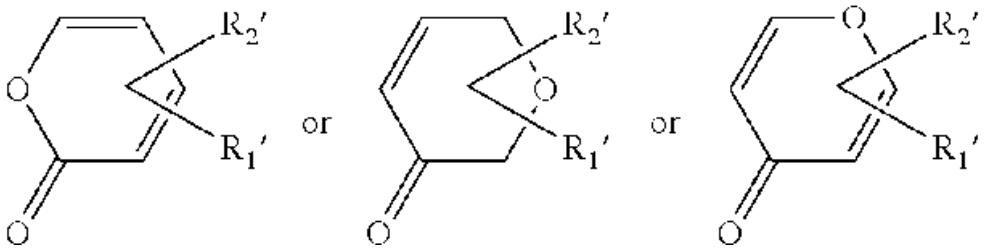
Y represents oxygen, sulphur, >NH or is absent;

Z represents >C=O, >O or >COO or is absent; and wherein at least one of X, Y and Z must be present;

Ar represents an indole nucleus ring system:



Ar′ represents an alpha-, beta- or gamma-pyrone nucleus ring system:



wherein each of R1-4 substitutes the ring system Ar at any available position (includingthe N-position) and each of $R_{1'}$-$R_{2'}$ substitutes the ring system Ar′ at any available position and wherein each of R_{1-4} and $R_{1'-2'}$ independently represents hydrogen,oxygen, halo, halo-C_{1-5} alkyl, aryl, acyl, a C_{5-7} heterocyclic group containing

1-3 hetero atoms independently selected from nitrogen, oxygen or sulphur; a C_{6-8} heteroaryl group containing 1-3 hetero atoms independently selected from nitrogen, oxygen or sulphur, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, aryl-C_{1-5} alkyl, aryl- C_{2-5} alkenyl, aryl-C_{2-5} alkynyl, hydroxy-C_{1-5} alkyl, nitro, amino, cyano, cyanamide, guanidino, amidino, acylamido, C_{1-5} alkylamine, C_{1-5} alkylamido, hydroxy, thiol, acyloxy, azido, C_{1-5} alkoxy, carboxy, carbonylamido or styryl; wherein said arylalkyl, arylalkenyl, aralalkynyl, or styryl group optionally can be ring-substituted by one to four substituents independently selected from the group consisting of hydrogen, halo, halo-C_{1-5} alkyl, aryl, a C_{5-7} heterocyclic group containing 1-3 hetero atoms independently selected from nitrogen, oxygen and sulphur; a heteroaryl group containing 1-3 hetero atoms independently selected from nitrogen, oxygen and sulphur; C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, aryl-C_{1-5} alkyl, aryl-C_{2-5} alkenyl, aryl-C_{2-5}alkynyl, hydroxy-C_{1-5} alkyl, nitro, amino, cyano, cyanamido, guanidino, amidino, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido, S-alkyl or alkylthiol;

and either of R_3 or R_4 further can include or represent a bond to B; wherein Ar is bonded to B at position 3 on the five-membered ring portion of the Ar ring and Ar′ can be bonded to B at any carbon on the Ar′ ring not substituted by $R_{1'}$ and $R_{2'}$; or a salt, stereoisomer, or racemic mixture thereof, and

at least one pharmaceutically acceptable diluent, preservative, antioxidant, solubilizer, emulsifier, gelling agent, adjuvant or carrier.

2. The use of claim 1, wherein X is -$(CH_2)_n$, wherein n is 0-6, Y is >NH or >O and Z is >CO.

3. The use of claim 1, wherein Ar' is an alpha-pyrone ring system.

4. The use of claim 1, wherein Ar' is a beta-pyrone ring system.

5. The use of claim 1, wherein Ar' is a gamma-pyrone ring system.

6. The use of claim 1, wherein X is -$(CH_2)_n$, Y is >NH or >O, and Z is >CO, Ar is an indole ring; R_3 is a bond to X on position 3 of the indole ring; R_1 is hydrogen or a methoxy group on position 5 of the indole ring, and each of R_2 and R_4 is hydrogen; Ar' is a gamma-pyrone ring bonded to Z at position 2 of the pyrone ring;

$R_{1'}$ is hydrogen or a hydroxy group on position 5 of the pyrone ring; and $R_{2'}$ is hydrogen or a carboxy group on position 6 of the gamma-pyrone ring; or a pharmaceutically acceptable salt, stereoisomer, or racemic mixture thereof.

7. The use of claim 1, wherein X is $-(CH_2)_n$, Y is >NH or >O and Z is >COO; Ar is an indole ring; R_3 is a bond to X on position 3 of the indole ring; R_1 is a methoxy group at position 5 of the indole ring and each of R_2 and R_4 is hydrogen; Ar' is an gamma-pyrone ring substituted by Z at position 4 of the pyrone ring; and R_1, and R_2 are each a methyl or hydrogen; or a pharmaceutically acceptable salt, stereoisomer, or racemic mixture thereof.

8. The use of claim 1, wherein the compound of formula (I) is selected from the group consisting of N-[2-(1H-indol-3-yl)-ethyl]-comanilamide, N-[2-(5-methoxy-indol-3-yl)-ethyl]-comanilamide, and 2-methyl-4-oxo-4H-pyran-3-yl [2-(5-methoxy-1H-indol-3-yl)ethyl]carbamate.

9. The use of any one of claims 1 to 8, wherein said composition or said medicament further comprises at least one of the following features: (i) it is adapted for oral, rectal, parenteral, transbuccal, intrapulmonary (e.g. by inhalation) transdermal or topical administration; (ii) it is in unit dosage form, each unit dosage comprising an effective amount of said at least one compound; (iii) it is a prolonged release formulation; (iv) it is in a depot form which will release the compound slowly in the body, over a preselected time period; (v) it is an ointment, cream, gel, emulsion, oil, foam, solution or aerosol spray suitable for topical use; (vi) it further comprises at least one additional therapeutic agent selected from a UV protectant, an analgesic, a tranquilizer, a vasoconstrictor, a vasodilator, and an anti-inflammatory agent.

10. The use of claim 9, wherein said composition or said medicament is a solid oral dosage form selected from capsules, tablets, pills, powders or granules.

11. The use of claim 10 wherein the compound of formula I is admixed with at least one inert pharmaceutically acceptable carrier selected from sucrose, lactose or starch.

12. The use of claim 11, wherein said composition or said medicament further comprises one or more lubricating agents.

13. The use of claim 12, wherein said composition or said medicament comprises magnesium stearate.

14. The use of any one of claims 11 to 13, wherein the said composition or said medicament further comprises one or more of the following:

- a binder,

- an excipient,

- a disintegrating agent;

- a sweetening agent;

- a flavoring agent.

15. The use of claim 14, wherein:

- the binder is selected from one or more of gum tragacanth, acacia, corn starch or gelatin,

-the excipient is microcrystalline cellulose;

-the disintegrating agent is selected from one or more of corn starch, pregelatinized starch or alginic acid;

-the sweetening agent is selected from one or more of sucrose, lactose or saccharin;

-the flavoring agent is peppermint, oil of wintergreen or cherry.

16. The use of claim 9, wherein said composition or said medicament is a topical formulation in the form of an ointment, a gel, a cream, an emulsion, an oil, a foam or a spray for dermal application.

17. The use of claim 1, wherein said composition or said medicament is a cream formulation comprising shea butter, coconut oil and a therapeutically effective amount of a pyrone-indole derivative of formula (I).

18. The use of claim 17, wherein the pyrone-indole derivative of formula (I) is N-[2-(1H-indol-3-yl)-ethyl]-comanilamide.

19. The use of claim 18, wherein N-[2-(1H-indol-3-yl)-ethyl]-comanilamide is at a concentration from 1 to 10%, or from 2 to 8%, or from 3 to 5%, or of 3%.