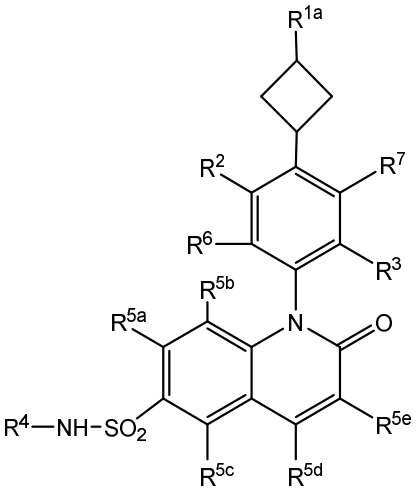
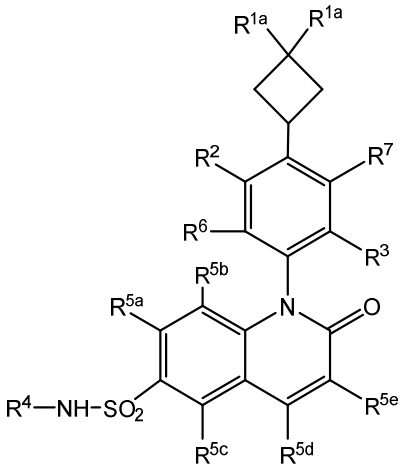
Wherein a P atropisomer of said compound of Formula (I) is selectively formed.

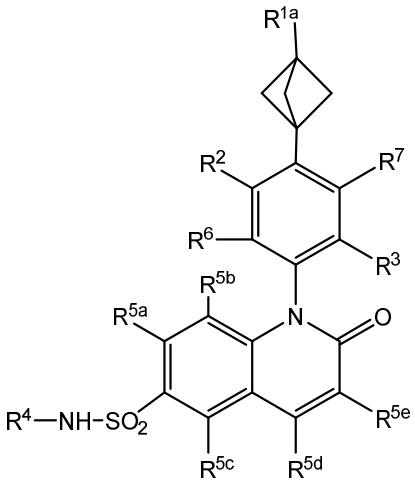
[0064a] In one example, the present disclosure refers to a compound of Formula (Ia), (Ib) or (Ic):



(Ia);



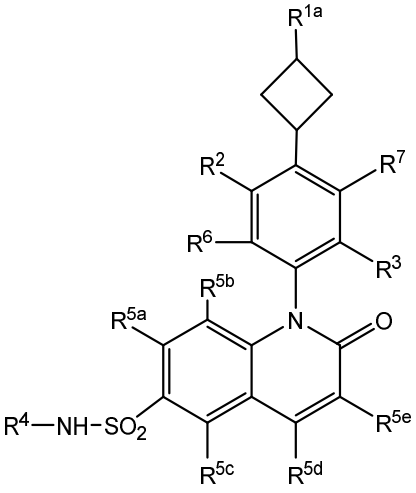
(Ib); or



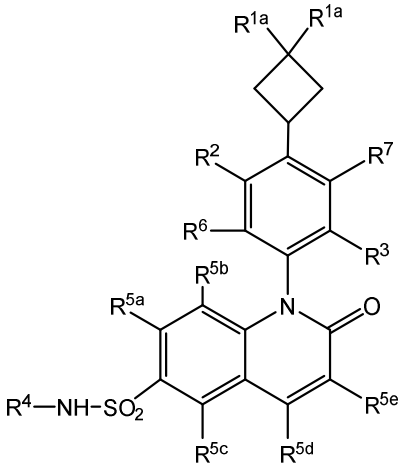
(Ic);

an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; wherein: R^{1a} is selected from halo, $C_{1\text{-}8}$alk, $C_{1\text{-}8}$haloalk or -O-$C_{1\text{-}4}$alk, wherein said $C_{1\text{-}8}$haloalk is C1-8fluoroalkyl; R^2 is H, halo, $C_{1\text{-}6}$alk, or $C_{1\text{-}6}$haloalk; R^3 is $C_{1\text{-}6}$alk, $C_{1\text{-}6}$haloalk, -O-$C_{1\text{-}6}$alk, or –CN; R^4 is a 5- to 6-membered heteroaryl; each of R^6 and R^7 is hydrogen; and each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is independently hydrogen or halo.

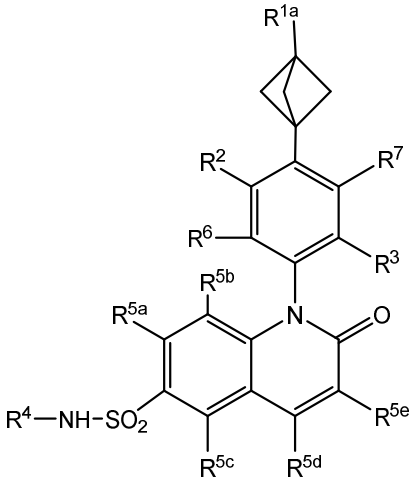
In one aspect, the present disclosure refers to a compound of Formula (Ia), (Ib) or (Ic):



(Ia);



(Ib); or



(Ic);

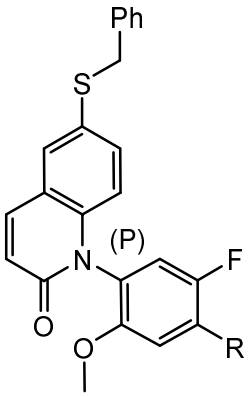
or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof; wherein: each R^{1a} is independently selected from fluoro, chloro, methyl, -O-CF_3, or CF_3; R^2 is H, halo, C_{1-6}alk, or C_{1-6}haloalk; R^3 is C_{1-6}alk, C_{1-6}haloalk, -O-C_{1-6}alk, or –CN; R^4 is a 5- to 6-membered heteroaryl; each of R^6 and R^7 is hydrogen; and each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is independently hydrogen or halo.

[0064b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, or the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0064c] In another aspect, the present disclosure refers to use of the compound as disclosed herein, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof; or the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a composition described herein in the manufacture of a medicament for treating pain, cough, or itch, wherein the pain is selected from chronic pain, acute pain, neuropathic pain, pain associated with rheumatoid arthritis, pain associated with osteoarthritis, pain associated with cancer, peripheral diabetic neuropathy, and neuropathic low back pain; and wherein the cough is selected from post viral cough, viral cough, or acute viral cough.

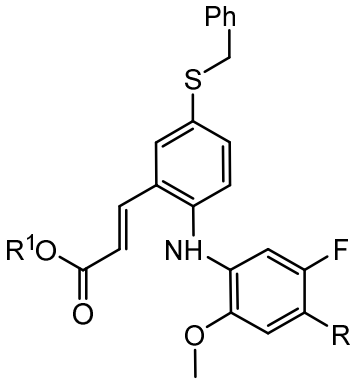
[0064d] In another aspect, the present disclosure refers to the compound as disclosed herein, an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof; or the compound as disclosed herein, or a pharmaceutically acceptable salt thereof; or a composition described herein for use in therapy.

[0064e] A method of preparation of a compound of Formula (A):



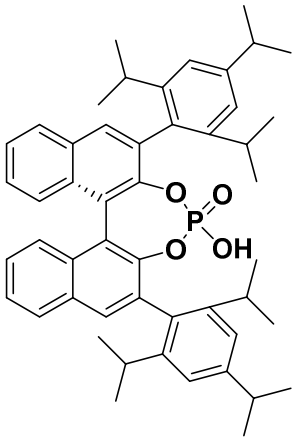
(A);

wherein R is halo; comprising: (1) reacting a trans olefin compound of Formula (B):



(B);

wherein R is halo; and R^1 is C_1-C_6alkyl; with a UV light or near UV light; to form a cis olefin compound (C); and (2) reacting said compound (C) with a chiral acid in an organic solvent to form said compound of Formula (A); wherein said chiral acid is a phosphorus chiral acid; or wherein said chiral acid is (S)-TRIP having the formula:



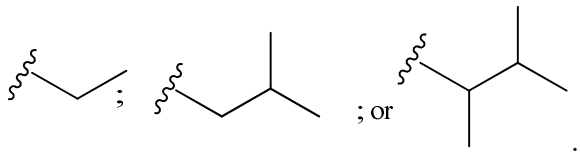
;

wherein said organic solvent is dichloromethane; wherein said R is bromo; wherein said R^1 is ethyl; or wherein in reaction (2), a P atropisomer of said compound of Formula (A) is selectively formed.

DETAILED DESCRIPTION OF THE INVENTION

[0065] The present invention provides compounds of Formula (I), as defined above, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof. The present invention also provides pharmaceutical compositions comprising a compound of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, and methods of treating diseases and/or conditions, such as pain, using compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof.

[0066] The term "$C_{\alpha\text{-}\beta}$alk" means an alkyl group comprising a minimum of α and a maximum of β carbon atoms in a branched or linear relationship or any combination of the two, wherein α and β represent integers. A designation of C_0alk indicates a direct bond. Examples of $C_{1\text{-}6}$alk include, but are not limited to, the following:



[0067] The term "halo" or "halogen" means a halogen atoms selected from F, Cl, Br or I.

[0068] The term "$C_{\alpha\text{-}\beta}$haloalk" means an alk group, as defined herein, in which at least one of the hydrogen atoms has been replaced with a halo atom, as defined herein. Common $C_{\alpha\text{-}\beta}$haloalk groups are $C_{1\text{-}3}$fluoroalk. An example of a common $C_{1\text{-}3}$fluoroalk group is $-CF_3$.

[0069] The term "heteroatom" as used herein means an oxygen, nitrogen or sulfur atom.

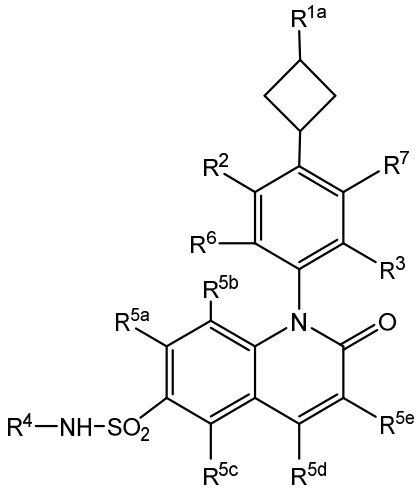
[0070] The term "monocyclic ring" as used herein means a group that features one single ring. A monocyclic ring can be carbocyclic (all of the ring atoms are carbons), or heterocyclic (the rings atoms include at least 1 heteroatom, for example, 1, 2 or 3 heteroatoms, such as N, O, or S, in addition to carbon atoms). Examples of monocyclic rings include, but are not limited to: cyclobutyl, cyclopentyl, or cyclohexyl.

[0071] The term "bicyclic ring" as used herein means a group that features two joined rings. A bicyclic ring can be carbocyclic (all of the ring atoms are carbons), or heterocyclic (the rings atoms include at least one heteroatom, for example, 1, 2 or 3 heteroatoms, such as N, O, or S, in addition to carbon atoms). The two rings can both be aliphatic (*e.g.* decalin and norbornane), or can be aromatic (*e.g.*naphthalene), or a combination of aliphatic and aromatic (*e.g.* tetralin). Bicyclic rings include (a) spirocyclic compounds, wherein the two rings share only one single atom, the spiro atom, which is usually a quaternary carbon. Examples of spirocyclic compound include, but are not limited to

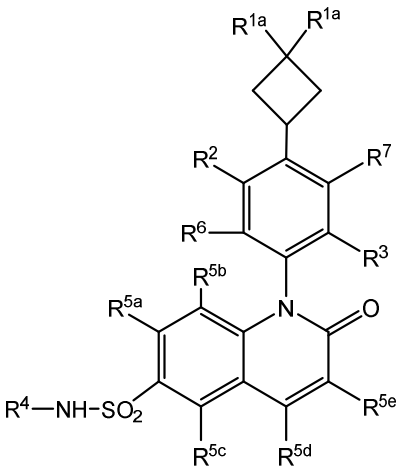
CLAIMS

What is claimed is:

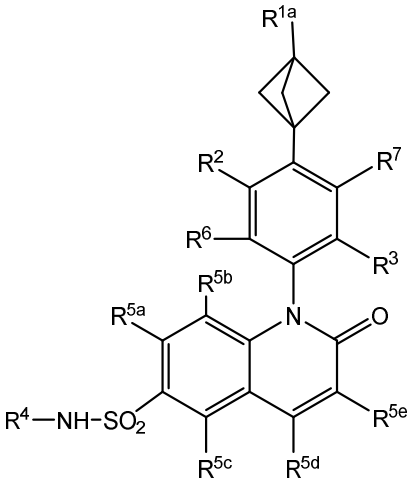
1. A compound of Formula (Ia), (Ib) or (Ic):



(Ia);



(Ib); or



(Ic);

or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof;

wherein: each R^{1a} is independently selected from fluoro, chloro, methyl, -O-CF_3, or CF_3;

R^2 is H, halo, $C_{1\text{-}6}$alk, or $C_{1\text{-}6}$haloalk;

R^3 is $C_{1\text{-}6}$alk, $C_{1\text{-}6}$haloalk, -O-$C_{1\text{-}6}$alk, or –CN;

R^4 is a 5- to 6-membered heteroaryl;

each of R^6 and R^7 is hydrogen; and

each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is independently hydrogen or halo.

2. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ia).

3. The compound according to Claim 1 or Claim 2, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ia); wherein said R^{1a} is CF_3 or -O-CF_3; R^2 is H, F, or methyl; and R^4 is isoxazolyl or pyridazinyl.

4. The compound according to any one of Claims 1-3, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ia); wherein said R^{1a} is CF_3; R^2 is F; and R^4 is isoxazolyl.

5. The compound according to Claim 1, or an enantiomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ia); wherein said R^{1a} is CF_3; the cyclobutyl ring is a *trans* isomer; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, or oxazolyl.

6. The compound according to any one of Claims 1-5, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ia); wherein each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is hydrogen.

7. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ib); wherein each R^{1a} is fluoro or CF_3.

8. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ib); wherein each R^{1a} is fluoro; R^2 is F; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

9. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ib); wherein each R^{1a} is fluoro; R^{5a} is F; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

10. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ib); wherein each R^{1a} is F; R^2 is F or Cl; and R^4 is isoxazolyl.

11. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ib); wherein each R^{1a} is F; R^2 is F; and R^4 is isoxazolyl.

12. The compound according to Claim 1, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound is of Formula (Ic); wherein R^{1a} is CF_3.

13. The compound according to any one of claims 1-12, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said atropisomer, when present, is a P atropisomer.

14. The compound according to claim 1, wherein said compound is *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein said compound is (P)-1-(5-chloro-4-(3,3-difluorocyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 1, wherein said compound is *trans*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, wherein said compound is (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-7-fluoro-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising the compound according to any one of claims 1-13, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof, or the compound according to any one of claims 14-17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

19. Use of the compound according to any one of claims 1-13, or an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof; or the compound according to any one of claims 14-17, or a pharmaceutically acceptable salt thereof; or the composition according to claim 18 in the manufacture of a medicament for treating pain, cough, or itch, wherein the pain is selected from chronic pain, acute pain, neuropathic pain, pain associated with rheumatoid arthritis, pain associated with osteoarthritis, pain associated with cancer, peripheral diabetic neuropathy, and neuropathic low back pain; and wherein the cough is selected from post viral cough, viral cough, or acute viral cough.

20. The compound according to anyone of claims 1-13, an enantiomer, diastereoisomer, atropisomer, or a mixture thereof, or a pharmaceutically acceptable salt thereof; or the

compound according to any one of claims 14-17, or a pharmaceutically acceptable salt thereof; or the composition according to claim 18 for use in therapy.