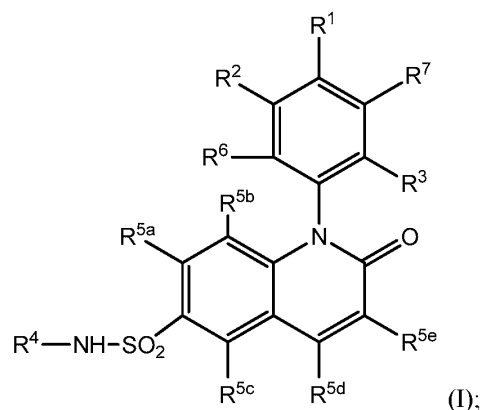


CLAIMS

What is claimed is:

1. A compound of Formula (I):



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

wherein: R¹ is a saturated or partially-saturated 4-membered monocyclic ring; or a 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic ring; wherein said monocyclic ring or bicyclic ring contains 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S; and wherein said monocyclic ring or bicyclic ring is substituted by 0, 1, 2 or 3 R^{1a} groups selected from hydroxy, halo, C₁₋₈alk, C₁₋₈haloalk, -O-C₁₋₄alk, -O-C₁₋₈haloalk, -C(=O)C₁₋₄alk, -O-C(=O)C₁₋₄alk, -NH₂, -NHC₁₋₄alk, or -N(C₁₋₄alk)C₁₋₄alk;

R² is H, halo, C₁₋₆alk, or C₁₋₆haloalk;

R³ is C₁₋₆alk, C₁₋₆haloalk, -O-C₁₋₆alk, or -CN;

R⁴ is a 5- to 6-membered heteroaryl;

Each of R⁶ and R⁷ 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, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R^{1a} group is selected from halo, C₁₋₈alk, -O-C₁₋₄alk, or C₁₋₈haloalk, wherein said C₁₋₈haloalk is C₁₋₈fluoroalkyl.

3. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a cyclobutyl ring; or a 5-, or 6-membered bicyclic ring; wherein said cyclobutyl ring or bicyclic ring contains 0 N, O, and S atoms; and wherein said cyclobutyl ring or bicyclic ring is substituted by 1, 2 or 3 R^{1a} groups selected from F, -CF₃, -O-CF₃, or -C(CH₃)₃.

4. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a

cyclobutyl ring or bicyclo[1.1.1]pentan-1-yl ring; wherein each ring is substituted by 1 or 2 F or -CF₃.

5. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a cyclobutyl ring substituted by 1 or 2 F or -CF₃.

6. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a cyclobutyl ring substituted by 1 or 2 -CF₃.

7. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a cyclobutyl ring substituted by 1 or 2 F.

8. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R¹ is a bicyclo[1.1.1]pentan-1-yl ring substituted by 1 or 2 F or -CF₃.

9. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R² is H, fluoro, chloro, methyl, CF₃, CHF₂, or CH₂F.

10. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R² is H, fluoro, chloro, or methyl.

11. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R² is H or fluoro.

12. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R³ is methoxy.

13. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R⁴ is a 5-membered heteroaryl.

14. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R⁴ is a 6-membered heteroaryl.

15. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R⁴ is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

16. The compound according to claim 15, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R^4 is isoxazolyl.

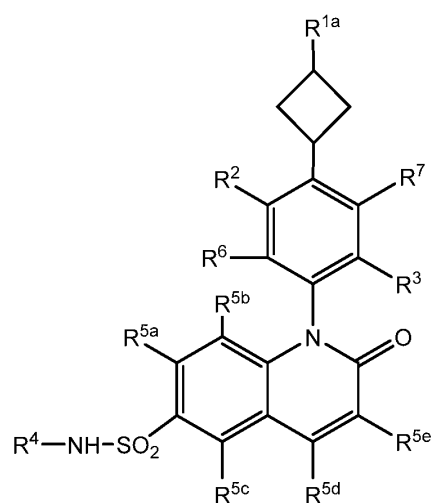
17. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein (a) each of R^{5a} , R^{5b} , R^{5c} , R^{5d} and R^{5e} is hydrogen; (b) R^{5a} is F; and each of R^{5b} , R^{5c} , R^{5d} , and R^{5e} is hydrogen; or (c) R^{5c} is F; and each of R^{5a} , R^{5b} , R^{5d} , and R^{5e} is hydrogen.

18. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said R^{5a} is F.

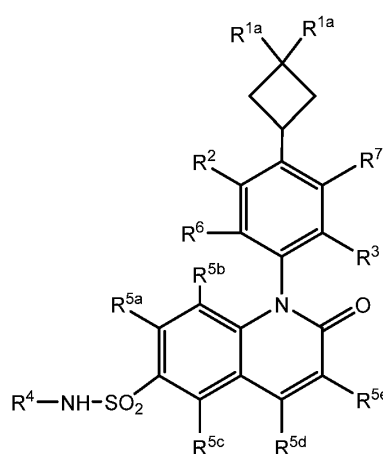
19. The compound according to claim 15, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein each of R^{5a} , R^{5b} , R^{5c} , R^{5d} and R^{5e} is hydrogen.

20. The compound according to claim 15, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is F; and each of R^{5b} , R^{5c} , R^{5d} , and R^{5e} is hydrogen.

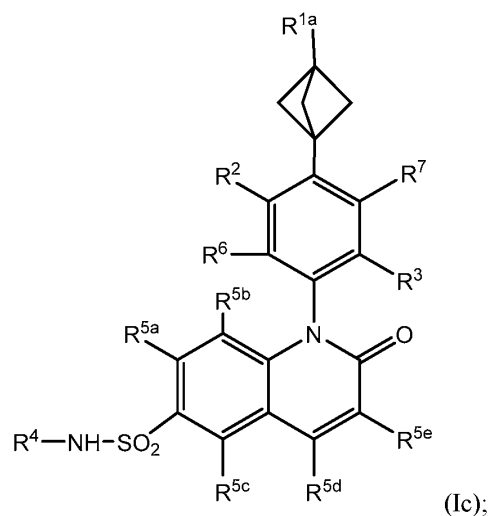
21. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is selected from compounds of Formula (Ia), (Ib), or (Ic):



(Ia);



(Ib); or



wherein each R^{1a} in said compounds of Formula (Ia), (Ib), or (Ic) is independently fluoro, chloro, methyl, $-O-CF_3$, or CF_3 .

22. The compound according to Claim 21, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound 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.

23. The compound according to Claim 21, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ia); wherein said R^{1a} is *cis* CF_3 ; the cyclobutyl ring is a *cis* isomer; R^2 is F; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, or oxazolyl.

24. The compound according to Claim 21, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ib); wherein each R^{1a} is fluoro; R^2 is F; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

25. The compound according to Claim 21, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ib); wherein each R^{1a} is fluoro; R^{5a} is F; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

26. The compound according to Claim 21, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ic); wherein each R^{1a} is CF_3 .

27. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

- a) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- b) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- c) *cis*-(P)-1-(5-chloro-2-methoxy-4-((1S,3S)-3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- d) *trans*-(P)-1-(5-chloro-2-methoxy-4-((1S,3S)-3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- e) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;
- f) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;
- g) *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- h) *trans*-(P)-1-(2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;
- i) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;
- j) (P)-7-fluoro-1-(5-fluoro-2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- k) (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- l) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethoxy)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- m) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethoxy)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- n) *trans*-(P)-5-fluoro-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or
- o) *trans* (P)-1-(5-chloro-2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

28. The compound according to claim 1, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

- a) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- b) (P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- c) *trans*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- d) *cis*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- e) *cis*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- f) *trans*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;
- g) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-7-fluoro-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or
- h) (P)-1-(5-chloro-4-(3,3-difluorocyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

29. The compound according to claim 1, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

- a) (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or
- b) (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide.

30. The compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said atropisomer is a P atropisomer.

31. A pharmaceutical composition comprising a compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

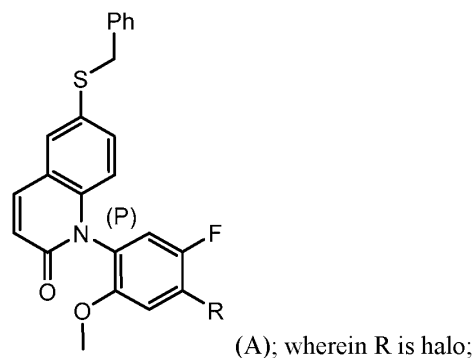
32. A method of treating pain, cough, or itch, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to Claim 1, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof.

33. The method according to claim 32; 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.

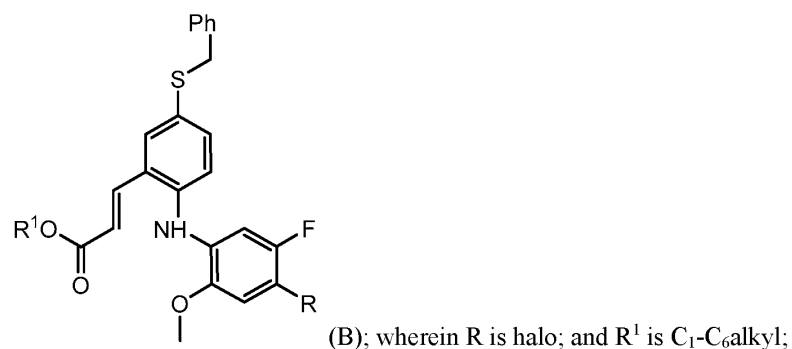
34. The method according to claim 32; wherein the cough is selected from post viral cough, viral cough, or acute viral cough.

35. A method of preparation of a compound of Formula (A):



comprising:

(1) reacting a trans olefin compound of Formula (B):

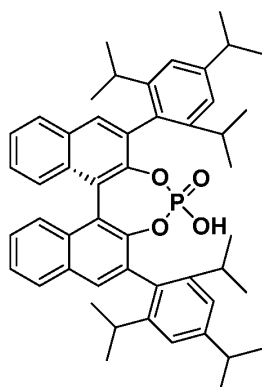


with a UV light or near UV light; to form a cis olefin compound (C); and

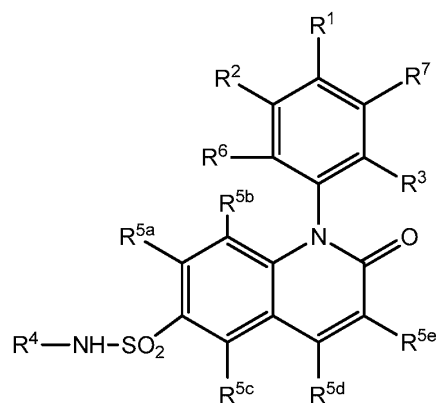
(2) reacting said compound (C) with a chiral acid in an organic solvent to form said compound of Formula (A).

36. The method of claim 35, wherein said chiral acid is a phosphorus chiral acid.

37. The method of claim 35 wherein said chiral acid is (S)-TRIP having the formula:



38. The method of claim 35, wherein said organic solvent is dichloromethane.
39. The method of claim 35, wherein said R is bromo.
40. The method of claim 35, wherein said R¹ is ethyl.
41. The method of claim 35, wherein in reaction (2), a P atropisomer of said compound of Formula (A) is selectively formed.
42. The method of claim 35, wherein said compound of Formula (A) is used as an intermediate compound in preparation of a compound of Formula (I):



(I); or a pharmaceutically acceptable salt thereof,

wherein:

R¹ is a saturated or partially-saturated 4-membered monocyclic ring; or a 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic ring; wherein said monocyclic ring or bicyclic ring contains 0, 1, 2 or 3 N atoms and 0, 1, or 2 atoms selected from O and S; and wherein said monocyclic ring or bicyclic ring is substituted by 0, 1, 2 or 3 R^{1a} groups selected from hydroxy, halo, C₁₋₈alk, C₁₋₈haloalk, -O-C₁₋₄alk, -O-C₁₋₈haloalk, -C(=O)C₁₋₄alk, -O-C(=O)C₁₋₄alk, -NH₂, -NHC₁₋₄alk, or -N(C₁₋₄alk)C₁₋₄alk;

R² is H, halo, C₁₋₆alk, or C₁₋₆haloalk;

R³ is C₁₋₆alk, C₁₋₆haloalk, -O-C₁₋₆alk, or -CN;

R⁴ is a 5- to 6-membered heteroaryl;

Each of R⁶ and R⁷ is hydrogen; and

Each of R^{5a} , R^{5b} , R^{5c} , R^{5d} , and R^{5e} is independently hydrogen or halo; and

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