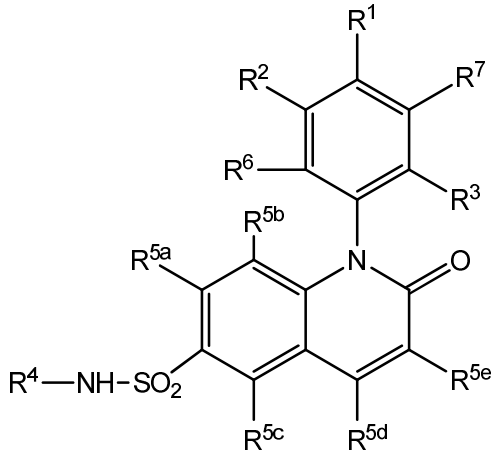
measured functions are normal, with the only reported abnormality being anosmia (inability to smell). These studies indicate that among the many possible targets in the pain pathway, Nav 1.7 governs one or more control points critical for pain perception.

[0006] Nonselective sodium channel inhibitors such as lidocaine, mexiletine, and carbamazepine show clinical efficacy in chronic pain, including neuropathic pain, but they are limited in dose and in use, likely due to effects on sodium channels outside the pain pathway. Lidocaine is a local anesthetic doctors use for minor surgery. Dentists use novocaine. However, these compounds do not distinguish between the various sodium channel subtypes, making them unsuitable for use as systemic pain killers. “If you give a drug that blocks Nav1.7 but also blocks Nav1.5, the patient will die of heart failure,” says Glenn F. King, a professor at Australia’s University of Queensland who studies venoms that block ion channels. “It will be a completely painless death, but the patient will die nonetheless.” Thus, selectivity for Nav1.7 is desired, particularly over Nav1.5. Researchers have tailored their efforts to find a molecule that inhibitors or block the activity of only Nav1.7. To compound this problem, the identity, every location, every function and/or the tertiary structures of each subtype of voltage gated sodium channel proteins are not known or completely understood.

[0007] Consequently, a number of researchers are attempting to identify small molecule inhibitors of Nav1.7. For example, Chafeev et al disclose spiro-oxindole compound for the treatment and/or prevention of sodium channel-mediated diseases, such as pain, in U.S. Patent No. 8,101,647. International Publications WO 2013/134518 and WO 2014/201206 disclose sulfonamide derivatives which are different from the sulfonamide derivatives of the present invention. Thus, there is a need to identify Nav1.7 inhibitors selective over at least Nav1.5 to treat pain. The present invention provides compounds that are selective inhibitors of Nav 1.7. over at least Nav1.5.

SUMMARY

[0008] In example 1, the present disclosure provides a compound of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,



(I);

wherein:

R^1 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, C_{1-8}alk, C_{1-8}haloalk, -O-C_{1-4}alk, -O-C_{1-8}haloalk, -C(=O)C_{1-4}alk, -O-C(=O)C_{1-4}alk, -NH_2, -NHC_{1-4}alk, or -N(C_{1-4}alk)C_{1-4}alk;

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

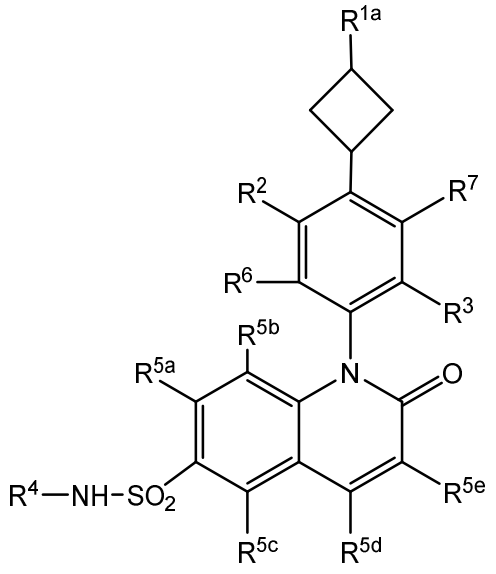
R^3 is C_{1-6}alk, C_{1-6}haloalk, -O-C_{1-6}alk, or –CN;

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.

[0009] In sub-example 1a of example 1, the compound of Formula (I) has a sub-Formula of (Ia):



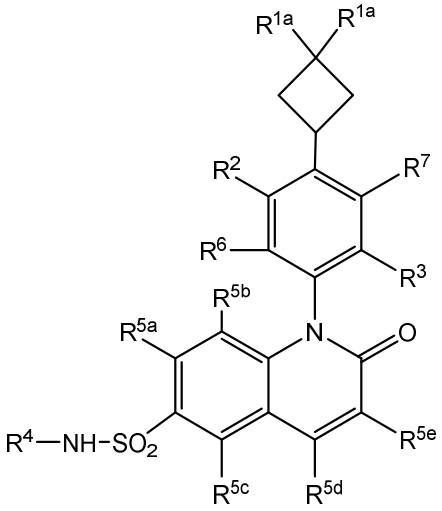
(Ia);

wherein R^{1a} is fluoro, chloro, methyl, -O-CF_3, or CF_3.

[0010] In a more preferred sub example 1a of example 1, R^{1a} is CF_3 or-O-CF_3; R^2 is H, F, or methyl; and R^4 is isoxazolyl or pyridazinyl.

[0011] In a most preferred sub example 1a of example 1, R^{1a} is CF_3; R^2 is F; and R^4 is isoxazolyl.

[0012] In sub-example 1b of example 1, the compound of Formula (I) has a sub-Formula of (Ib):



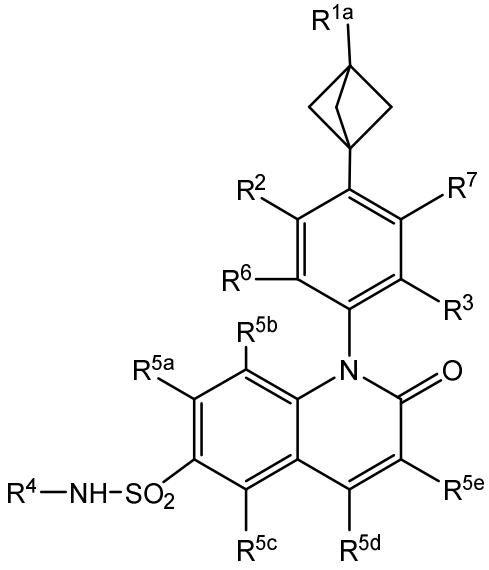
(Ib);

wherein each R^{1a} is fluoro or CF_3.

[0013] In a more preferred sub example 1b of example 1, each R^{1a} is F; R^2 is F or Cl; and R^4 is isoxazolyl.

[0014] In a most preferred sub example 1b of example 1, each R^{1a} is F; R^2 is F; and R^4 is isoxazolyl.

[0015] In sub-example 1c of example 1, the compound of Formula (I) has a sub-Formula of (Ic):



(Ic);

wherein R^{1a} is CF_3.

[0016] In a more preferred sub example 1c of example 1, R^{1a} is CF_3; R^2 is F; and R^4 is isoxazolyl or pyrimidyl.

[0017] In a most preferred sub example 1c of example 1, R^{1a} is CF_3; R^2 is F; and R^4 is isoxazolyl.

[0018] In example 2, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the R^{1a} group is selected from halo, C_{1-8}alk, -O-C_{1-4}alk, or C_{1-8}haloalk, wherein said C_{1-8}haloalk is C_{1-8}fluoroalkyl.

[0019] In example 3, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 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, -CF_3, -O-CF_3, or -$C(CH_3)_3$.

[0020] In example 4, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyclobutyl ring or bicyclo[1.1.1]pentan-1-yl ring; wherein each ring is substituted by 1 or 2 F or -CF_3.

[0021] In example 5, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyclobutyl ring substituted by 1 or 2 F or -CF_3.

[0022] In sub-example 5a of example 5, the compound of Formula (I) has the above sub-Formula of (Ia) and R^{1a} is F.

[0023] In sub-example 5b of example 5, the compound of Formula (I) has the above sub-Formula of (Ib) and R^{1a} is -CF_3.

[0024] In sub-example 5c of example 5, R^1 is a cyclobutyl ring substituted by 1 -CF_3.

[0025] In sub-example 5d of example 5, R^1 is a cyclobutyl ring substituted by 1 or 2 F.

[0026] In sub-example 5c of example 5, the compound of Formula (I) has the above sub-Formula of (Ic) and R^{1a} is -CF_3.

[0027] In example 6, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 is a bicyclo[1.1.1]pentan-1-yl ring substituted by 1 or 2 F or -CF_3.

[0028] In example 7, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, fluoro, chloro, methyl, CF_3, CHF_2, or CH_2F. In sub example 7a of example 7, R^2 is fluoro.

[0029] In example 8, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, fluoro, chloro, or methyl.

[0030] In example 9, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or fluoro.

[0031] In example 10, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^3 is methoxy.

[0032] In example 11, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is a 5-membered heteroaryl.

[0033] In example 12, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is a 6-membered heteroaryl.

[0034] In example 13, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl.

[0035] In a sub example of example 13a of example 13, R^4 is isoxazolyl, pyridazinyl, or pyrimidyl.

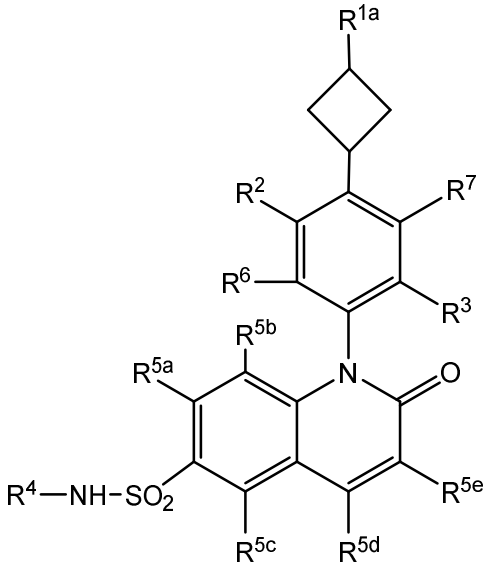
[0036] In another sub example 13b of example 13, R^4 is isoxazolyl.

[0037] In example 14a, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or 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.

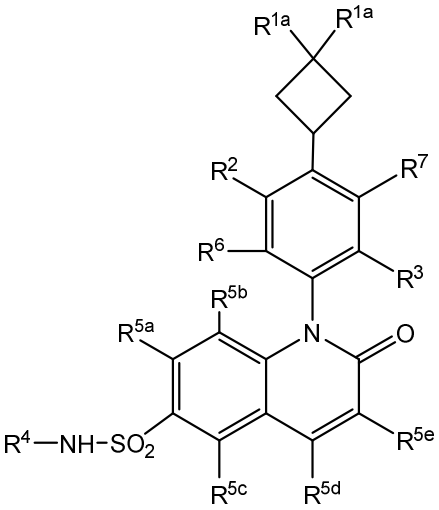
[0038] In example 14b, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^{5a} is F; and each of R^{5b};R^{5c}; R^{5d}; and R^{5e} is hydrogen.

[0039] In example 14c, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^{5c} is F; and each of R^{5a}; R^{5b};R^{5d}; and R^{5e} is hydrogen.

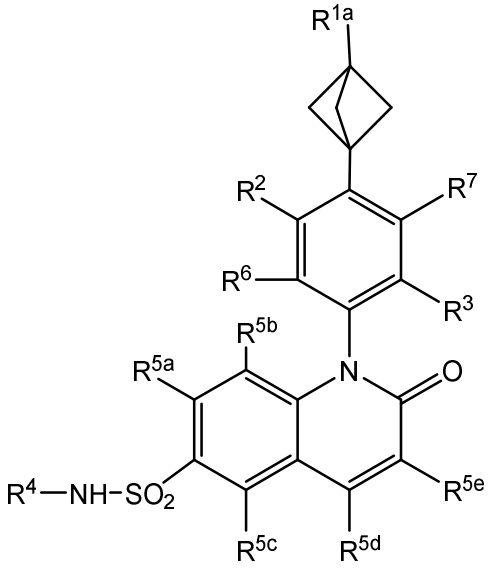
[0040] In example 15, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is selected from compounds of Formula (Ia), (Ib), or (Ic):



(Ia);



(Ib); or



(Ic);

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

[0041] In example 16, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein said compound of Formula (I) is a compound of Formula (Ia); wherein R^{1a} is CF_3; the cyclobutyl ring is a *trans* isomer; and R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, or oxazolyl.

[0042] In example 16a, said compound of Formula (I) is a compound of Formula (Ia); wherein 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.

[0043] In example 16b, 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.

[0044] In example 16c, 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.

[0045] In example 16d, said compound of Formula (I) is a compound of Formula (Ic); wherein each R^{1a} is CF_3.

[0046] In example 17, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

1) (M)-1-(4-(3-(tert-Butyl)cyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

2) 1-(4-(3-(tert-butyl)cyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

3) (P)-1-(4-(3-(tert-butyl)cyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

4) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

5) (P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

6) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

7) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

8) *trans*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

9) *cis*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

10) *cis*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

11) *trans*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

12) *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;

13) *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;

14) (P)-1-(4-cyclobutyl-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

15) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

16) *cis*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

17) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

18) (P)-1-(5-chloro-4-cyclobutyl-2-methoxyphenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

19) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

20) *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

21) (P)- 1-(5-chloro-4-cyclobutyl-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

22) (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

23) (P)-1-(4-cyclobutyl-5-fluoro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

24) (P)-1-(4-cyclobutyl-5-fluoro-2-methoxyphenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

25) (P)-1-(4-cyclobutyl-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

26) (P)-1-(4-cyclobutyl-2-methoxyphenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

27) (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-N-(4-methoxybenzyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

28) (P)-1-(4-cyclobutyl-5-fluoro-2-methoxyphenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

29) (P)-1-(4-cyclobutyl-2-methoxyphenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

30) (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

31) (P)-1-(4-cyclobutyl-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

32) (P)-1-(5-chloro-4-cyclobutyl-2-methoxyphenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

33) (P)-1-(5-chloro-4-cyclobutyl-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

34) (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

35) *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

36) *trans*-(P)-1-(2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

37) *trans*-(P)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

38) *trans*-(P)-1-(2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

39) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

40) (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;

41) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-7-fluoro-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

42) (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;

43) (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

44) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethoxy)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

45) *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;

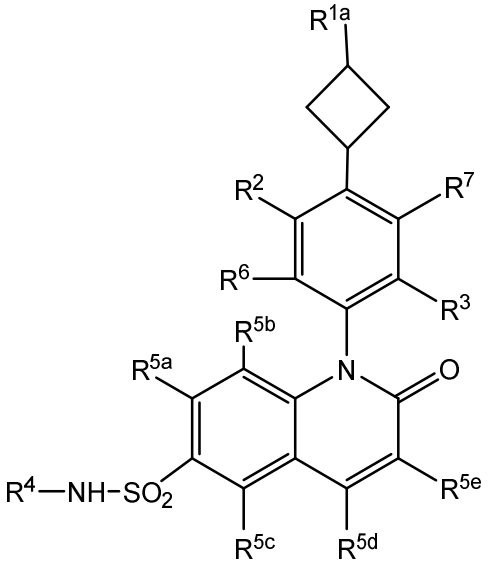
46) *trans*-(P)-5-fluoro-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

47) (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;

48) (P)-1-(5-chloro-4-(3,3-difluorocyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or

49) 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.

[0047] In example 18, the present disclosure provides a compound of Formula (I), having sub-Formula of (Ia):



(Ia); an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

1) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

2) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

3) *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;

4) *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;

5) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

6) *trans*-(P)-1-(5-chloro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

7) *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

8) *trans*-(P)-1-(2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

9) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

10) (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;

11) (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

12) *cis*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethoxy)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

13) *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;

14) *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

15) trans (P)-1-(5-chloro-2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)

16) phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

[0048] In sub-example 18a of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

1) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

2) *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

3) *trans*-(P)-1-(2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide;

4) *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide;

5) *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; or

6) *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.

[0049] In sub-example 18b of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the 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.

[0050] In sub-example 18c of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *trans*-(P)-N-(isoxazol-3-yl)-1-(2-methoxy-5-methyl-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

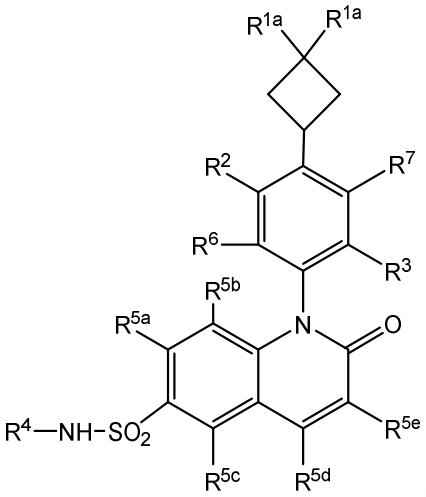
[0051] In sub-example 18d of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *trans*-(P)-1-(2-methoxy-4-((1R,3R)-3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide.

[0052] In sub-example 18e of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *trans*-(P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-2-oxo-N-(pyridazin-3-yl)-1,2-dihydroquinoline-6-sulfonamide.

[0053] In sub-example 18f of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *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.

[0054] In sub-example 18g of example 18, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ia), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *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.

[0055] In example 19, the present disclosure provides a compound of Formula (I), having sub-Formula of (Ib):  (Ib); an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is selected from:

1) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

2) (P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

3) *trans*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

4) *cis*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

5) *cis*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

6) *trans*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

7) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-7-fluoro-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or

8) (P)-1-(5-chloro-4-(3,3-difluorocyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

[0056] In sub-example 19a of example 19 the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ib), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is selected from:

1) (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

2) *trans*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide;

3) *cis*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or

4) *trans*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

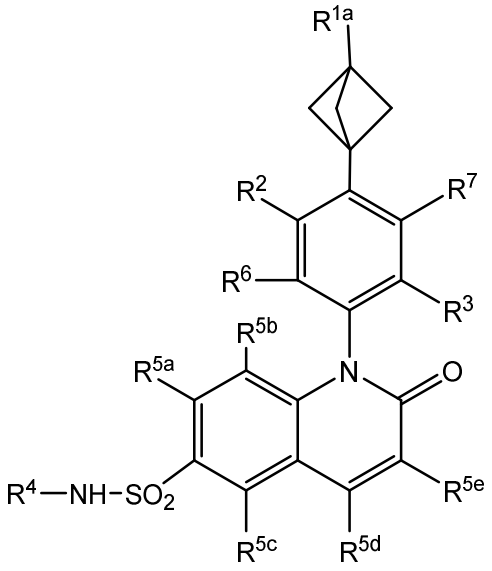
[0057] In sub-example 19b of example 19, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ib), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

[0058] In sub-example 19c of example 19, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ib), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *trans*-(P)-1-(5-fluoro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

[0059] In sub-example 19d of example 19, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ib), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is *cis*-(P)-1-(5-chloro-4-(3-fluoro-3-(trifluoromethyl)cyclobutyl)-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide.

[0060] In sub-example 19e of example 19, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ib), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which 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.

[0061] In example 20, the present disclosure provides a compound of Formula (I) having a sub-Formula of (Ic):



(Ic); an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is selected from:

[0062] (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

[0063] (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.

[0064] In sub-example 20a of example 20, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ic), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is (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.

[0065] In sub-example 20b of example 20, the present disclosure provides a compound of Formula (I), having the above sub-Formula of (Ic), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is (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.

[0001] In example 21, the present disclosure provides a P atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 18, 19, and 20, or any sub-example thereof.

[0052] In example 22, the present disclosure provides an M atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 18, 19, and 20, or any sub-example thereof.

[0053] In example 23, the present disclosure provides pharmaceutical compositions comprising a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof,

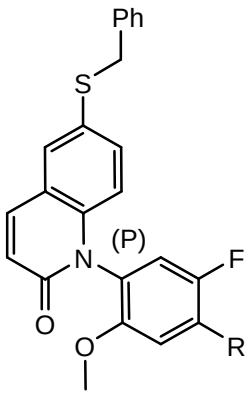
or pharmaceutically acceptable salts thereof, in accordance with any one of examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or any sub example thereof, and a pharmaceutically acceptable excipient.

[0054] In example 24, the present disclosure provides methods of treating pain, cough, or itch, the methods comprising administering to a patient in need thereof a therapeutically effective amount of a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, in accordance with any one of examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or any sub example thereof.

[0055] In example 25, the present disclosure provides methods of example 24 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.

[0056] In example 26, the present disclosure provides methods of example 24 wherein the cough is selected from post viral cough, viral cough, or acute viral cough. See Dib-Hajj. et. al., "The $Na_V1.7$ sodium channel: from molecule to man", *Nature Reviews Neuroscience* (2013), 14, 49-62.

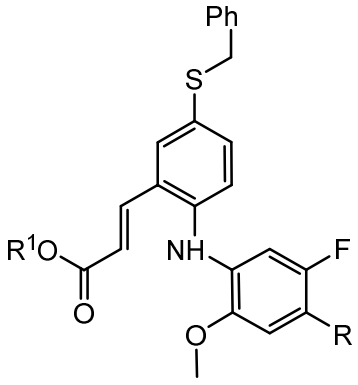
[0057] In example 27, the present disclosure provides a method of preparation of an intermediate compound used in the preparation of a compound of Formula (I), having the Formula (A):



(A); wherein R is halo;

comprising:

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



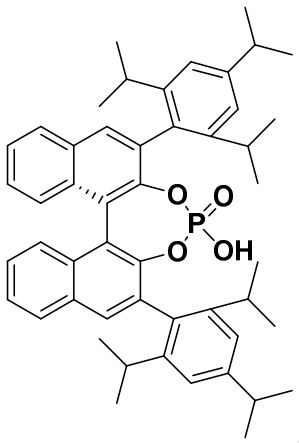
(B); wherein R is halo; and R^1 is C_1-C_6alkyl;

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).

[0058] In example 28, the present disclosure provides a method of example 27, wherein said chiral acid is a phosphorus chiral acid.

[0059] In example 29, the present disclosure provides a method of example 27, wherein said chiral acid is (S)-TRIP having the Formula:

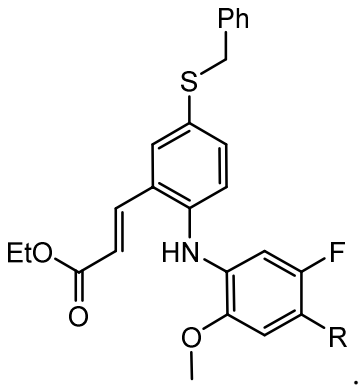


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[0060] In example 30, the present disclosure provides a method of example 27, wherein said organic solvent is dichloromethane.

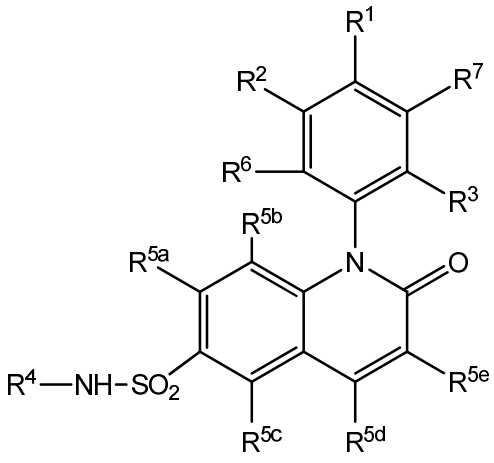
[0061] In example 31, the present disclosure provides a method of example 27, wherein said R is bromo.

[0062] In example 32, the present disclosure provides a method of example 27, wherein said R^1 is ethyl; wherein the compound of Formula (B) has the formula:



[0063] In example 33, the present disclosure provides a method of example 27, wherein in reaction (2), a P atropisomer of said compound of Formula (A) is selectively formed.

[0064] In example 34, the present disclosure provides a method of example 27, 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,

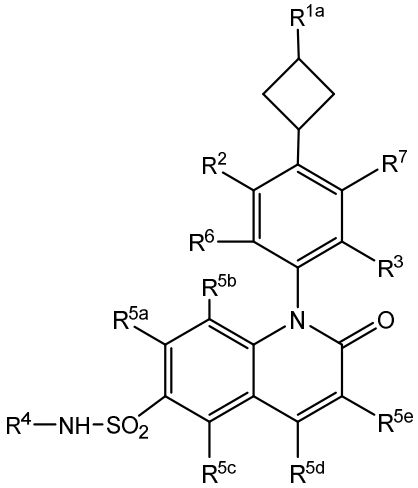
wherein:

R^1 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, C_{1-8}alk, C_{1-8}haloalk, -O-C_{1-4}alk, -O-C_{1-8}haloalk, -C(=O)C_{1-4}alk, -O-C(=O)C_{1-4}alk, $-NH_2$, -NHC_{1-4}alk, or -N(C_{1-4}alk)C_{1-4}alk;

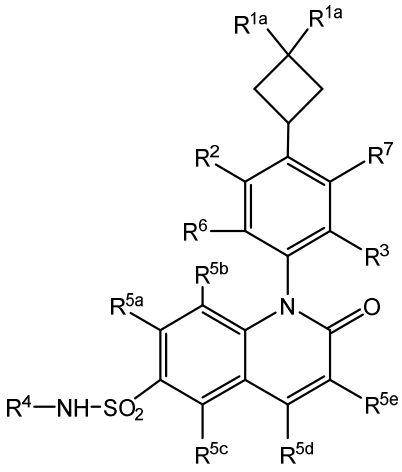
R^2 is H, halo, C_{1-6}alk, or C_{1-6}haloalk;
R^3 is C_{1-6}alk, C_{1-6}haloalk, -O-C_{1-6}alk, or –CN;
R^4 is a 5- to 6-membered heteroaryl;
Each of R^6 and R^7 is hydrogen; and
Each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is independently hydrogen or halo; and

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

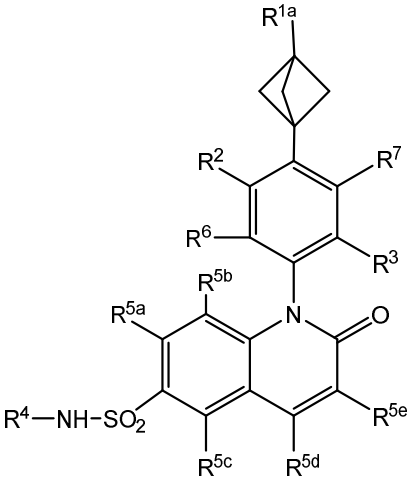
[0064a] In one aspect, the present disclosure refers to a compound of Formula (Ia), (Ib) or (Ic):



(Ia);



(Ib); or



(Ic);

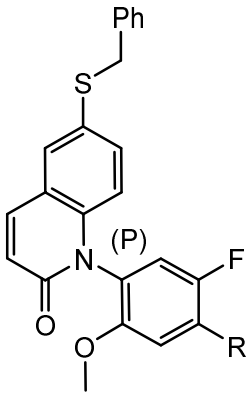
an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; wherein: R^{1a} is selected from halo, $C_{1\text{-}8}$alk, $C_{1\text{-}8}$haloalk or -O-$C_{1\text{-}4}$alk, wherein said $C_{1\text{-}8}$haloalk is C1-8fluoroalkyl; R^2 is H, halo, $C_{1\text{-}6}$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.

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

[0064c] In another aspect, the present disclosure refers to use of a compound as disclosed herein, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; or a 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.

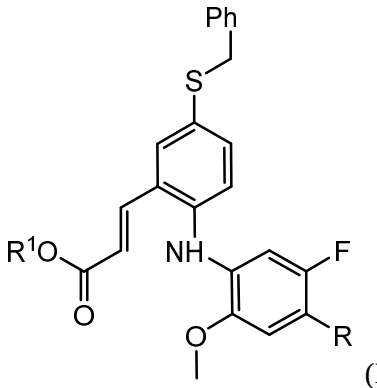
[0064d] In another aspect, the present disclosure refers to a compound as disclosed herein, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; or a composition according to claim 18 for use in therapy.

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



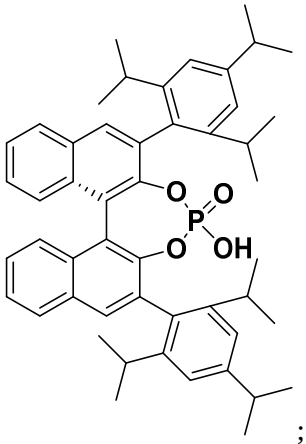
(A);

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:



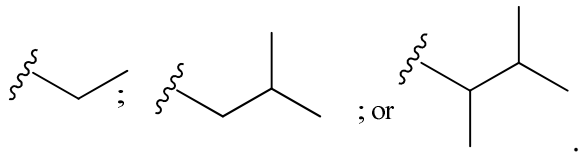
;

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:



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[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 $-CF_3$.

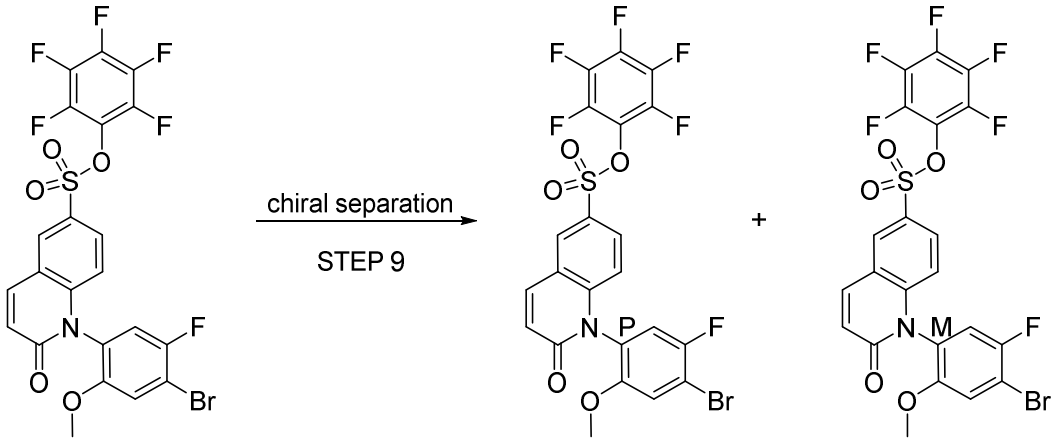
[0069] The term "heteroatom" as used herein means an oxygen, nitrogen or sulfur atom.

[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

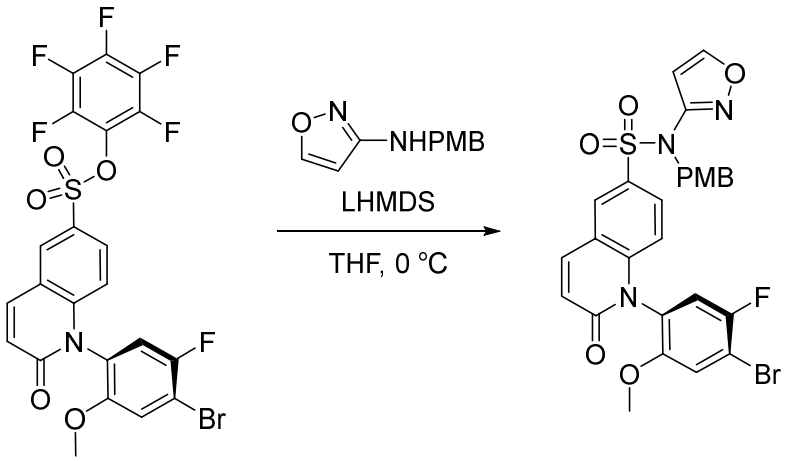
STEPS 7 + 8: PERFLUOROPHENYL 1-(4-BROMO-5-FLUORO-2-METHOXYPHENYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONATE

To a solution of 6-(benzylthio)-1-(4-bromo-5-fluoro-2-methoxyphenyl)quinolin-2(1H)-one (250.0 g, 531.5 mmol, 1.0 equiv) in acetonitrile (2.5 L) were added acetic acid (200 mL) and water (130 mL). The resulting mixture was cooled to 0 °C and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (188.5 g, 956.7 mmol, 1.8 equiv, Aldrich) was added portion-wise over 20 min keeping the internal temperature below 5 °C. The resulting suspension was stirred at 0-5 °C under nitrogen for 45 min. Then a solution of pentafluorophenol (127.2 g, 690.95 mmol, 1.3 equiv, Apollo) in acetonitrile (200 mL) was added over 5 min followed by NEt_3 (307.7 mL, 2.12 mol, 4.0 equiv) over 20 min keeping the internal temperature below 5 °C. The mixture was continued to be stirred at 0-5 °C for 30 min. Water (4.0 L) was added and extracted with ethyl acetate (2 x 2.0 L). The organic layer was washed with brine (1.0 L), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the initial material which was purified by stirring with isopropyl alcohol : hexanes (1:1, 1.0 L) and filtered to obtain racemic perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate (190 g, 60%) as white solid. TLC solvent system: 30 % ethyl acetate in pet ether, Product's R_f : 0.4. MS (ESI, positive ion) m/z; 594.2 (M+1). ^{1}H-NMR (400 MHz, DMSO) δ 8.60 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 9.8 Hz, 1H), 7.95 (dd, J = 2.2, 9.1 Hz, 1H), 7.70 (t, J = 8.6 Hz, 2H), 6.95 - 6.88 (m, 2H), 3.72 (s, 3H).



STEP 9: (P)-PERFLUOROPHENYL 1-(4-BROMO-5-FLUORO-2-METHOXYPHENYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONATE

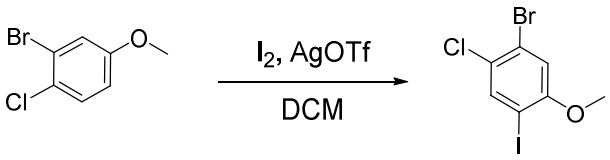
[00192] Racemic perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate was separated via Chiralcel OJ column (40% MeOH/60% CO_2) to give (P)-perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate and (M)-perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate as pale yellow flocculent solids. Data for peak 1: m/z (ESI) 594.0 $(M+H)^+$. Data for peak 2: m/z (ESI) 594.0 $(M+H)^+$.



STEP 10: (P)-1-(4-BROMO-5-FLUORO-2-METHOXYPHENYL)-N-(ISOXAZOL-3-YL)-N-(4-METHOXYBENZY 1)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

[00193] A 250-mL round-bottom flask was charged with (P)-perfluorophenyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-l,2-dihydroquinoline-6-sulfonate (11.34 g, 19.08 mmol) and N-(4-methoxybenzyl)isoxazol-3-amine (4.09 g, 20.04 mmol), then purged with nitrogen. Tetrahydrofuran (191 mL) was introduced, and the resultant brown solution cooled to 0 °C. A solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 21.0 mL, 21.0 mmol) was added dropwise via syringe to the stirred reaction mixture over 10 min. After 15 min, 1.0 N HCl (100 mL) was introduced and the resultant reaction mixture was allowed to warm to rt. The mixture was diluted with and EtOAc (100 mL) and the layers were separated, and the aqueous layer was further extracted with EtOAc (2 x 100 mL). The combined organic layers were then washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (100-g BIOTAGE® column, eluent: gradient, 0 to 100% EtOAc in heptane with 10 % CH_2Cl_2 as an additive) to afford (P)-l-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzy 1)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (9.54 g, 15.53 mmol, 81% yield) as a white amorphous solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 8.82 (d, J=2.0 Hz, 1H), 8.38 (d, J=2.3 Hz, 1H), 8.17 (d, J=9.4 Hz, 1H), 7.76 (t, J=5.1 Hz, 1H), 7.68 (d, J=6.1 Hz, 1H), 7.63 (d, J=8.5 Hz, 1H), 7.26 (d, J=7.9 Hz, 2H), 6.91 - 6.78 (m, 4H), 6.74 (d, J=2.0 Hz, 1H), 4.92 (s, 2H), 3.73 - 3.69 (m, 6H), 3.32 (s, 1H). m/z (ESI) 615.1 $(M+H)^+$.

[00194] INTERMEDIATE G: 1-BROMO-2-CHLORO-4-IODO-5-METHOXYBENZENE



the initial product which was purified by stirring with 5% ethyl acetate in hexane (1.5 L) for 30 min and filtered to obtain ethyl (E)-3-(5-(benzylthio)-2-((4-bromo-5-chloro-2-methoxyphenyl)amino)phenyl)acrylate (290 g, 85% yield) as yellow solid. m/z (ESI) 532.2 $(M+H)^+$.

[00201] STEP 2: 6-(BENZYLTHIO)-l-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)QUINOLIN-2(1H)-ONE

[00202] To a solution of ethyl (E)-3-(5-(benzylthio)-2-((4-bromo-5-chloro-2-methoxyphenyl)amino)phenyl)acrylate (300.0 g, 5630.0 mmol) in methanol (3.0 L) was added tri(n-butyl)phosphine (50% solution in ethyl acetate, 56.2 mL, 1126 mmol) and the reaction mixture was heated at 70 °C for 5 h. The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure to obtain the initial product which was purified by stirring with 5% ethyl acetate in hexane (1.0 mL) and filtered to obtain 6-(benzylthio)-l-(4-bromo-5-chloro-2-methoxyphenyl)quinolin-2(1H)-one (210.0 g, 76.6 %) as an off white solid, m/z (ESI) 486.0 $(M+H)^+$.

[00203] STEP 3: PERFLUOROPHENYL l-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONATE

[00204] To a solution of 6-(benzylthio)-1-(4-bromo-5-chloro-2-methoxyphenyl)quinolin-2(1H)-one (400.0 g, 824.9 mmol) in acetonitrile (2.5 L) and THF (2.5 L) were added acetic acid (1.0 L) and water (700 mL). The resulting mixture was cooled to 0 °C and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (292 g, 1484.8 mmol) was added portionwise over 30 min keeping the internal temperature below 5 °C. The resulting suspension was stirred at 0 °C under nitrogen for 45 min. Then a solution of pentafluorophenol (197.4 g, 1072.3 mmol) in acetonitrile (500 mL) was added over 5 min followed by triethylamine (477 mL, 3299 mmol) over 30 min keeping the internal temperature below 5 °C. The mixture was continued to be stirred at 0 °C for 50 min. Water (4.0 L) was added and extracted with ethyl acetate (3 x 2.0 L). The organic layer was washed with brine (2.0 L), dried over sodium sulfate, filtered and concentrated under reduced pressure to obtain the initial product which was purified by stirring with isopropyl alcohol/hexane (1:1, 2.0 L) and filtered to obtain perfluorophenyl l-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-l,2-dihydro quinoline-6-sulfonate (360 g, 72%) as a white solid. m/z (ESI) 610.6 $(M+H)^+$.

[00205] STEP 4: (P)-PERFLUOROPHENYL l-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)-2-OXO-1,2-DIHYDRO QUINOLINE-6-SULFONATE & (M)-PERFLUOROPHENYL 1-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)-2-OXO-l,2-DIHYDRO QUINOLINE-6-SULFONATE

[00206] Perfluorophenyl l-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-1,2-dihydro quinoline-6-sulfonate (156 g, 255 mmol) was purified via chiral SFC chromatography ((S,S) Whelk-O, 45% isopropanol) to afford (P)-perfluorophenyl 1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate (72.66 g, 93% yield) and (M)-perfluorophenyl 1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate (76.13 g, 98% yield) as white solids, m/z (ESI) 610.6 $(M+H)^+$.

[00207] STEP 5: (P)-1-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)-N-(4-METHOXYBENZYL)-2-OXO-N-(PYRIMIDIN-2-YL)-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

[00208] N-(4-Methoxybenzyl)pyrimidin-2-amine (9.72 g, 45.1 mmol) and (P)-perfluorophenyl 1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-6-sulfonate (25.06 g, 41.0 mmol) were added to a 500-mL flask. The flask was flushed with N_2 stream then tetrahydrofuran (136 mL) was added and the reaction was cooled to 2 °C under N_2. Sodium tert-pentoxide (30% solution in THF, 197 mL, 492 mmol) was added over 30 min via addition funnel maintaining internal temperature around 5°C, and the pale yellow solution turned orange upon the addition. The reaction was stirred for 30 min in the ice bath. The reaction was then quenched with sat. aq. NH_4Cl and diluted with EtOAc. The layers were separated and the water layer was extracted twice with EtOAc. The combined organics were dried with Na_2SO_4, filtered, and evaporated. IPA was added and a white precipitate crashed out. The solvent was evaporated to approximately 100 mL then additional IPA was added and the reaction was stirred for 18 h. The slurry was filtered and the solid was washed with IPA.

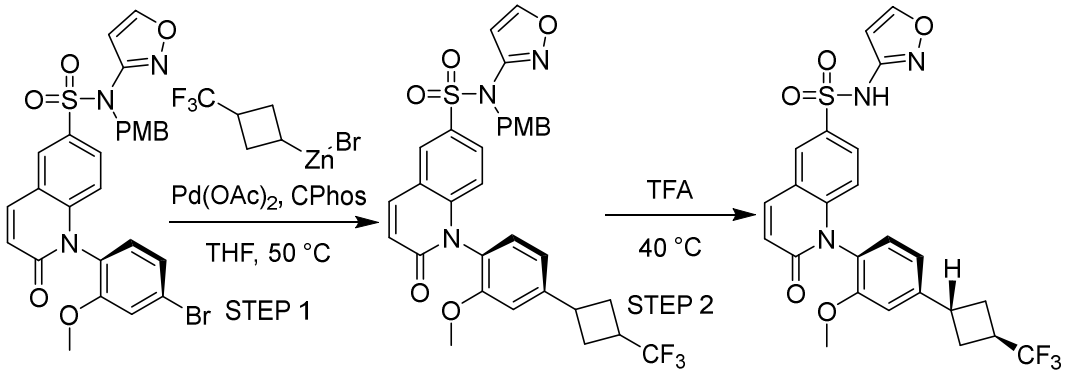
[00209] The solid was taken up in 150 mL of MTBE and heated at 40 °C for 2 hours. The slurry was cooled to ambient temperature and filtered to obtain a white solid. The impure material was dissolved in 500 mL of 10% MeOH/DCM and stirred with 500 mL of sat. aq. $NaHCO_3$ for 30 minutes. The layers were separated and the water layer was extracted twice with 10% MeOH/DCM. The combined organics layers were dried and evaporated. The filtrates from IPA and MTBE titrations were combined and loaded onto 25 g silica cartridge and purified by column chromatography (RediSep Rf Gold 120g column, gradient elution 10% to 50% 3:1 EtOAc:EtOH in heptane with 10% dichloromethane additive). The pure product of the column and the product from the $NaHCO_3$ extraction were combined to afford (P)-1-(4-bromo-5-chloro-2-methoxyphenyl)-N-(4-methoxybenzyl)-2-oxo-N-(pyrimidin-2-yl)-1,2-dihydroquinoline-6-sulfonamide (16.94 g, 26.4 mmol, 64% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.58 (d, J=4.9 Hz, 2 H), 8.39 (d, J=2.1 Hz, 1 H), 8.13 (d, J=9.6 Hz, 1 H), 7.96 (dd, J=9.1, 2.3 Hz, 1 H), 7.76 (s, 1 H), 7.73 (s, 1 H), 7.29 (d, J=8.8 Hz, 2 H), 7.13 (t, J=4.9 Hz, 1 H), 6.87 (d,

acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (gradient elution 0-30% [3:1 EtOAc/EtOH]:heptane with 10% dichloromethane co-eluent) to provide (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-N-(2,4-dimethoxybenzyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (255 mg, 0.414 mmol, 69% yield) as a white solid. m/z (ESI, positive ion) 616.2 $(M+H)^+$.

[00374] STEP 2: (P)-1-(4-CYCLOBUTYL-2-METHOXY-5-METHYLPHENYL)-N-(OXAZOL-2-YL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

[00375] (P)-1-(4-Cyclobutyl-2-methoxy-5-methylphenyl)-N-(2,4-dimethoxybenzyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (255 mg, 0.414 mmol) was taken up in TFA (3 mL) and heated to 50 °C. After stirring for 1 h, the reaction was concentrated and purified using a Torus 2-PIC, 3x15 cm column. The mobile phase was run under gradient elution conditions; supercritical CO_2 with 10-40% methanol; flow rate: 100 mL/min. This afforded (P)-1-(4-cyclobutyl-2-methoxy-5-methylphenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (71 mg, 0.15 mmol, 25% yield over 2 steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 12.12 (br s, 1 H), 8.29 (d, *J*=1.8 Hz, 1 H), 8.15 (d, *J*=9.4 Hz, 1 H), 7.83 (dd, *J*=8.9, 2.0 Hz, 1 H), 7.59 (d, *J*=1.5 Hz, 1 H), 7.26 (d, *J*=1.5 Hz, 1 H), 7.09 (s, 1 H), 6.99 (s, 1 H), 6.74 (d, *J*=9.4 Hz, 1 H), 6.65 (d, *J*=8.7 Hz, 1 H), 3.63 - 3.75 (m, 4 H), 2.33 - 2.44 (m, 2 H), 2.27 (quin, *J*=9.7 Hz, 1 H), 2.12 - 2.21 (m, 4 H), 1.97 - 2.10 (m, 1 H), 1.80 - 1.92 (m, 1 H). m/z (ESI, positive ion) 466.0 $(M+H)^+$.

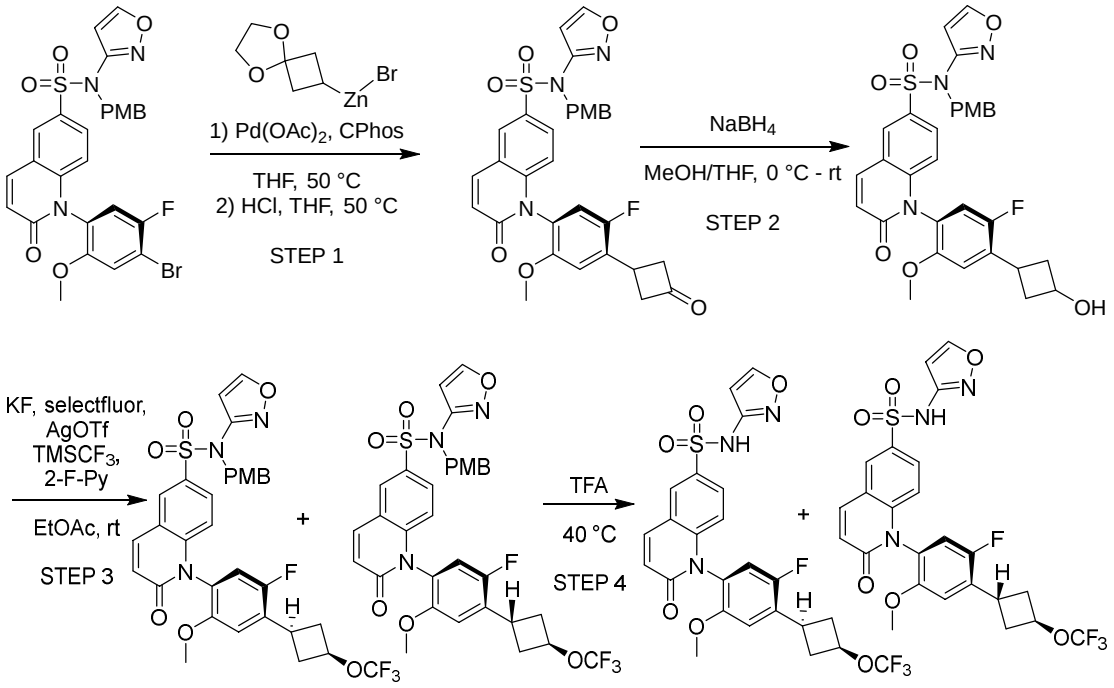
[00376] EXAMPLE 35: *TRANS*-(P)-N-(ISOXAZOL-3-YL)-1-(2-METHOXY-4-((TRIFLUOROMETHYL)CYCLOBUTYL)PHENYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE



[00377] STEP 1: (P)-N-(ISOXAZOL-3-YL)-1-(2-METHOXY-4-(3-(TRIFLUOROMETHYL)CYCLOBUTYL)PHENYL)-N-(4-METHOXYBENZYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

[00418] (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(4-methoxybenzyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (0.384 g, 0.584 mmol) was dissolved in 1,1,1-trifluoroacetic acid (1.348 g, 1.348 mL, 11.82 mmol) and stirred under a nitrogen atmosphere at 40 °C for 2.5 hours. After cooling to ambient temperature, excess TFA was removed under vacuum and the resulting solid was triturated with diethyl ether and filtered. The initial product was purified by column chromatography (gradient elution of 0-100% EtOAc in heptane with 10% dichloromethane as additive) to afford (P)-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(oxazol-2-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (70.8 mg, 0.132 mmol, 23% yield). ^{1}H NMR (500 MHz, DMSO-*d6*) δ ppm 12.13 (br s, 1 H), 8.31 (d, *J*=2.21 Hz, 1 H), 8.17 (d, *J*=9.60 Hz, 1 H), 7.84 (dd, *J*=8.89 Hz, 2.14 Hz, 1 H), 7.59 (d, *J*=1.56 Hz, 1 H), 7.34 – 7.25 (m, 3 H), 6.75 (d, *J*=9.32 Hz, 1 H), 6.70 (d, *J*=8.76 Hz, 1 H), 3.95 (quin, *J*=8.99 Hz, 1 H), 3.72 (s, 3 H), 3.29 – 3.21 (m, 1 H), 2.75 – 2.56 (m, 4 H). m/z (ESI, positive ion) 538.0 (M+H)+.

[00419] EXAMPLES 44 & 45: CIS-(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 and 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



[00420] STEP 1: (P)-1-(5-FLUORO-2-METHOXY-4-(3-OXOCYCLOBUTYL)PHENYL)-N-(ISOXAZOL-3-YL)-N-(4-METHOXYBENZYL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (0.208 g, 0.308 mmol, 61% yield) as a light pink solid. m/z (ESI, positive ion) 676.2 (M+H)+.

[00448] STEP 10: 5-FLUORO-1-(5-FLUORO-2-METHOXY-4-(3-(TRIFLUOROMETHYL)CYCLOBUTYL)PHENYL)-N-(ISOXAZOL-3-YL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

[00449] A 40 mL vial was charged with 5-fluoro-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-N-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (0.208 g, 0.308 mmol), triethylsilane (0.179 g, 0.249 mL, 1.539 mmol) and 1,1,1-trifluoroacetic acid (2.282 g, 2.282 mL, 20.01 mmol). The mixture was stirred at 40 °C for 2 hours. Solvent was removed in vacuo. The mixture was purified by column chromatography (BIOTAGE® ISOLERA ONE, BIOTAGE SFÄR SILICA HC D 10g, 0-100% ethyl acetate in heptane with 10% dichloromethane as additive) to afforded 5-fluoro-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (0.153 g, 0.275 mmol, 89% yield) as an off white solid. m/z (ESI, positive ion) 556.2 (M+H)+.

[00450] STEP 11: *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

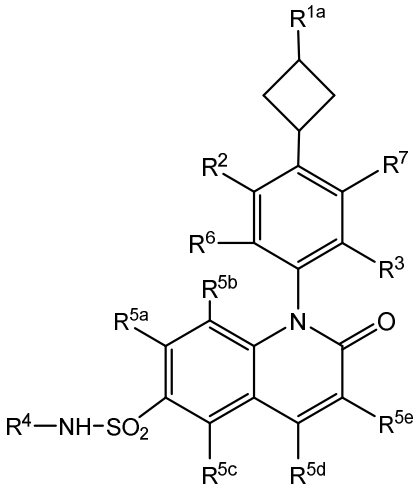
[00451] 5-fluoro-1-(5-fluoro-2-methoxy-4-(3-(trifluoromethyl)cyclobutyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide (0.153 g, 0.275 mmol) was purified by SFC via 2 steps. Step 1: a Regis Whelk-O s,s 2x15 cm, 5 µm column; a mobile phase of 35% methanol using a flowrate of 60mL/min; Step 2: (separation of Peak1 & Peak2): two Chiralpak AD-H , 5 µm columns(3x15 cm +3x25 cm); a mobile phase of 30% ethanol using a flowrate of 80mL/min. Peak 1 was lyophilized to yield *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 (0.0305 g, 0.055 mmol, 18% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-*d6*) δ ppm 12.01 (br s, 1 H), 8.72 (d, *J*=1.8 Hz, 1 H), 8.18 (d, *J*=9.9 Hz, 1 H), 7.87 (t, *J*=8.1 Hz, 1 H), 7.34 (s, 1 H), 7.33 (d, *J*=3.4 Hz, 1 H), 6.83 (d, *J*=9.9 Hz, 1 H), 6.59 (d, *J*=9.2 Hz, 1 H), 6.37 (d, *J*=1.8 Hz, 1 H), 3.95 (t, *J*=9.0 Hz, 1 H), 3.73 (s, 3 H), 3.22 - 3.28 (m, 1 H), 2.55 - 2.72 (m, 4 H). m/z (ESI, positive ion) 556.2 (M+H)+.

[00452] EXAMPLE 47: (P)- 1-(5-FLUORO-2-METHOXY-4-(3-(TRIFLUOROMETHYL)BICYCLO[1.1.1]PENTAN-1-YL)PHENYL)-N-(PYRIMIDIN-2-YL)-2-OXO-1,2-DIHYDROQUINOLINE-6-SULFONAMIDE

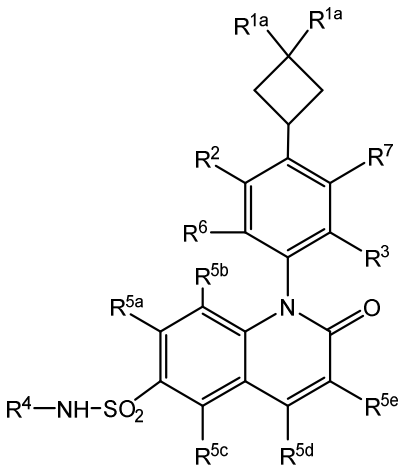
CLAIMS

What is claimed is:

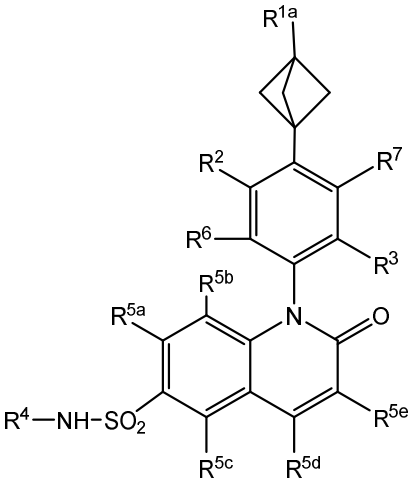
1. A compound of Formula (Ia), (Ib) or (Ic):



(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_{1-8}alk, C_{1-8}haloalk or -O-C_{1-4}alk, wherein said C_{1-8}haloalk is C1-8fluoroalkyl ;

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.

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

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

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

14. The compound according to any one of claims 1-13, 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 any one of claims 1-13, 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 any one of claims 1-13, 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.

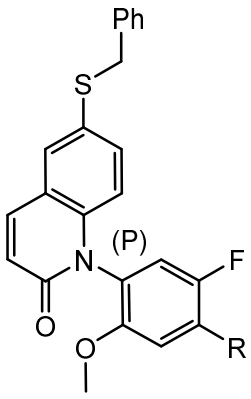
17. The compound according to any one of claims 1-13, wherein said compound is (P)-1-(4-(3,3-difluorocyclobutyl)-5-fluoro-2-methoxyphenyl)-7-fluoro-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide; or a pharmaceutically acceptable salt thereof.

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

19. Use of a compound according to any one of claims 1-17, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; or a 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. A compound according to anyone of claims 1-17, an enantiomer, diastereoisomer, atropisomer thereof, a mixture thereof, or a pharmaceutically acceptable salt thereof; or a composition according to claim 18 for use in therapy

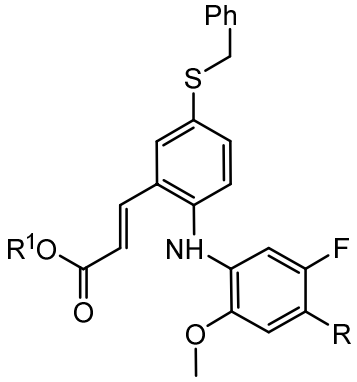
21. A method of preparation of a compound of Formula (A):



(A); wherein R is halo;

comprising:

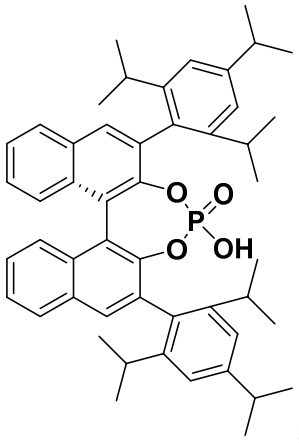
(1) reacting a trans olefin compound of Formula (B):



(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:



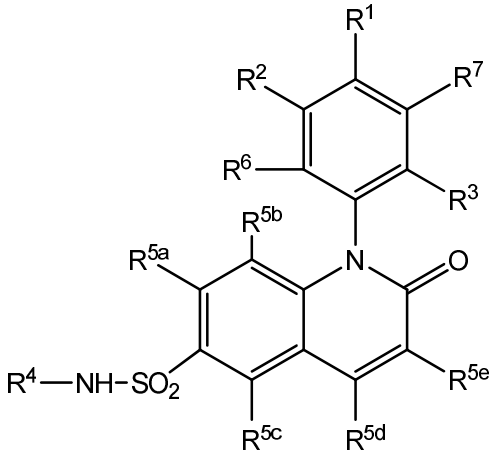
;

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.

22. The method of claim 21, 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:

R^1 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, C_{1-8}alk, C_{1-8}haloalk, -O-C_{1-4}alk, -O-C_{1-8}haloalk, -C(=O)C_{1-4}alk, -O-C(=O)C_{1-4}alk, $-NH_2$, -NHC_{1-4}alk, or -N(C_{1-4}alk)C_{1-4}alk;

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; and

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