

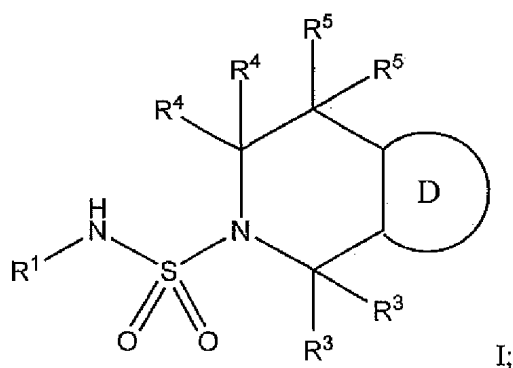
that among the many possible targets in the pain pathway, Nav 1.7 governs one or more control points critical for pain perception.

[0005] 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. So is the dentists office staple novocaine. But these compounds don't 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 inhibits 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.

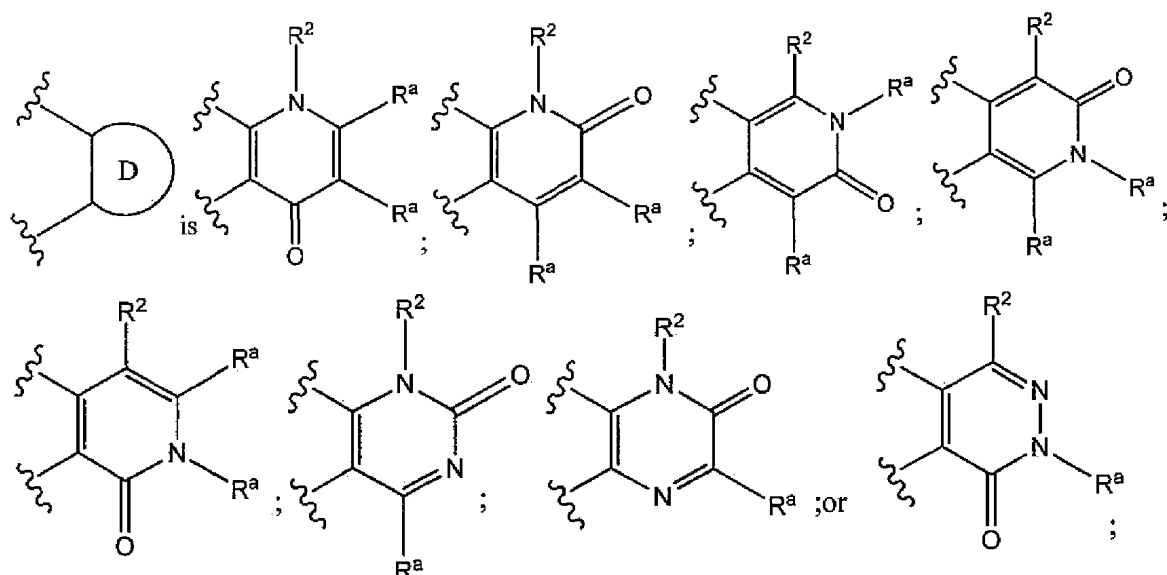
[0006] Consequently, a number of researchers are attempting to identify small molecule inhibitors of Nav1.7. For example, Chafeev et al disclose spiro-oxindole compound for the treatment and/or prevention of sodium channel-mediated diseases, such as pain, in US patent no. 8,101,647. International Publications 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

[0007] In one example, provided herein is a compound of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,



Wherein the group:



R^1 is a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- membered cycloalkyl or heterocycloalkyl group, wherein the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group, and the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl group is substituted with 0, 1, 2, 3, or 4 substituents independently selected from halo, -CN, -C₁₋₆alkyl, haloC₁₋₆alkyl, -OH, -O-C₁₋₆alkyl, -O-haloC₁₋₆alkyl,

-C(=O)OR^a, or -(CR^bR^b)_nNR^aR^a;

R^2 is C₁₋₆alkyl, or a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- membered cycloalkyl or heterocycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group, and the alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl group is substituted with from 1 to 5 R⁶ substituents independently selected from halo, -CN, -C₁₋₆alkyl, haloC₁₋₆alkyl, -OH, -O-C₁₋₆alkyl,

-O-haloC₁₋₆alkyl, -(CR^bR^b)_mA, -C₂₋₆alkenyl-A, -C₂₋₆alkynyl-A, or -O(CR^bR^b)_m-A;

R^3 is independently selected from H, -C₁₋₆alkyl, haloC₁₋₆alkyl, or halo;

R^4 is independently selected from H, -C₁₋₆alkyl, haloC₁₋₆alkyl, or halo;

R^5 is independently selected from H, -C₁₋₆alkyl, haloC₁₋₆alkyl, or halo;

A is a 4 to 9 membered aryl, heteroaryl, or heterocycloalkyl group, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- membered cycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S; and the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl group is substituted with 0, 1, 2, 3, or 4 R⁷ substituents independently selected from halo, -NR^aR^a, -C₁₋₆alkyl, -OC₁₋₆alkyl, -(CR^bR^b)_mOH,

hydroxyC₁₋₆alkyl, -CF₃, -CHF₂, -CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -CN, -C(=O)NR^aR^a, -O-(CR^bR^b)_mB or -(CR^bR^b)_mB;

B is a 5 to 6 membered aryl, heteroaryl, or heterocycloalkyl group, or a 3 to 5 membered cycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S; and the aryl, heteroaryl, cycloalkyl or heterocycloalkyl group is substituted with 0, 1, 2, 3, or 4 R⁸ substituents independently selected from halo, -NR^aR^a, -C₁₋₆alkyl, -OC₁₋₆alkyl, hydroxyC₁₋₆alkyl, -CF₃, -CHF₂, -CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -CN or -C(=O)NR^aR^a;

each R^a is independently H, halo, -CN, -NR^cR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;

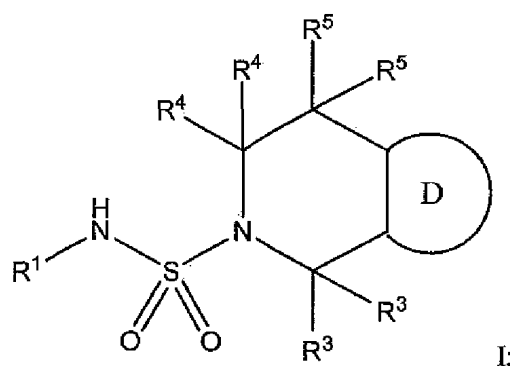
each R^b is independently H, halo, -CN, -NR^cR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;

each R^c is independently H or -C₁₋₆alkyl;

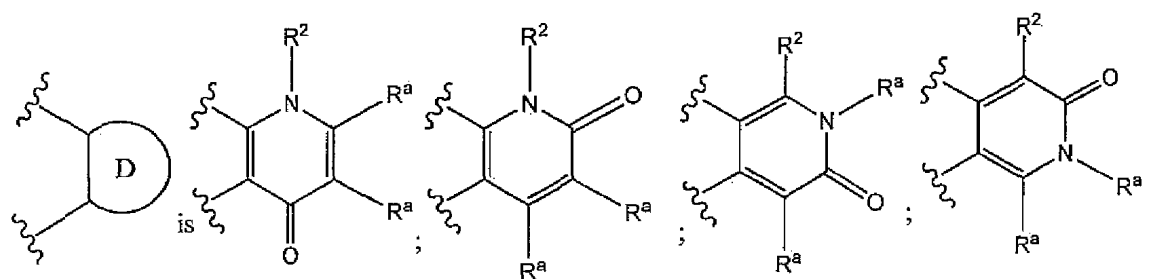
each n is independently 0, 1, 2, 3 or 4; and

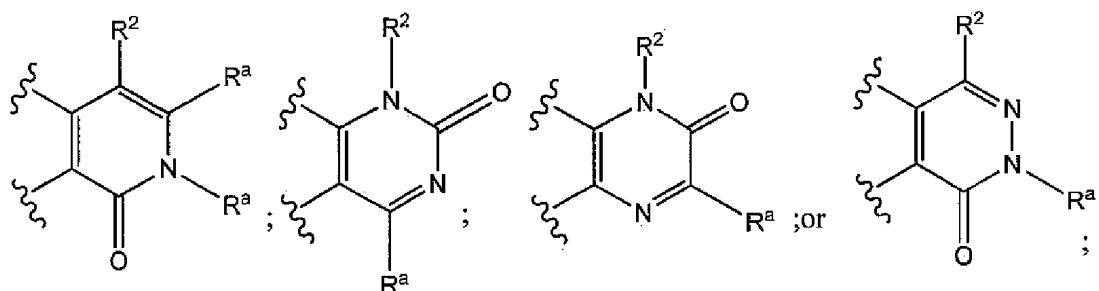
each m is independently 0, 1, 2, 3 or 4.

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



Wherein the group:





R^1 is a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkyl or heterocycloalkyl group, wherein the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group, and the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl group is substituted with 0, 1, 2, 3, or 4 substituents independently selected from halo, -CN, -C₁₋₆alkyl, haloC₁₋₆alkyl, -OH, -O-C₁₋₆alkyl, -O-haloC₁₋₆alkyl, -C(=O)OR^a, or -(CR^bR^b)_nNR^aR^a;

R^2 is C₁₋₆alkyl, or a 5-, 6-, 7-, 8-, 9-, or 10-membered aryl or heteroaryl, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkyl or heterocycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S, or a carbon atom in the cycloalkyl or heterocycloalkyl group can be part of a C=O group, and the alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl group is optionally substituted with from 1 to 5 R⁶ substituents independently selected from halo, -CN, -C₁₋₆alkyl, haloC₁₋₆alkyl, -OH, -O-C₁₋₆alkyl, -O-haloC₁₋₆alkyl, -(CR^bR^b)_mA, -C₂₋₆alkenyl-A, -C₂₋₆alkynyl-A, or -O(CR^bR^b)_m-A;

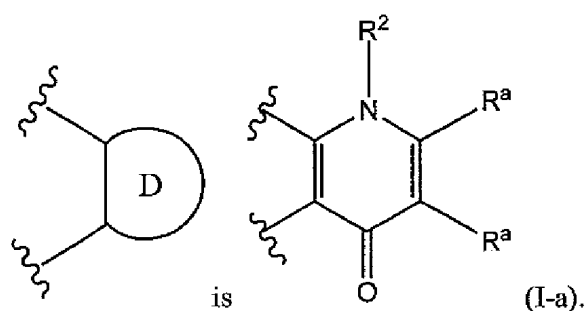
Each of R³, R⁴, and R⁵ is independently selected from H, -C₁₋₆alkyl, haloC₁₋₆alkyl, or halo;

A is a 4 to 9 membered aryl, heteroaryl, or heterocycloalkyl group, or a 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S; and the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl group is substituted with 0, 1, 2, 3, or 4 R⁷ substituents independently selected from halo, -NR^aR^a, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -(CR^bR^b)_mOH, hydroxyC₁₋₆alkyl, haloC₁₋₆alkyl, -O-haloC₁₋₆alkyl, -CN, -C(=O)NR^aR^a, -O-(CR^bR^b)_mB or -(CR^bR^b)_mB;

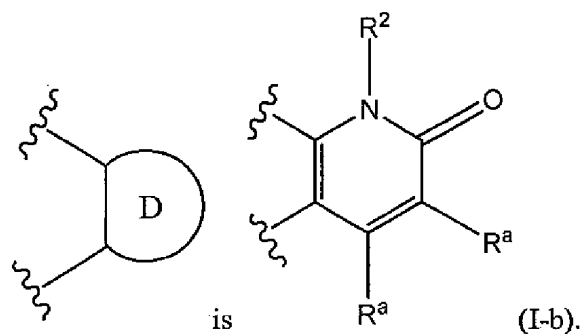
B is a 5 to 6 membered aryl, heteroaryl, or heterocycloalkyl group, or a 3 to 5 membered cycloalkyl group, where the heteroaryl or heterocycloalkyl group can have from 1 to 3 heteroatoms independently selected from O, N or S; and the aryl, heteroaryl, cycloalkyl or heterocycloalkyl group is substituted with 0, 1, 2, 3, or 4 R⁸ substituents independently selected from halo, -NR^aR^a, -C₁₋₆alkyl, -OC₁₋₆alkyl, hydroxyC₁₋₆alkyl, -CF₃, -CHF₂, -CH₂F, -OCF₃, -OCHF₂, -OCH₂F, -CN or -C(=O)NR^aR^a;

each R^a and R^b is independently H, halo, -CN, -NR^cR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;
 each R^c is independently H or -C₁₋₆alkyl;
 each n is independently 0, 1, 2, 3 or 4; and
 each m is independently 0, 1, 2, 3 or 4.

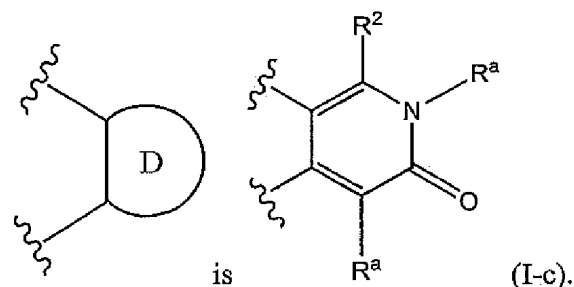
[0009] In embodiment 1a, provided herein are compounds of Formula (I)-a, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



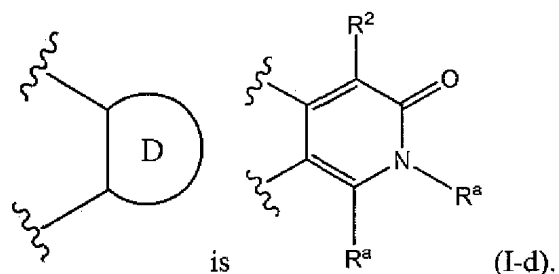
[0010] In embodiment 1b, provided herein are compounds of Formula (I)-b, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



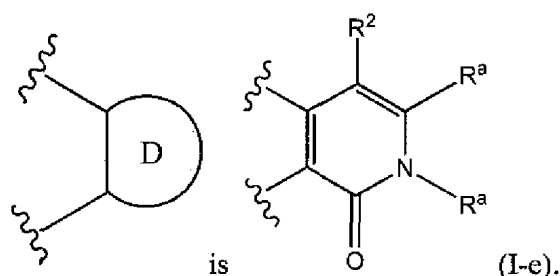
[0011] In embodiment 1c, provided herein are compounds of Formula (I)-c, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



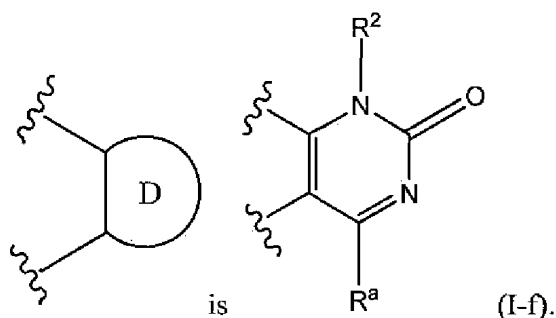
[0012] In embodiment 1d, provided herein are compounds of Formula (I)-d, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



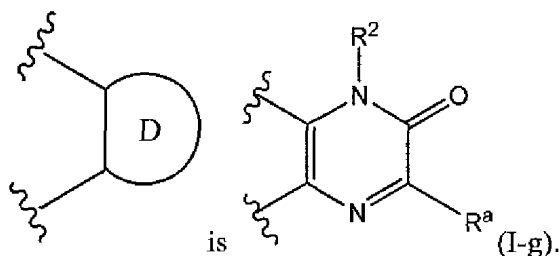
[0013] In embodiment 1e, provided herein are compounds of Formula (I)-e, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



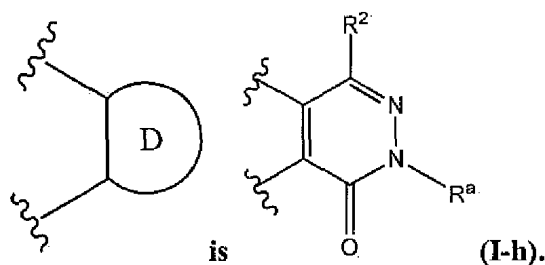
[0014] In embodiment 1f, provided herein are compounds of Formula (I)-f, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



[0015] In embodiment 1g, provided herein are compounds of Formula (I)-g, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



[0016] In embodiment 1h, provided herein are compounds of Formula (I)-h, an enantiomer or diastereoisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



[0017] In embodiment 2, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein each R^2 is a 6 membered aryl or 6 membered heteroaryl group.

[0018] In embodiment 2a, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein each R^2 is phenyl.

[0019] In embodiment 2b, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein each R^2 is pyridinyl.

[0020] In embodiment 3, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, 2, 2a-2b, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein each R^2 is substituted with from 1 to 3 R^6 substituents independently selected from $-OC_{1-6}alkyl$, halo, $-C_{1-6}alkyl$, halo $C_{1-6}alkyl$, $-(CR^bR^b)_m-A$, or $-C_{2-6}alkynyl-A$.

[0021] In embodiment 3a, provided herein are compounds in accordance with embodiment 3, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein in said $R^6-(CR^bR^b)_m-A$ group, A is a ring selected from phenyl, pyridyl, or pyrimidinyl, wherein the ring is substituted with 0, 1, 2, 3, or 4 R^7 substituents independently selected from chloro, fluoro, methyl, methoxy, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$; each R^b is independently H or $-C_{1-6}alkyl$; and m is 0 or 1.

[0022] In embodiment 3b, provided herein are compounds in accordance with embodiment 3, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein in said $R^6-C_{2-6}alkynyl-A$ group, A is a C_3 - $cycloalkyl$ ring, such as cyclopentyl or cyclohexyl ring, substituted with 0, 1, 2, 3, or 4 R^7 substituents selected from chloro, fluoro, methyl, methoxy, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$.

[0023] In embodiment 3c, provided herein are compounds in accordance with embodiment 3, an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein in said R^6 $-(CR^bR^b)_m$ -A group, A is a ring selected from phenyl, pyridyl, or pyrimidinyl, wherein the ring is substituted with 0, 1, 2, 3, or 4 R^7 substituents independently selected from chloro, fluoro, methyl, methoxy, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OCH_2CF_3$, or $-CN$; each R^b is independently H or $-C_{1-6}alkyl$; and m is 0 or 1.

[0024] In embodiment 4, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R^2 is phenyl or pyridinyl ring substituted with 3 R^6 substituents comprising:

- (a) *ortho* to ring D: R^6 is selected from methyl, methoxy or ethoxy;
- (b) *meta* to ring D: R^6 is selected from methyl, F, or Cl; and
- (c) *para* to ring D: R^6 is selected from phenyl or pyridyl ring substituted with 0, 1, 2, 3, or 4 R^7 substituents selected from F, Cl, methyl, cyclopropyl, methoxy, ethoxy, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$.

[0025] In embodiment 4a, provided herein are compounds in accordance with embodiment 4, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R^6 *ortho* to ring D is methoxy.

[0026] In embodiment 4b, provided herein are compounds in accordance with embodiment 4, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R^6 *meta* to ring D is F or Cl.

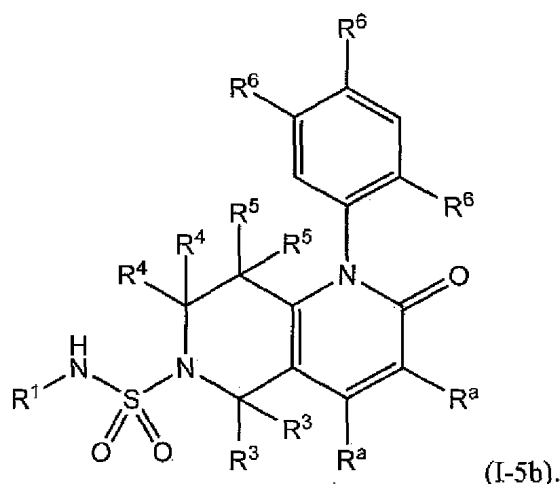
[0027] In embodiment 4c, provided herein are compounds in accordance with embodiment 4, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R^6 *para* to ring D is phenyl substituted with 1 to 3 R^7 substituents selected from F, Cl, methyl, cyclopropyl, methoxy, or $-CF_3$.

[0028] In embodiment 4d, provided herein are compounds in accordance with any one of embodiments 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R^2 is phenyl or pyridinyl ring substituted with 3 R^6 substituents comprising:

- (a) *ortho* to ring D: R^6 is selected from methyl, methoxy or ethoxy;
- (b) *meta* to ring D: R^6 is selected from absent, methyl, F, or Cl; and
- (c) *para* to ring D: R^6 is selected from halo, phenyl ring, or pyridyl ring; wherein each of said phenyl ring or pyridyl ring is substituted with 0, 1, 2, 3, or 4 R^7 substituents selected from F, Cl, methyl, cyclopropyl, methoxy, ethoxy, $-CF_3$, $-CHF_2$, $-CH_2F$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, or $-CN$.

[0029] In embodiment 5, provided herein are compounds in accordance with embodiments 1, 1a-1h, 2, 2a-2b, 3, 4a-4d, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R² is phenyl ring.

[0030] In embodiment 5a, provided herein are compounds in accordance with embodiment 5, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said compound of formula (I) has the formula:



[0031] In embodiment 5b, provided herein are compounds in accordance with embodiments 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, 4a-4d, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R² is pyridinyl ring.

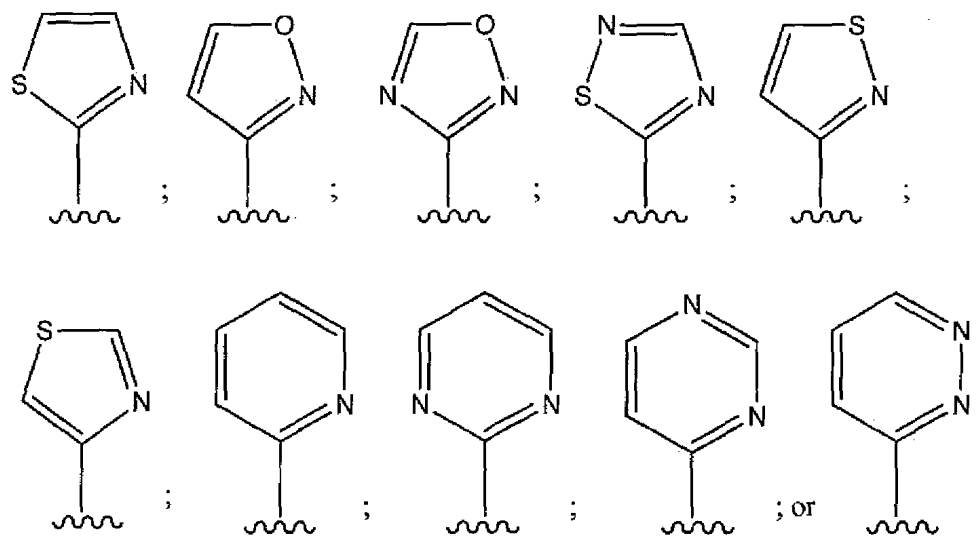
[0032] In embodiment 6, provided herein are compounds in accordance with embodiments 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, 4a-4d, 5, 5a-5b, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein each of R³, R⁴, and R⁵ is independently selected from H or methyl.

[0033] In embodiment 7, provided herein are compounds in accordance with embodiments 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, 4a-4d, 5, 5a-5b, 6, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R¹ is a 5 to 6 membered heteroaryl group.

[0034] In embodiment 7a, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R¹ is isoxazolyl, thiazolyl, thiadiazolyl, pyridazinyl, pyridyl, or pyrimidinyl ring, wherein the ring is unsubstituted or is substituted with 0, 1, 2, 3, or 4 substituents independently selected from halo or -C₁₋₆alkyl.

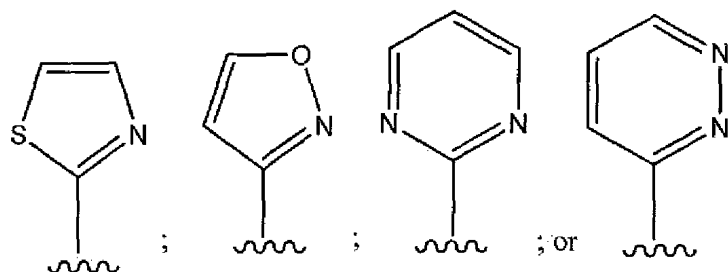
[0035] In embodiment 7b, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or

pharmaceutically acceptable salts thereof, wherein said R^1 is

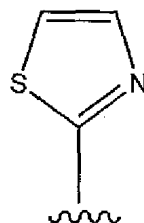


wherein the ring is unsubstituted or is substituted with 0, 1, 2, 3, or 4 substituents independently selected from halo or $-C_{1-6}$ alkyl.

[0036] In embodiment 7c, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R^1 is unsubstituted

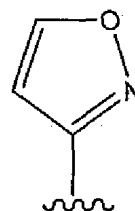


[0037] In embodiment 7d, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



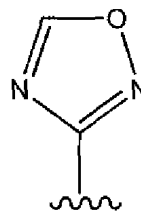
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or $-C_{1-6}$ alkyl.

[0038] In embodiment 7e, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



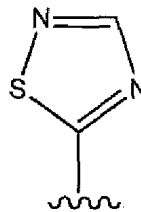
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or -C₁₋₆alkyl.

[0039] In embodiment 7f, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



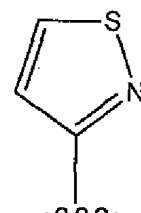
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or -C₁₋₆alkyl.

[0040] In embodiment 7g, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



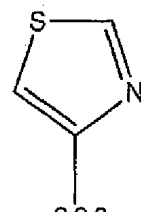
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or -C₁₋₆alkyl.

[0041] In embodiment 7h, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



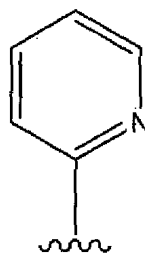
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or -C₁₋₆alkyl.

[0042] In embodiment 7i, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



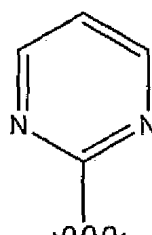
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0043] In embodiment 7j, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



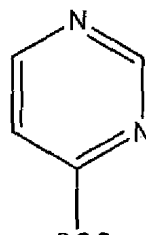
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0044] In embodiment 7k, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



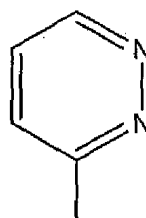
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0045] In embodiment 7l, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0046] In embodiment 7m, provided herein are compounds in accordance with embodiment 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0047] In embodiment 8, provided herein is a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, selected from:

- [00390] 1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00391] 1-(3'-chloro-2,5'-difluoro-5-methoxy-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00392] 1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-2-oxo-N-1,3-thiazol-2-yl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00393] 1-(2,3'-difluoro-5-methoxy-5'-(trifluoromethyl)-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00394] 1-(3'-cyclopropyl-2-fluoro-5-methoxy-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00395] 1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00396] 2-oxo-N-3-pyridazinyl-1-(2,3',4',5'-tetrafluoro-5-methoxy-4-biphenyl)-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00397] 1-(2,4'-dichloro-3',5'-dimethoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00398] 1-(2,3'-dichloro-5'-fluoro-5-methoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00399] 1-(2-chloro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide; and
- [00400] 1-(2-fluoro-3',5'-dimethoxy-4'-methyl-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide.
- [00401] In embodiment 10, provided herein is a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in embodiments 8 and 9-9a.
- [00402] In embodiment 11, provided herein is a P atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in embodiments 8 and 9-9a.
- [00403] In embodiment 12, provided herein is an M atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in embodiments 8 and 9-9a.
- [00404] In embodiment 13, provided herein are 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 embodiments 1, 1a-1i, 2, 2a-2b, 3, 4a-4d, 5, 5a-5b, 6, 7, 7a-7m, 8, 9-9a, 10, 11, 12, and a pharmaceutically acceptable excipient.

[00405] In embodiment 14, provided herein are 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 embodiments 1, 1a-1i, 2, 2a-2b, 3, 4a-4d, 5, 5a-5b, 6, 7, 7a-7m, 8, 9-9a, 10, 11, 12, or a pharmaceutically acceptable salt thereof. In one aspect, the present invention provides the use of the compound in accordance with the present invention, or a pharmaceutically acceptable salt thereof 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, or pain associated with diabetes; wherein the cough is selected from post viral cough, viral cough, or acute viral cough; and wherein the itch is selected from a) psoriatic pruritis, itch due to hemodialysis, allergic pruritis, and itching caused by skin disorders, systemic disorders, neuropathy, psychogenic factors or a mixture thereof, b) itch caused by allergic reactions, insect bites, hypersensitivity, inflammatory conditions or injury, c) itch associated with vulvar vestibulitis, d) skin irritation or inflammatory effect from administration of another therapeutic selected from antibiotics, antivirals, or antihistamines, or e) itch due to activation of PAR-2 G-protein coupled receptors.

[00406] In embodiment 15, provided herein are methods of embodiment 14 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, cancer, or pain associated with diabetes.

[00407] In embodiment 16, provided herein are methods of embodiment 14 wherein the cough is selected from post viral cough, viral cough, or acute viral cough. See Dib-Hajj. et. al., "The Nav1.7 sodium channel: from molecule to man", *Nature Reviews Neuroscience* (2013), 14, 49-62.

[00408] In embodiment 17, provided herein is a method of preparing a compound of Formula (I) as described above. In a sub embodiment, said method is as described in any of Scheme A below.

[00409] In embodiment 18, provided herein is an intermediate compound used in the method of preparing a compound of Formula (I) as described above. In a sub embodiment, said intermediate compound is as described in Scheme A below.

DETAILED DESCRIPTION OF THE INVENTION

[00411] 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), compound, 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), compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof.

[00412] The term "alkyl" means a straight or branched chain hydrocarbon. Representative examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, sec-butyl, pentyl and hexyl. Typical alkyl groups are alkyl groups having from 1 to 8 carbon atoms, which groups are commonly represented as C₁₋₈alkyl.

[00413] The term "haloC₁₋₆alkyl" means a straight or branched alkyl chain having one to six carbons and substituted with one or more halo groups. Representative examples of haloC₁₋₆alkyl groups include methyl bromide (-CH₂Br), 2-fluoroethyl, 3-chloropropyl, 2, 3-dichloropropyl (-CH₂CH(Cl)CH₂Cl), 3-iodoisopropyl, 4-fluorobutyl and the like. Typical

24. The compound in accordance with Claim 23, wherein the compound is a P atropisomer.

25. A pharmaceutical composition comprising the compound in accordance with any one of claims 1 to 24, an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

26. Use of the compound in accordance with any one of claims 1-24, or a pharmaceutically acceptable salt thereof 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, or pain associated with diabetes; wherein the cough is selected from post viral cough, viral cough, or acute viral cough; and wherein the itch is selected from a) psoriatic pruritis, itch due to hemodialysis, allergic pruritis, and itching caused by skin disorders, systemic disorders, neuropathy, psychogenic factors or a mixture thereof, b) itch caused by allergic reactions, insect bites, hypersensitivity, inflammatory conditions or injury, c) itch associated with vulvar vestibulitis, d) skin irritation or inflammatory effect from administration of another therapeutic selected from antibiotics, antivirals, or antihistamines, or e) itch due to activation of PAR-2 G-protein coupled receptors.