

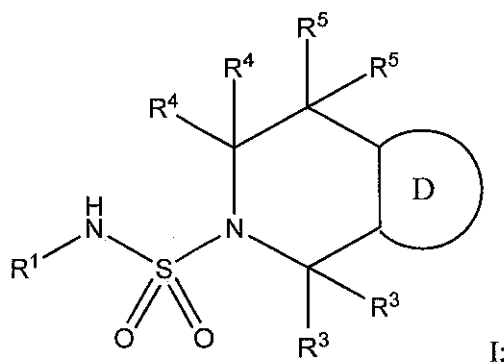
that among the many possible targets in the pain pathway, Nav 1.7 governs one or more control points critical for pain perception.

[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.

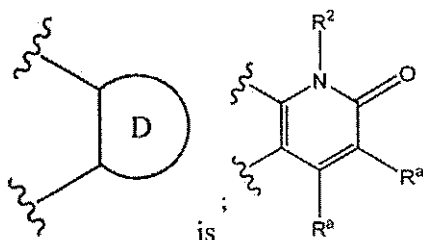
[0006] Consequently, a number of researchers are attempting to identify small molecule inhibitors of Nav1.7. For example, Chafeev et al disclose spiro-oxindole compound for the treatment and/or prevention of sodium channel-mediated diseases, such as pain, in US patent no. 8,101,647. International Publications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

[0006a] In one aspect, the present invention refers to a compound of Formula (I), an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,



Wherein the group:



R^1 is a 5- or 6-membered heteroaryl, , wherein the heteroaryl or group can have from 1 to 3 heteroatoms independently selected from O, N or S, , and the, heteroaryl, 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 a 5- or 6-membered aryl or heteroaryl, where the heteroaryl group can have from 1 to 3 heteroatoms independently selected from O, N or S, and the, aryl or heteroaryl group is optionally substituted with from 1 to 5 R^6 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 R^3 is independently selected from H, -C₁₋₆alkyl;

each R^4 is independently selected from H, -C₁₋₆alkyl;

each R^5 is H, ;

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 R^7 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 R^8 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^eR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;

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

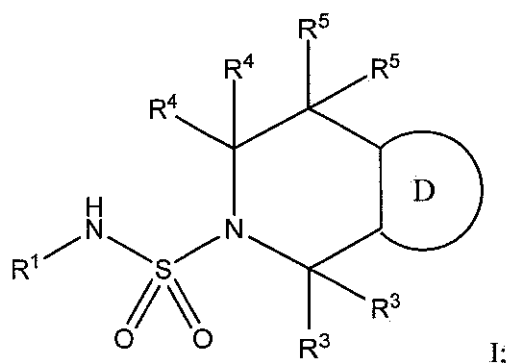
each n is independently 0, 1, 2, 3 or 4; and

each m is independently 0.

[0006b] In another aspect, the present invention refers to a pharmaceutical composition comprising the compound in accordance to the present invention, an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0006c] In yet another aspect, the present invention refers to use of the compound in accordance to 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, agnogenic 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.

[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,



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;

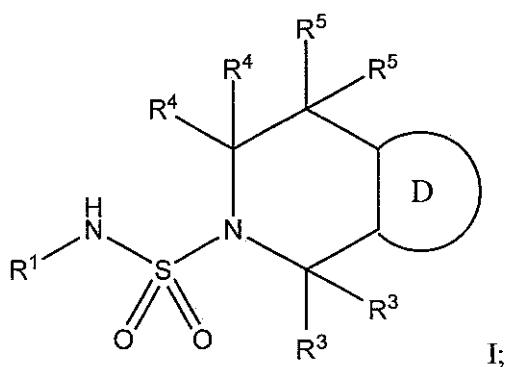
each R^b is independently H, halo, -CN, -NR^cR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;

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

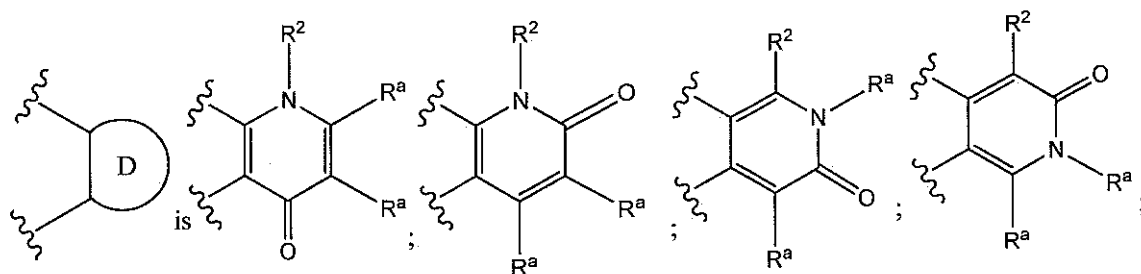
each n is independently 0, 1, 2, 3 or 4; and

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

[0008] In one 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:



Wherein the group:



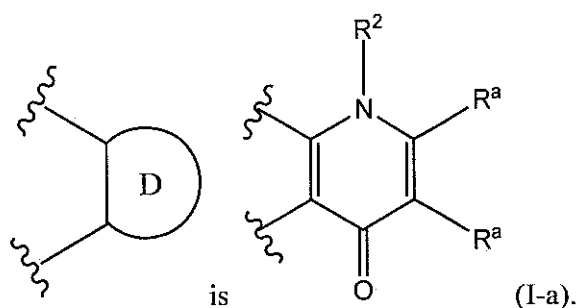
each R^a and R^b is independently H, halo, -CN, -NR^cR^c, -OH, -C₁₋₆alkyl, -C₁₋₆haloalkyl, -OC₁₋₆haloalkyl, or -OC₁₋₆alkyl;

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

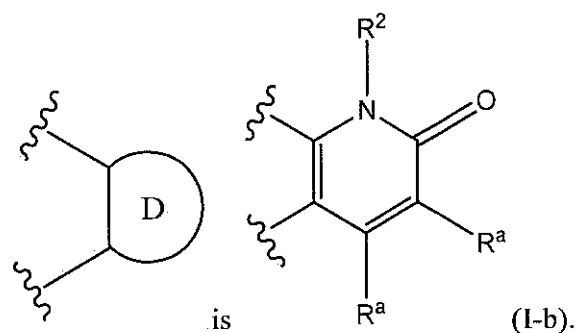
each n is independently 0, 1, 2, 3 or 4; and

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

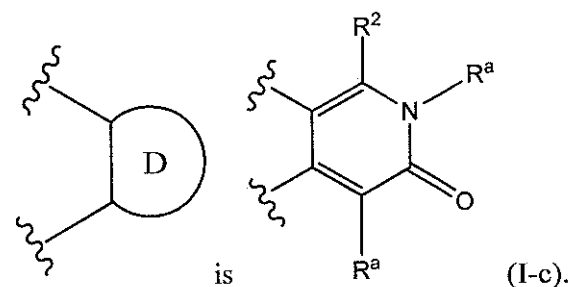
[0009] In example 1a, provided herein are compounds of Formula (I)-a, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



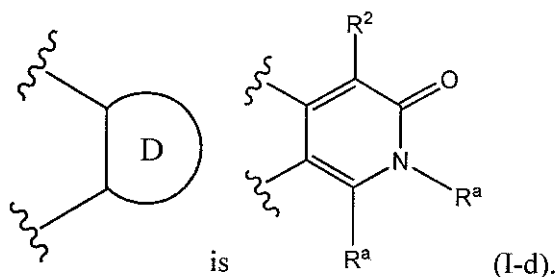
[0010] In example 1b, provided herein are compounds of Formula (I)-b, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



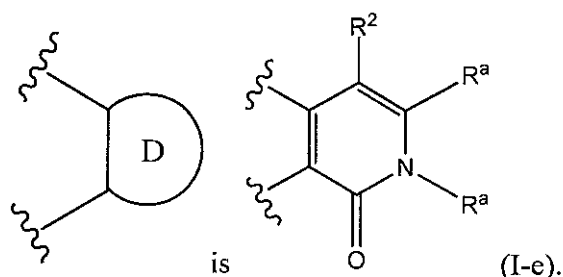
[0011] In example 1c, provided herein are compounds of Formula (I)-c, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



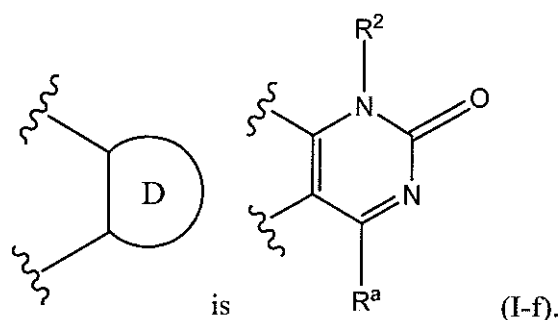
[0012] In example 1d, provided herein are compounds of Formula (I)-d, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



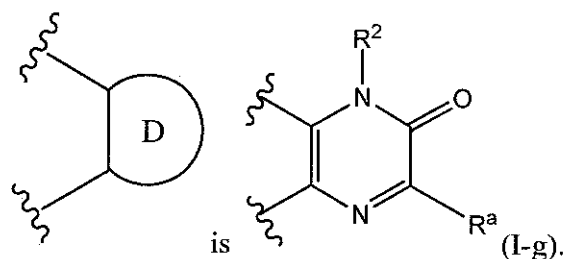
[0013] In example 1e, provided herein are compounds of Formula (I)-e, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



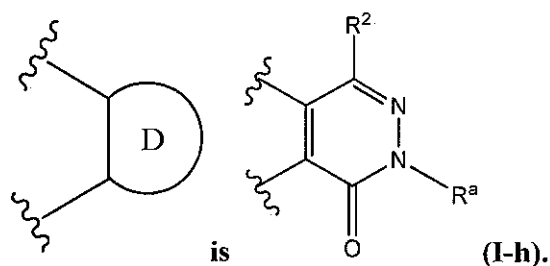
[0014] In example 1f, provided herein are compounds of Formula (I)-f, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein



[0015] In example 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 example 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 example 2, provided herein are compounds in accordance with any one of examples 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 example 2a, provided herein are compounds in accordance with any one of examples 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 example 2b, provided herein are compounds in accordance with any one of examples 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 example 3, provided herein are compounds in accordance with any one of examples 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 $-\text{OC}_{1-6}\text{alkyl}$, halo, $-\text{C}_{1-6}\text{alkyl}$, $\text{haloC}_{1-6}\text{alkyl}$, $-(\text{CR}^b\text{R}^b)_m\text{-A}$, or $-\text{C}_{2-6}\text{alkynyl-A}$.

[0021] In example 3a, provided herein are compounds in accordance with example 3, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein in said $R^6-(\text{CR}^b\text{R}^b)_m\text{-A}$ 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, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{F}$, or $-\text{CN}$; each R^b is independently H or $-\text{C}_{1-6}\text{alkyl}$; and m is 0 or 1.

[0022] In example 3b, provided herein are compounds in accordance with example 3, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein in said $R^6-\text{C}_{2-6}\text{alkynyl-A}$ 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, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{F}$, or $-\text{CN}$.

[0023] In example 3c, provided herein are compounds in accordance with example 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 example 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 example 4a, provided herein are compounds in accordance with example 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 example 4b, provided herein are compounds in accordance with example 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.

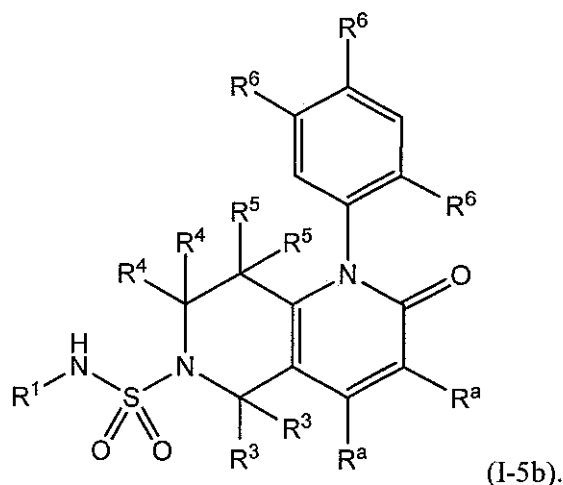
[0027] In example 4c, provided herein are compounds in accordance with example 4, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R^6 *para* to ring D is phenyl substituted with 1 to 3 R^7 substituents selected from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

[0028] In example 4d, provided herein are compounds in accordance with any one of examples 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 example 5, provided herein are compounds in accordance with examples 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 example 5a, provided herein are compounds in accordance with example 5, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said compound of formula (I) has the formula:



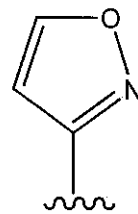
[0031] In example 5b, provided herein are compounds in accordance with examples 1, 1a-1h, 2, 2a-2b, 3, 3a-3c, 4a-4d, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein R² is pyridinyl ring.

[0032] In example 6, provided herein are compounds in accordance with examples 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 example 7, provided herein are compounds in accordance with examples 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.

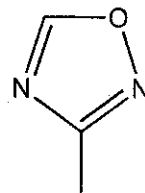
[0034] In example 7a, provided herein are compounds in accordance with example 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, wherein said R¹ is isoxazolyl, thiazolyl, thiadiazolyl, pyridazinyl, pyridyl, or pyrimidinyl ring, 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 example 7b, provided herein are compounds in accordance with example 7, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or



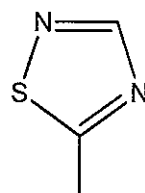
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or $-C_{1-6}$ alkyl.

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



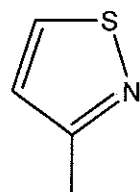
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or $-C_{1-6}$ alkyl.

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



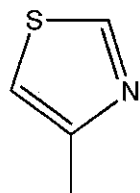
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or $-C_{1-6}$ alkyl.

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



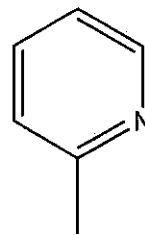
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 3 substituents independently selected from halo or $-C_{1-6}$ alkyl.

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



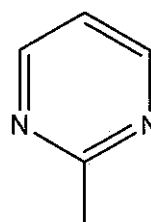
pharmaceutically acceptable salts thereof, wherein R^1 is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or $-C_{1-6}$ alkyl.

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



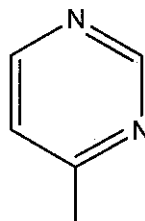
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

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



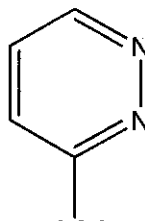
pharmaceutically acceptable salts thereof, wherein R¹ is unsubstituted or substituted with from 1 to 4 substituents independently selected from halo or -C₁₋₆alkyl.

[0045] In example 7l, provided herein are compounds in accordance with example 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 example 7m, provided herein are compounds in accordance with one example, 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 example 8, provided herein is a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, selected from:

- [00356] (*Rac*)-1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide;
- [00357] P-1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide; and
- [00358] M-1-(4-bromo-5-chloro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide.
- [00359] In example 9, the present disclosure provides a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, selected from:
- [00360] P-1-(4'-chloro-2-fluoro-3',5'-dimethoxy-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00361] P-1-(4'-chloro-2-fluoro-3',5'-dimethoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00362] *Rac*-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00363] P-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00364] P-1-(3'-chloro-2,5'-difluoro-5-methoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00365] *Rac*-1-(5-fluoro-2-methoxy-4-(2-methoxy-5-(trifluoromethyl)-3-pyridinyl)phenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00366] P-1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00367] P-1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-2-oxo-N-2-pyrimidinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00368] P-2-oxo-N-3-pyridazinyl-1-(2,3',4'-trifluoro-5-methoxy-4-biphenyl)-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00369] P-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;
- [00370] P-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;
- [00371] *Rac*-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;
- [00372] P-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;

- [00373] P-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;
- [00374] P-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;
- [00375] P-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;
- [00376] P-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;
- [00377] P-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;
- [00378] P-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
- [00379] P-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.
- [00380] In example 9a, the present disclosure provides a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, selected from:
- [00381] 1-(4'-chloro-2-fluoro-3',5'-dimethoxy-4-biphenyl)-2-oxo-N-3-pyridazinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00382] 1-(4'-chloro-2-fluoro-3',5'-dimethoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00383]
- [00384] 1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00385] 1-(3'-chloro-2,5'-difluoro-5-methoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00386] 1-(5-fluoro-2-methoxy-4-(2-methoxy-5-(trifluoromethyl)-3-pyridinyl)phenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00387] 1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00388] 1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-2-oxo-N-2-pyrimidinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [00389] 2-oxo-N-3-pyridazinyl-1-(2,3',4'-trifluoro-5-methoxy-4-biphenyl)-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;
- [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 example 10, provided herein is a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 8 and 9-9a.
- [00402] In example 11, provided herein is a P atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 8 and 9-9a.
- [00403] In example 12, provided herein is an M atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 8 and 9-9a.
- [00404] In example 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 examples 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 example 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 examples 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 example, the present disclosure provides the use of the compound in accordance with the present disclosure, 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, agnogenic 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 example 15, provided herein are methods of example 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 example 16, provided herein are methods of example 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 example 17, provided herein is a method of preparing a compound of Formula (I) as described above. In a sub example, said method is as described in any of Scheme A below.

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

DETAILED DESCRIPTION OF THE INVENTION

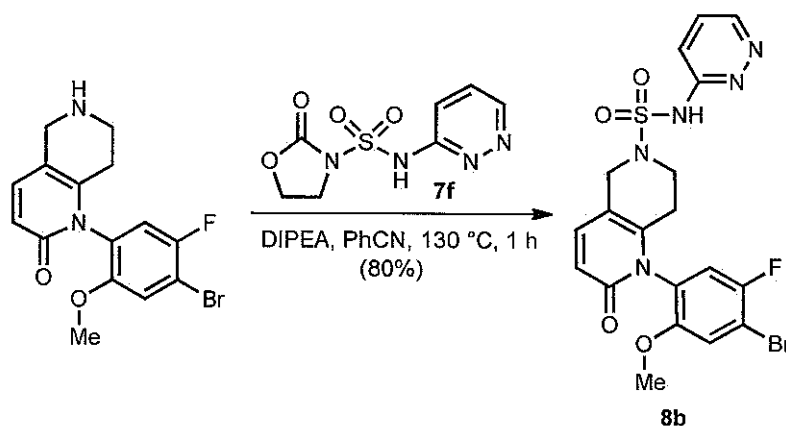
[00411] The present invention provides compounds of Formula (I), as defined above, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof,. The present invention also provides pharmaceutical compositions comprising a compound of Formula (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

[00557] Preparation 8b: (*Rac*)-; (*P*)-; and (*M*)-1-(4-BROMO-5-FLUORO-2-METHOXYPHENYL)-2-OXO-N-(PYRIDAZIN-3-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE



[00558] A 250-mL sealed tube was charged with 1-(4-bromo-5-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (See Preparation 8a, step 2, 5.65 g, 16.0 mmol), 2-oxo-N-(pyridazin-3-yl)oxazolidine-3-sulfonamide (Preparation 7f, 5.86 g, 24.0 mmol), *N,N*-diisopropylethylamine (19.5 ml, 112 mmol), and benzonitrile (32.0 ml). The reaction vessel was sealed and warmed to 130 °C. After 1 h, the reaction was cooled to ambient temperature and transferred to a 250-mL round-bottomed flask and concentrated under reduced pressure (1 mbar at 80-90 °C). The resultant black oil was diluted with DCM (200 mL) and washed with a solution of aqueous HCl (1.0 M, 100 mL). The aqueous layer was back-extracted with DCM (3 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified (200-g silica gel Grace, 0 to 10% MeOH in DCM) to afford 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (6.53 g, 12.80 mmol, 80% yield) as a brown solid. ¹H NMR (400MHz, DMSO-*d*₆) δ = 7.66 (dd, *J*=4.1, 9.6 Hz, 1H), 7.56 (d, *J*=6.3 Hz, 1H), 7.45 (d, *J*=8.6 Hz, 1H), 7.37 (d, *J*=9.4 Hz, 1H), 6.36 (d, *J*=9.3 Hz, 1H), 4.15 - 3.97 (m, 2H), 3.76 (s, 3H), 3.29 - 3.18 (m, 2H), 2.40 (td, *J*=5.7, 17.0 Hz, 1H), 2.10 (td, *J*=5.5, 17.4 Hz, 1H). *m/z* (ESI) 510.0 (*M*+*H*)⁺.

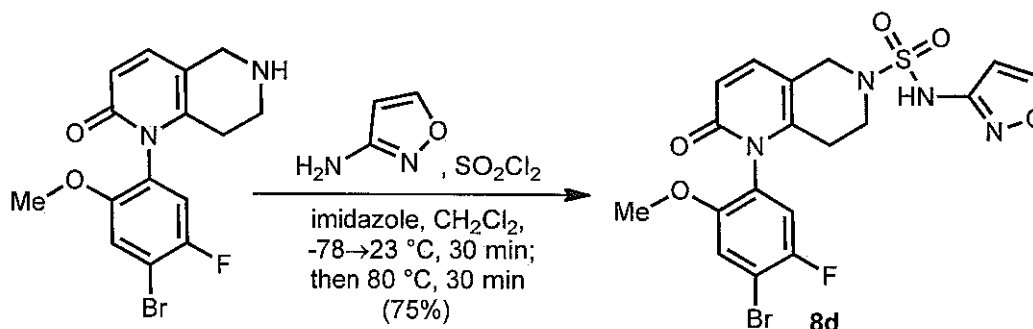
[00559] Separation Step: Racemic product of Preparation 8b was subjected to chiral SFC (Regis Whelk-O (s,s), 50% methanol) to give (Preparation 8b-P, 1.78 g, 3.49 mmol, 21.8% yield) (peak 1) and (Preparation 8b-M, 1.99 g, 3.90 mmol, 24.4% yield) (peak 2) as tan solids.

[00560] Preparation 8c: (*Rac*); -(*P*)-; and (*M*) 1-(4-BROMO-5-CHLORO-2-METHOXYPHENYL)-N-(ISOXAZOL-3-YL)-2-OXO-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

- 4.25 (m, 2 H) 3.76 (s, 3 H) 3.35 - 3.43 (m, 2 H) 2.30 - 2.46 (m, 1 H) 1.96 - 2.11 (m, 1 H).
m/z (ESI) 515.0 (M+H)⁺.

[00567] Separation Step: Racemic product of Preparation 8c was subjected to chiral SFC (Regis Whelk-O (s,s), 40% methanol) to give (Preparation 8c-P, 1.05 g, 2.04 mmol, 27.7% yield) (peak 1) and (Preparation 8c-M, 1.13 g, 2.19 mmol, 29.8% yield) (peak 2) as tan solids.

[00568] Preparation 8d: (*Rac*)-1-(4-BROMO-5-FLUORO-2-METHOXYPHENYL)-N-(ISOXAZOL-3-YL)-2-OXO-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

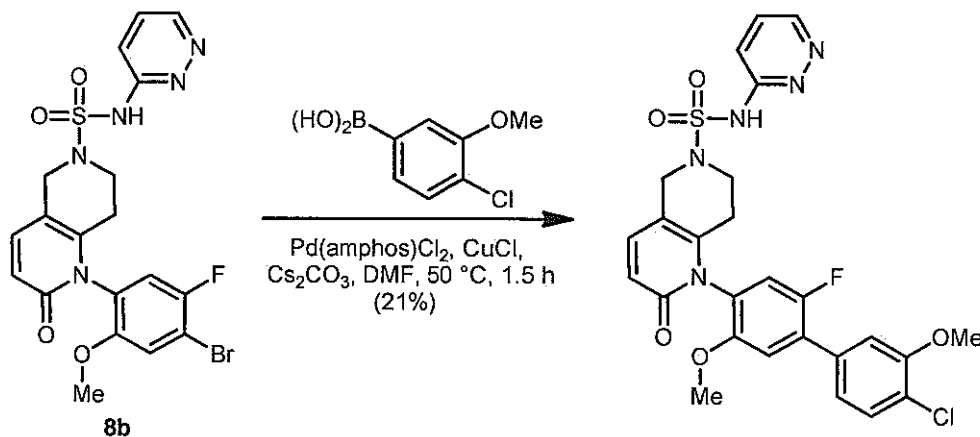


[00569] A 40-mL vial was charged with imidazole (922 mg, 13.6 mmol) and 3-aminoisoxazole (320 μL, 4.34 mmol) then purged with nitrogen. CH₂Cl₂ (10 mL) was introduced and the reaction mixture was cooled to -78 °C in a dry ice-acetone bath. Sulfuryl chloride (352.0 μL, 4.32 mmol) was added dropwise via syringe to the reaction mixture. Following addition, the cold bath was removed and the resultant mixture was allowed to warm to ambient temperature. After 30 minutes, (*Rac*)-1-(4-bromo-5-fluoro-2-methoxyphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (See Preparation 8a, step 2, 957 mg, 2.71 mmol) was introduced in a single portion followed by CH₂Cl₂ (10.0 mL). The vial was sealed with a PTFE lined cap and the reaction mixture was warmed to 80 °C. After 30 min, the reaction mixture was cooled to ambient temperature and diluted with an aqueous solution of citric acid (1.0 M, 25 mL), brine (25 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure and purified (100-g silica gel SNAP Ultra column, 0 to 50% 3:1 EtOAc/EtOH in heptane with DCM as a 10% additive) to afford (*Rac*)-1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (1.01 g, 2.023 mmol, 74.7 % yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.13 (s, 1 H) 8.73 (d, *J*=1.76 Hz, 1 H) 7.55 (d, *J*=6.22 Hz, 1 H) 7.37 (d, *J*=8.60 Hz, 1 H) 7.32 (d, *J*=9.54 Hz, 1 H) 6.38 (d, *J*=1.76 Hz, 1 H) 6.34 (d, *J*=9.43 Hz, 1 H) 4.12 - 4.30 (m, 2 H) 3.73 (s, 3 H) 3.32 - 3.44 (m, 2 H) 2.33 - 2.44 (m, 1 H) 2.03 (dt, *J*=17.62, 5.75 Hz, 1 H). m/z (ESI) 499.0 (M+H)⁺.

NAPHTHYRIDINE-6(5H)-SULFONAMIDE (Example 1-M) was not isolated in this example.

Example 2

(*Rac*)-; (*P*)-; and (*M*)-1-(4'-CHLORO-2-FLUORO-3',5-DIMETHOXY-[1,1']-BIPHENYL-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE



[00583] A 3-mL vial was charged with (*Rac*)-1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (Preparation 8b, 100 mg, 0.20 mmol), (Matrix Scientific, 4-chloro-3-methoxyphenyl)boronic acid (110 mg, 0.59 mmol), cesium carbonate (255 mg, 0.784 mmol), copper chloride (58.2 mg, 0.588 mmol), and 1,1-bis[(di-*t*-butyl-*p*-methylaminophenyl)palladium(II) chloride (27.7 mg, 0.039 mmol), then purged with nitrogen. DMF (980 μ L) was introduced, the vial was sealed with a PTFE line cap, and the resultant orange reaction mixture was warmed to 50 $^\circ$ C. After 1.5 h, the reaction mixture was allowed to cool to ambient temperature and diluted with aqueous HCl solution (1.0 M, 5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer extracted with additional EtOAc (2 $\times$ 5 mL). The combined organic layers were, dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure and purified reverse phase HPLC in 2 separate injections (XBridge Prep Shield RP18 19 $\times$ 100 mm Mobile phase: 0.1% TFA in water/acetonitrile Flow rate: 40 ml/min Inj: 1000 μ L Gradient: 12 min 25-70%). The fractions containing product were frozen and lyophilized to afford (*Rac*)-1-(4'-chloro-2-fluoro-3',5-dimethoxy-[1,1'-biphenyl]-4-yl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (24.0 mg, 0.042 mmol, 21.4 % yield) as a off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 7.67 (dd, J =9.54, 4.15 Hz, 1 H) 7.57 (d, J =8.19 Hz, 1 H) 7.29 - 7.44 (m, 4 H) 7.23 (dt, J =8.16, 1.83 Hz, 1 H) 6.39 (d, J =9.43 Hz, 1 H) 4.01 - 4.17 (m, 2 H) 3.95 (s, 3 H) 3.81 (s, 3 H) 3.21 - 3.29 (m, 2 H) 2.40 - 2.46 (m, 1 H) 2.07 - 2.23 (m, 1 H). m/z (ESI) 572.1 ($\text{M}+\text{H}$) $^+$.

(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (11.75 g, 27.4 mmol, 117 % yield) as a yellow solid.

[00587] Step 2: (*Rac*)-*tert*-BUTYL 7-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-CARBOXYLATE and (*Rac*)-*tert*-BUTYL 5-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-CARBOXYLATE

[00588] A 20-mL vial was charged with a mixture of (*Rac*)-(E)-*tert*-butyl 3-(3-methoxy-3-oxoprop-1-en-1-yl)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate and (*Rac*)-(E)-*tert*-butyl 3-(3-methoxy-3-oxoprop-1-en-1-yl)-2-methyl-4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (716 mg, 1.668 mmol), 2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-amine (Preparation 4h, 352 mg, 1.39 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (101 mg, 0.174 mmol), cesium carbonate (1.36 g, 4.17 mmol), tris(dibenzylideneacetone)dipalladium(0) (63.9 mg, 0.07 mmol), and 1,4-dioxane (6.95 mL) then sparged with nitrogen for 10 min. The needle was then removed and the reaction was heated to 100 °C. After 3 h, the reaction mixture was allowed to cool to ambient temperature and was diluted with EtOAc (15 mL) and filtered through a Celite® pad. The pad was rinsed with EtOAc (3 × 15 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (50-g silica gel Biotage column, eluent: gradient, 0 to 35% 3:1 EtOAc/EtOH in heptane with DCM as a 10% additive) to afford a mixture of (*Rac*)-*tert*-butyl 7-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate and (*Rac*)-*tert*-butyl 5-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (587 mg, 1.17 mmol, 84.0%) as a brown solid, m/z (ESI) 501.2 (M+H)⁺.

[00589] Step 3: (*Rac*)-7-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE and (*Rac*)-5-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE

[00590] A 20-mL vial was charged with a mixture of (*Rac*)-7-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE and (*Rac*)-5-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE (587 mg, 1.173 mmol) and trifluoroacetic acid (5.86 mL) at ambient temperature. After 30 min, the reaction mixture was concentrated under reduced pressure, dissolved in DCM (15 mL) and carefully

poured into saturated aqueous sodium bicarbonate solution (15 mL). The layers were separated and the aqueous layer extracted with additional DCM (3 × 15 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to afford a mixture of (*Rac*)-*tert*-butyl 7-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate and (*Rac*)-*tert*-butyl 5-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (400 mg, 1.00 mmol, 85.0%) as a tan amorphous solid, which was used without further purification.

[00591] Step 4: (*Rac*)-N-(ISOXAZOL-3-YL)-7-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE and (*Rac*)-N-(ISOXAZOL-3-YL)-5-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

[00592] A 20-mL vial was charged with a mixture of (*Rac*)-7-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE and (*Rac*)-5-METHYL-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE (400 mg, 1.00 mmol), N-(isoxazol-3-yl)-2-oxooxazolidine-3-sulfonamide (Preparation 7c, 349 mg, 1.50 mmol), acetonitrile (5.00 mL), and triethylamine (975 µL, 6.99 mmol). The vial was sealed with a PTFE lined cap and heated to 130 °C. After 1 h, the resultant brown reaction mixture was cooled to ambient temperature and diluted to 3 mL total volume with DMSO and filtered through a 0.4 micron filter. The filtrate was purified by reverse phase HPLC in 3 separate injections (XBridge Prep Shield RP18 19 × 100 mm Mobile phase: 0.1% TFA in water/acetonitrile Flow rate: 40 ml/min Inj: 2000 uL Gradient: 12 min 25-70%). The fractions containing product were frozen and lyophilized to afford (*Rac*)-N-(isoxazol-3-yl)-7-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide and (*Rac*)-N-(isoxazol-3-yl)-5-methyl-2-oxo-1-(2,3',5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (212 mg, 0.39 mmol, 38.8 % yield) as an orange solid, which was a mixture of 8 isomers.

[00593] Separation Step: Examples 3a-P, 3a-M, 3b-P, 3b-M, 3c-P, 3c-M, 3d-P, and 3d-M; which are named:

[00594] Example 3a-P: (P)-(R)-N-(ISOXAZOL-3-YL)-5-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

[00595] Example 3a-M: (M)-(R)-N-(ISOXAZOL-3-YL)-5-METHYL-2-OXO-1-(2,3',5'-TRIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

The combined organic layers were washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure and purified by flash column chromatography (25-g silica gel Biotage column, eluent: gradient, 0 to 50% 3:1 EtOAc/EtOH in heptane with DCM as a 10% additive) to afford (*Rac*)-*tert*-butyl 1-(3'-chloro-2,5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (678 mg, 1.35 mmol, 76 % yield) as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.61 - 7.65 (m, 1 H) 7.57 (dd, *J*=9.02, 1.55 Hz, 1 H) 7.36 - 7.45 (m, 2 H) 6.41 (d, *J*=9.43 Hz, 1 H) 4.30 (s, 2 H) 3.82 (s, 3 H) 3.48 - 3.60 (m, 1 H) 3.37 - 3.48 (m, 1 H) 2.26 - 2.39 (m, 1 H) 1.97 - 2.10 (m, 1 H) 1.42 (s, 9 H). *m/z* (ESI) 503.2 (M+H)⁺.

[00619] Step 2: (*Rac*)-1-(3'-CHLORO-2,5'-DIFLUORO-5-METHOXY[1,1'-BIPHENYL]-4-YL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE

[00620] A 50-mL round-bottom flask was charged with (*Rac*)-*tert*-butyl 1-(3'-chloro-2,5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (678 mg, 1.35 mmol) and trifluoroacetic acid (10.0 mL) then stirred for 30 min at ambient temperature. The reaction mixture was concentrated under reduced pressure, dissolved in DCM (25 mL) and carefully poured into saturated aqueous sodium bicarbonate solution (25 mL). The layers were separated and the aqueous layer extracted with additional DCM (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to afford (*Rac*)-1-(3'-chloro-2,5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (500 mg, 1.24 mmol, 92 % yield) as a brown foam which was used without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.63 (d, *J*=1.35 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 7.31 - 7.40 (m, 2 H) 7.26 (d, *J*=9.33 Hz, 1 H) 6.34 (d, *J*=9.33 Hz, 1 H) 3.55 - 3.73 (m, 2 H) 3.33 (s, 3 H) 2.83 (t, *J*=5.44 Hz, 2 H) 2.09 - 2.25 (m, 1 H) 1.85 - 1.99 (m, 1 H). *m/z* (ESI) 403.2 (M+H)⁺.

[00621] Step 3: (*Rac*)-1-(3'-CHLORO-2,5'-DIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-N-(6-METHYLPYRIMIDIN-4-YL)-2-OXO-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

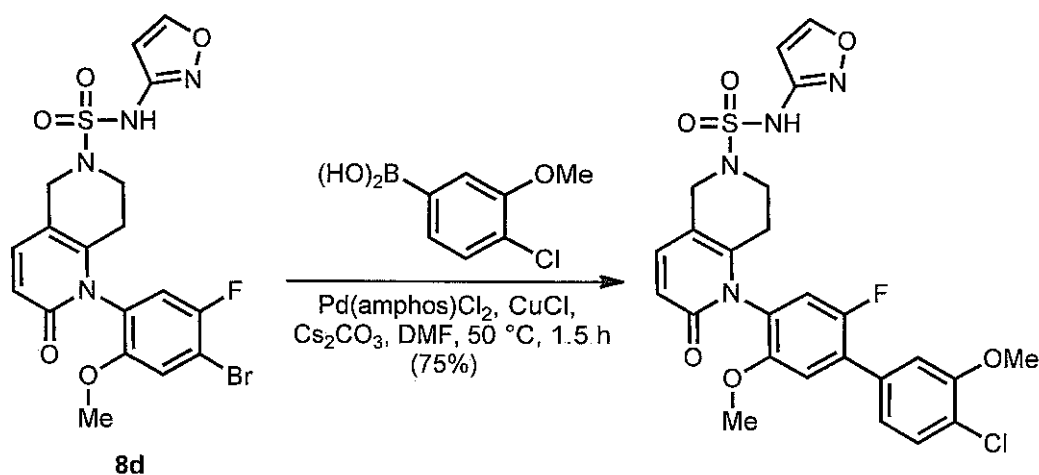
[00622] A 3-mL vial was charged with (*Rac*)-1-(3'-chloro-2,5'-difluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (100 mg, 0.25 mmol), N-(4-methoxybenzyl)-N-(6-methylpyrimidin-4-yl)-1H-imidazole-1-sulfonamide (Preparation 7e, 134 mg, 0.37 mmol), acetonitrile (2 mL), and triethylamine (242 μL, 1.74 mmol). The vial was sealed with a PTFE lined cap and heated to 130 °C. After 30 min, the resultant brown reaction mixture was cooled to ambient temperature and diluted to 3 mL total volume with DMSO and filtered through a 0.4 micron filter. The filtrate was purified by reverse phase HPLC in 2 separate injections (XBridge Prep Shield RP18 19 × 100 mm Mobile phase: 0.1% TFA in water/acetonitrile Flow rate: 40 ml/min Inj: 1500 uL Gradient: 12 min 25-70%). The

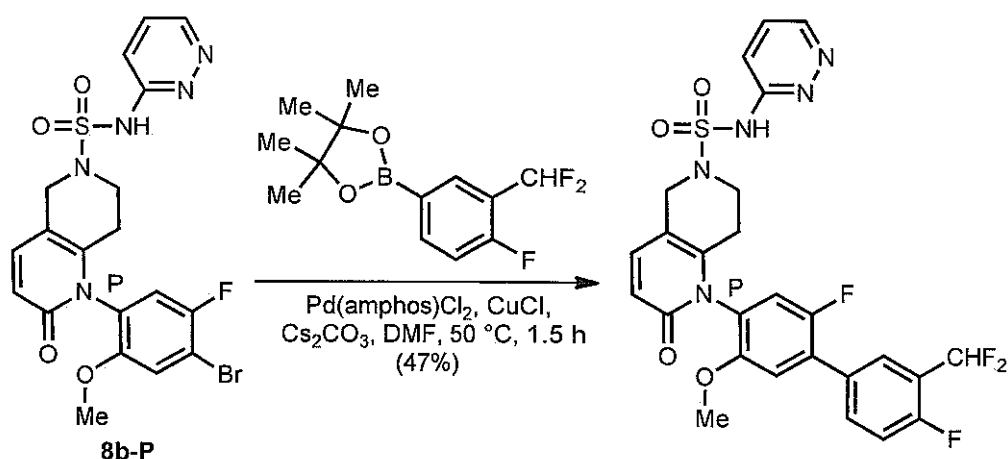
reaction mixture. Following addition, the cold bath was removed and the resultant mixture was allowed to warm to ambient temperature. After 30 minutes, (*Rac*)-1-(2,3,5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (See Example 10, step 2, 125 mg, 0.32 mmol) was introduced in a single portion followed by CH₂Cl₂ (1.0 mL). The vial was sealed with a PTFE lined cap and the reaction mixture was warmed to 80 °C. After 30 min, the reaction mixture was cooled to ambient the resultant brown temperature mixture was cooled to ambient temperature and and diluted with an aqueous solution of citric acid (1.0 M, 5 mL), brine (5 mL), and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure and purified by reverse phase HPLC in 2 separate injections (XBridge Prep Shield RP18 19 × 100 mm Mobile phase: 0.1% TFA in water/acetonitrile Flow rate: 40 ml/min Inj: 1500 uL Gradient: 12 min 25-70%). The fractions containing product were frozen and lyophilized to afford (*Rac*)-N-(6-fluoropyridin-2-yl)-2-oxo-1-(2,3,5'-trifluoro-5-methoxy-[1,1'-biphenyl]-4-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (47.2 mg, 0.08 mmol, 26.0 % yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.96 (s, 1 H) 7.88 (q, *J*=7.98 Hz, 1 H) 7.26 - 7.47 (m, 6 H) 6.92 (dd, *J*=7.83, 1.92 Hz, 1 H) 6.75 (dd, *J*=7.98, 2.18 Hz, 1 H) 6.37 (d, *J*=9.54 Hz, 1 H) 4.25 - 4.36 (m, 2 H) 3.77 (s, 2 H) 2.35 - 2.48 (m, 1 H) 2.05 - 2.14 (m, 1 H). *m/z* (ESI) 559.0 (M+H)⁺.

[00661] Separation Step: Racemic product of Example 14 was subjected to chiral SFC separation ((*S,S*) Whelk-O column, 35% methanol) to afford Example 14-P (peak 1) and Example 14-M (peak 2) as off-white solids.

Example 15

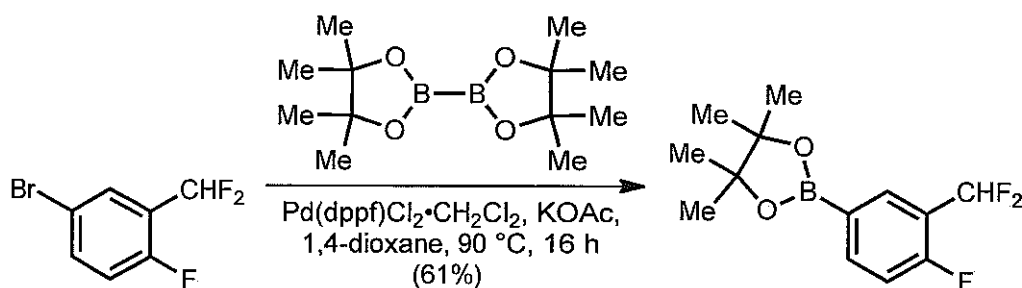
(*Rac*)-; (*P*)-; and (*M*)-1-(2-FLUORO-3',5-DIMETHOXY-4'-CHLORO-[1,1'-BIPHENYL]-4-YL)-N-(ISOXAZOL-3-YL)-2-OXO-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE





[00782] This compound was prepared analogous to the procedure of Example 41 from (P)-1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-N-(pyridazin-3-yl)-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (Preparation 8b-P) and 2-(3-(difluoromethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, which was prepared below, as the boronic ester. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 14.21 (br. s., 1 H) 8.27 (br. s., 1 H) 7.89 (d, $J=6.01$ Hz, 3 H) 7.66 (dd, $J=9.59, 4.09$ Hz, 1 H) 7.56 (t, $J=9.64$ Hz, 1 H) 7.11 - 7.46 (m, 4 H) 6.38 (d, $J=9.38$ Hz, 1 H) 3.96 - 4.16 (m, 2 H) 3.81 (s, 3 H) 3.25 (br. s., 2 H) 2.36 - 2.49 (m, 1 H) 2.03 - 2.23 (m, 1 H). m/z (ESI) 576.2 ($\text{M}+\text{H}$) $^+$.

[00783] Preparation of 2-(3-(difluoromethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[00784] A 500-mL round-bottom flask was charged with 4-bromo-2-(difluoromethyl)-1-fluorobenzene (Combi-Blocks Inc., 10.0 g, 44.4 mmol), bis(pinacolato)diboron (13.5 g, 53.3 mmol), potassium acetate (13.1 g, 133 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (3.63 g, 4.44 mmol), and 1,4-dioxane (150 mL). The reaction mixture was sparged with nitrogen for 15 min then warmed to 90 °C. After 16 h, the reaction mixture was allowed to cool to ambient temperature, filtered through a pad of Celite[®] (3 cm), and the Celite[®] pad was rinsed with EtOAc (250 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (120-g silica gel Redi-Sep column, eluent: gradient, 0 to 10% EtOAc in hexane) to afford 2-(3-(difluoromethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-

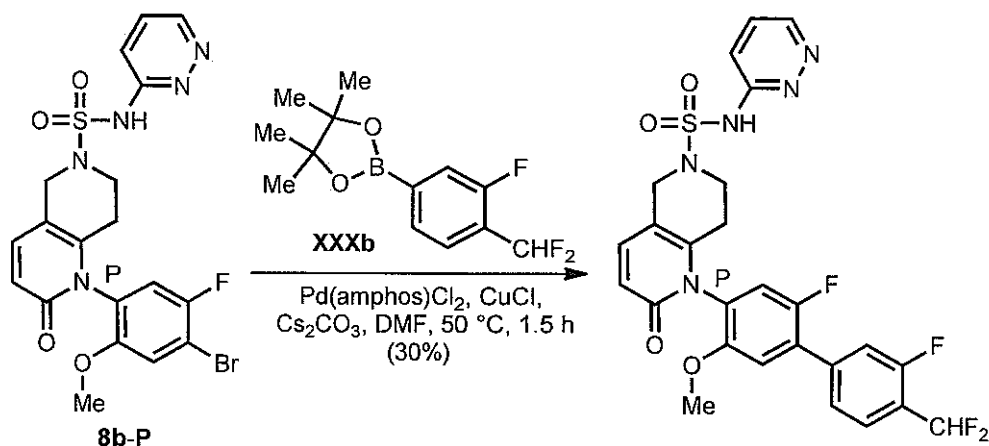
the reaction mixture via syringe, which was subsequently allowed to warm to ambient temperature. After 2 h, saturated aqueous sodium bicarbonate was introduced (100 mL) and the layers were separated. The aqueous layer was extracted with DCM (2 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure to afford 5-bromo-1-(difluoromethyl)-2,3-difluorobenzene (10.1 g, 41.6 mmol, 92% yield) as yellow oil, which was used without further purification. ¹H NMR (400 MHz, Chloroform-d) δ 7.52 – 7.46 (m, 2 H), 6.86 (t, J = 54.4 Hz, 1 H).

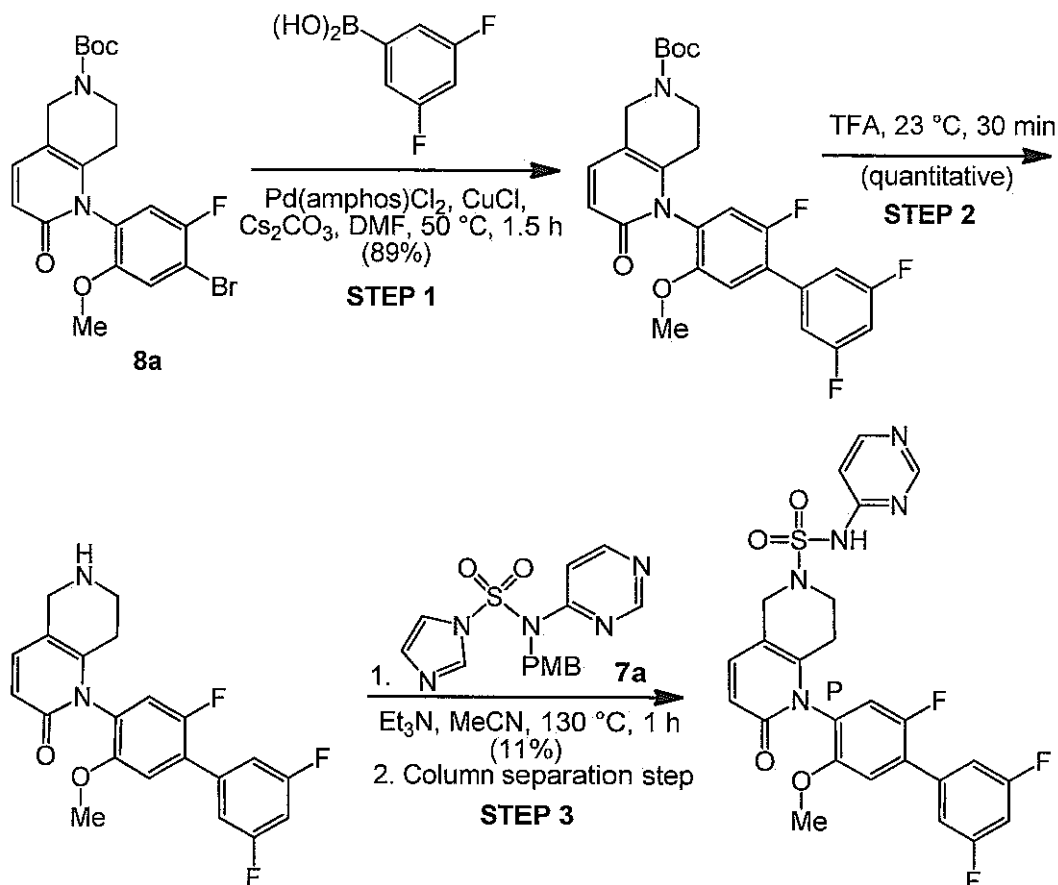
Step-2: 2-(3-(DIFLUOROMETHYL)-4,5-DIFLUOROPHENYL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE

[00788] A 500-mL round-bottom flask was charged with 5-bromo-1-(difluoromethyl)-2,3-difluorobenzene (10.1 g, 41.6 mmol), bis(pinacolato)diboron (12.7 g, 49.9 mmol), potassium acetate (12.2 g, 125 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (3.39 g, 4.16 mmol), and 1,4-dioxane (150 ml). The reaction mixture was sparged with nitrogen for 15 min then warmed to 90 °C. After 2 h, the reaction mixture was allowed to cool to ambient temperature, filtered through a pad of Celite® (3 cm), and the Celite® pad was rinsed with EtOAc (500 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography (120-g silica gel Redi-Sep column, eluent: gradient, 0 to 10% EtOAc in hexane) to afford 2-(3-(difluoromethyl)-4,5-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.80 g, 20.0 mmol, 48.1% yield) as yellow oil. ¹H NMR (400 MHz, DMSO- *d*₆) δ 7.83 – 7.57 (m, 2 H), 7.29 (t, J = 53.8 Hz, 1 H), 1.31 (s, 12 H).

Example 87

(P)-1-(4'-(DIFLUOROMETHYL)-2,3'-DIFLUORO-5-METHOXY-[1,1'-BIPHENYL]-4-YL)-2-OXO-N-(PYRIDAZIN-3-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

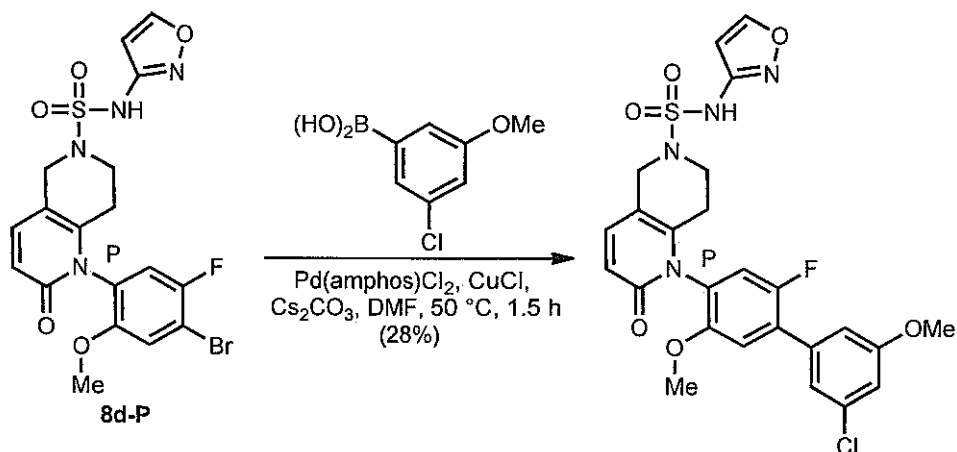




[00792] This compound was prepared analogous to the procedure of Example 1 from *(Rac)*-*tert*-butyl 1-(4-bromo-5-fluoro-2-methoxyphenyl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (See Preparation 8a, step 1). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.62 (s, 1 H) 8.34 (br. s., 1 H) 7.23 - 7.59 (m, 7 H) 6.98 (d, $J=4.98$ Hz, 1 H) 6.39 (d, $J=9.43$ Hz, 1 H) 4.12 - 4.35 (m, 2 H) 3.79 (s, 3 H) 3.39 (br. s., 2 H) 2.35 - 2.48 (m, 1 H) 2.04 - 2.20 (m, 1 H). m/z (ESI) 544.2 ($\text{M}+\text{H}$) $^+$.

Example 89

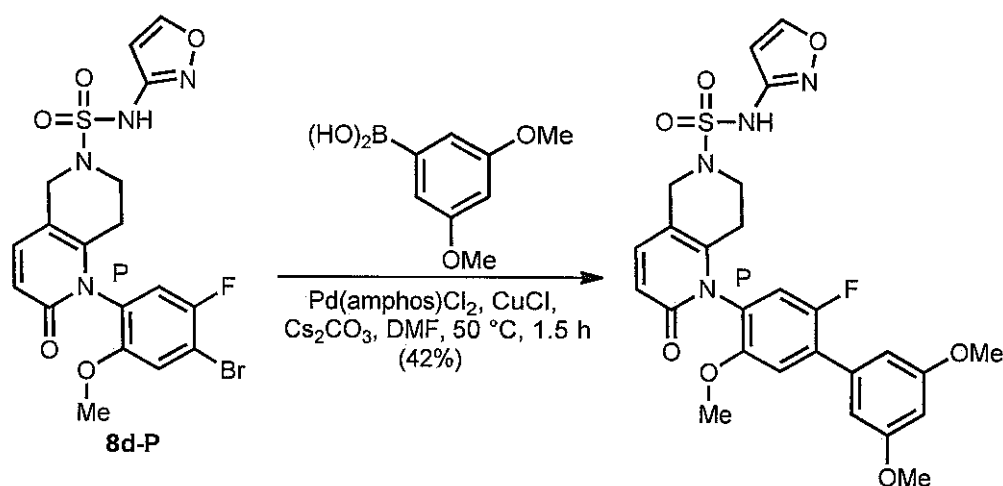
(P)-N-(ISOXAZOL-3-YL)-2-OXO-1-(3'-CHLORO-2-FLUORO-5,5'-DIMETHOXY-[1,1'-BIPHENYL]-4-YL)-1,5,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(2H)-SULFONAMIDE



[00793] This compound was prepared analogous to the procedure of Example 15 from 1-(3'-chloro-2-fluoro-5,5'-dimethoxy-[1,1'-biphenyl]-4-yl)-N-(isoxazol-3-yl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (Preparation 8d-P) and (3-chloro-5-methoxyphenyl)boronic acid (purchased from Alfa Asar) as the boronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.17 (s, 1 H) 7.11 - 7.39 (m, 7 H) 6.31 - 6.42 (m, 2 H) 4.12 - 4.33 (m, 2 H) 3.86 (s, 3 H) 3.79 (s, 3 H) 3.36 - 3.49 (m, 2 H). *m/z* (ESI) 561.0 (M+H)⁺.

Example 90

(P)-1-(2-FLUORO-3',5,5'-TRIMETHOXY-[1,1'-BIPHENYL]-4-YL)-N-(ISOXAZOL-3-YL)-2-OXO-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE



[00794] This compound was prepared analogous to the procedure of Example 15 from (P)-1-(4-bromo-5-fluoro-2-methoxyphenyl)-N-(isoxazol-3-yl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-sulfonamide (Preparation 8d-P) and (3,5-dimethoxyphenyl)boronic acid (purchased from Sigma-Aldrich Chemical Company, Inc.) as the boronic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.64 - 8.81 (m, 1 H) 7.21 - 7.37 (m, 3 H) 6.76 (d, *J*=1.45 Hz, 2 H) 6.58 - 6.64 (m, 1 H) 6.34 - 6.41 (m, 2 H) 4.15 - 4.31 (m, 2 H) 3.75 - 3.87 (m, 9 H) 3.36 - 3.49 (m, 2 H) 2.40 - 2.48 (m, 1 H) 2.01 - 2.16 (m, 1 H). *m/z* (ESI) 557.0 (M+H)⁺.

Example 91

(*Rac*)-; (*P*)-; and (*M*)-1-(2-CHLORO-5-METHOXY-3'-(TRIFLUOROMETHYL)-[1,1'-BIPHENYL]-4-YL)-2-OXO-N-(PYRIDAZIN-3-YL)-1,2,7,8-TETRAHYDRO-1,6-

Celite® pad was rinsed with DCM (3 × 50 mL). The brown filtrate was concentrated under reduced pressure and purified by flash column chromatography (100-g Biotage column, eluent: gradient, 0 to 35% 3:1 EtOAc/EtOH in heptane with DCM as a 10% additive) to afford (*Rac*)-*tert*-butyl 1-(4-bromo-2-methoxy-5-methylphenyl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (1.87 g, 4.16 mmol, 37.9 % yield) as a tan foam. ¹H NMR (400MHz, DMSO-*d*₆) δ = 7.42 (s, 1H), 7.39 - 7.32 (m, 1H), 7.39 - 7.32 (m, 1H), 7.39 - 7.32 (m, 1H), 7.25 - 7.18 (m, 1H), 7.25 - 7.18 (m, 1H), 7.22 (s, 1H), 6.37 (d, *J*=9.4 Hz, 1H), 4.27 (s, 2H), 3.73 (s, 3H), 3.57 - 3.36 (m, 2H), 2.35 - 2.17 (m, 4H), 2.08 - 1.89 (m, 1H), 1.41 (s, 9H). *m/z* (ESI) 449.0 (M+H)⁺.

Step 2: (*Rac*)-1-(4-BROMO-2-METHOXY-5-METHYLPHENYL)-5,6,7,8-TETRAHYDRO-1,6-NAPHTHYRIDIN-2(1H)-ONE

[00801] A 40-mL vial was charged with (*Rac*)-*tert*-butyl 1-(4-bromo-2-methoxy-5-methylphenyl)-2-oxo-1,2,7,8-tetrahydro-1,6-naphthyridine-6(5H)-carboxylate (1.87 g, 4.16 mmol) and trifluoroacetic acid (20.8 mL) then stirred for 30 min at ambient temperature. The reaction mixture was concentrated under reduced pressure, dissolved in DCM (50 mL) and carefully poured into saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated and the aqueous layer extracted with additional DCM (3 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure to afford (*Rac*)-1-(4-bromo-2-methoxy-5-methylphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (1.45 g, 4.15 mmol, quantitative) as a tan foam which was used without further purification. ¹H NMR (400MHz, DMSO-*d*₆) δ = 7.41 (s, 1H), 7.23 (d, *J*=9.3 Hz, 1H), 7.15 (d, *J*=0.6 Hz, 1H), 6.30 (d, *J*=9.3 Hz, 1H), 3.73 (s, 3H), 3.66 - 3.49 (m, 2H), 2.80 (dt, *J*=1.9, 5.8 Hz, 2H), 2.29 (s, 3H), 2.15 - 1.98 (m, 1H), 1.87 (td, *J*=5.6, 17.4 Hz, 1H). *m/z* (ESI) 349.0 (M+H)⁺.

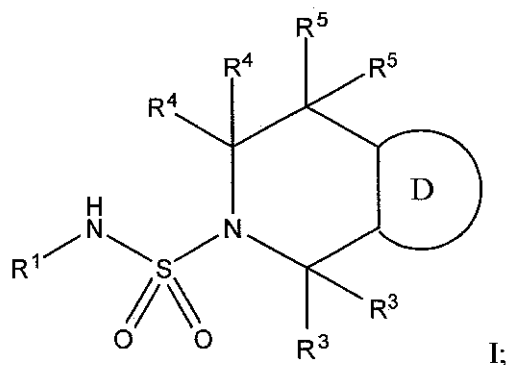
Step 3: (*Rac*)-1-(4-BROMO-2-METHOXY-5-METHYLPHENYL)-2-OXO-N-(PYRIDAZIN-3-YL)-1,2,7,8-TETRAHYDRO-1,6-NAPHTHYRIDINE-6(5H)-SULFONAMIDE

[00802] A 25-mL sealed tube was charged with 1-(4-bromo-2-methoxy-5-methylphenyl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2(1H)-one (1.45 g, 4.15 mmol), 2-oxo-N-(pyridazin-3-yl)oxazolidine-3-sulfonamide (Preparation 7f, 2.028 g, 8.30 mmol), N,N-diisopropylethylamine (5.06 mL, 29.1 mmol), and benzonitrile (8.30 mL). The reaction vessel was sealed and warmed to 130 °C. After 30 min, the reaction mixture was cooled to ambient temperature and transferred to a 100-mL round-bottomed flask and concentrated under reduced pressure (1 mbar at 80-90 °C). The resultant black oil was diluted with DCM (50 mL) and washed with a solution of aqueous HCl (1.0 M, 50 mL). The aqueous layer was back-extracted with DCM (3 × 25 mL). The combined organic layers were dried over magnesium

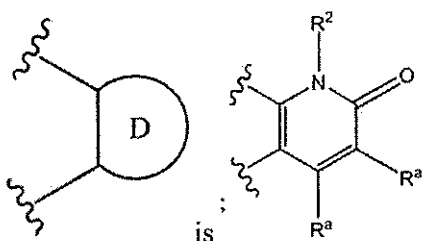
CLAIMS

What is claimed is:

1. A compound of Formula (I), an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,



Wherein the group:



R^1 is a 5- or 6-membered heteroaryl, wherein the heteroaryl or group can have from 1 to 3 heteroatoms independently selected from O, N or S, and the heteroaryl 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 a 5- or 6-membered aryl or heteroaryl, where the heteroaryl group can have from 1 to 3 heteroatoms independently selected from O, N or S,

and the, aryl or heteroaryl group is optionally substituted with from 1 to 5 R^6 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 R^3 is independently selected from H, -C₁₋₆alkyl;

each R^4 is independently selected from H, -C₁₋₆alkyl;

each R^5 is H, ;

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 R^7 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 R^8 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.

2. The compound in accordance with claim 1, an enantiomer, diastereomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein the group

1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

1-(3'-chloro-2,5'-difluoro-5-methoxy-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

1-(5-fluoro-2-methoxy-4-(2-methoxy-5-(trifluoromethyl)-3-pyridinyl)phenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-N-3-isoxazolyl-2-oxo-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

1-(4'-chloro-2-fluoro-5-methoxy-3'-methyl-4-biphenyl)-2-oxo-N-2-pyrimidinyl-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

2-oxo-N-3-pyridazinyl-1-(2,3',4'-trifluoro-5-methoxy-4-biphenyl)-1,5,7,8-tetrahydro-1,6-naphthyridine-6(2H)-sulfonamide;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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

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.