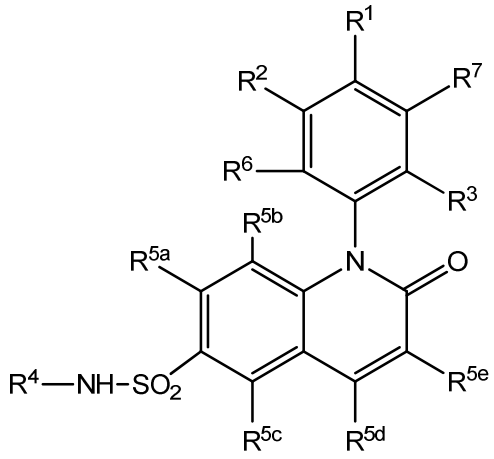
disorder is inherited in Mendelian recessive manner with 100% penetrance. The phenotype associated with CIP is extreme: affected individuals are reported to have experienced painless burns, childbirth, appendicitis, and bone fractures, as well as to have insensitivity to clinical measures of pain such as pinprick or tendon pressure. Yet sensory, motor, autonomic, and other measured functions are normal, with the only reported abnormality being anosmia (inability to smell). These studies indicate that among the many possible targets in the pain pathway, Nav 1.7 governs one or more control points critical for pain perception.

[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. Dentists use novocaine. However these compounds do not distinguish between the various sodium channel subtypes, making them unsuitable for use as systemic pain killers. "If you give a drug that blocks Nav1.7 but also blocks Nav1.5, the patient will die of heart failure," says Glenn F. King, a professor at Australia's University of Queensland who studies venoms that block ion channels. "It will be a completely painless death, but the patient will die nonetheless." Thus, selectivity for Nav1.7 is desired, particularly over Nav1.5. Researchers have tailored their efforts to find a molecule that inhibitors or block the activity of only Nav1.7. To compound this problem, the identity, every location, every function and/or the tertiary structures of each subtype of voltage gated sodium channel proteins are not known or completely understood.

[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 U.S. Patent No. 8,101,647. International Publications WO 2013/134518 and WO 2014/201206 disclose sulfonamide derivatives which are different from the sulfonamide derivatives of the present invention. Thus, there is a need to identify Nav1.7 inhibitors selective over at least Nav1.5 to treat pain. The present invention provides compounds that are selective inhibitors of Nav 1.7. over at least Nav1.5.

SUMMARY OF THE INVENTION

[0006a] In one aspect, the present invention provides a compound of Formula I, or a pharmaceutically acceptable salt thereof,



(I);

wherein:

R^1 is selected from $-CH_2-CF_3$, $-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CH_2-CF_3$, $-CH_2-CH(CH_3)-CF_3$, $-CH_2-CF_2-CF_3$, $-CH_2-C(CH_3)_2-CF_3$, $-C(CH_3)_2-CH_2-CF_3$, $-CF_2-CH_2-CF_3$, or $-CH_2-CH_2-CHF_2$;

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

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

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

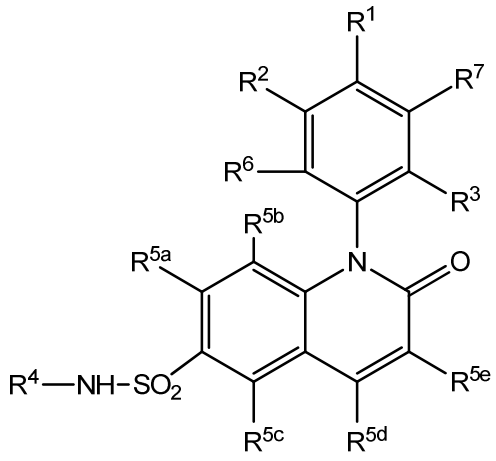
Each of R^6 and R^7 is hydrogen; and

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

[0006b] In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of the compound or the pharmaceutically acceptable salt thereof as disclosed herein, and a pharmaceutically acceptable excipient.

[0006c] In another aspect, the present invention provides the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating pain, cough, or itch.

[0007] In example 1, the present disclosure provides a compound of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof,



(I);

wherein:

R^1 is (a) C_{1-8}alk wherein said C_{1-8}alk is substituted by 0, 1, 2 or 3 groups selected from hydroxy, -OC_{1-4}alk, -NH_2, -NHC_{1-4}alk, -$OC(=O)C_{1-4}$alk, or -$N(C_{1-4}alk)C_{1-4}$alk; or (b) C_{1-8}haloalk;

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

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

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

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

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

[0008] In example 2, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{4-8}alk or C_{1-6}haloalk, wherein said C_{1-6}haloalk is C_{1-6}fluoroalkyl.

[0009] In example 3, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from -CH_2-CF_3, -CH_2-CH_2-CF_3, -CH_2-CH_2-CH_2-CF_3, -CH_2-$CH(CH_3)$-CF_3, -CH_2-CF_2-CF_3, -CH_2-$C(CH_3)_2$-CF_3, -$C(CH_3)_2$-CH_2-CF_3, -CF_2-CH_2-CF_3, or -CH_2-CH_2-CHF_2.

[0010] In example 4, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, fluoro, chloro, methyl, CF_3, CHF_2, or CH_2F.

[0011] In example 5, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or fluoro. In sub example of example 5, R^2 is fluoro.

[0012] In example 6, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^3 is methoxy.

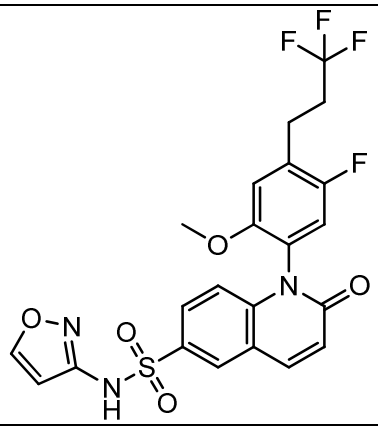
[0013] In example 7, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is a 5-membered heteroaryl.

[0014] In example 8, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is a 6-membered heteroaryl.

[0015] In example 9, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein R^4 is isoxazolyl, pyridazinyl, thiazolyl, thiadiazolyl, oxazolyl, or pyrimidinyl. In a sub example of example 8, R^4 is isoxazolyl or pyridazinyl. In another sub example of example 8, R^4 is isoxazolyl.

[0016] In example 10, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, wherein each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is hydrogen.

[0017] In example 11, the present disclosure provides compounds of Formula (I), an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof, which is:

Ex.	Structure	Chemical Name
1		1-(5-fluoro-2-methoxy-4-(3,3,3-trifluoropropyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide

[0018] In example 11a, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(3,3,3-trifluoropropyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0019] In example 11b, the present disclosure provides a compound of Formula (I), which is 1-(5-chloro-2-methoxy-4-(3,3,3-trifluoropropyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0020] In example 11c, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(3,3,3-trifluoropropyl)phenyl)-2-oxo-N-3-pyridazinyl-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0021] In example 11d, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-((2R)-3,3,3-trifluoro-2-methylpropyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0022] In example 11e, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-((2S)-3,3,3-trifluoro-2-methylpropyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0023] In example 11f, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(2,2,2-trifluoroethyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0024] In example 11g, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(4,4,4-trifluorobutyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0025] In example 11h, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(2,2,2-trifluoroethyl)phenyl)-N-3-isoxazolyl-2-oxo-1,2-dihydro-6-quinolinesulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0026] In example 11i, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(2,2,3,3,3-pentafluoropropyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0027] In example 11j, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(3,3,3-trifluoro-2,2-dimethylpropyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0028] In example 11k, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(4,4,4-trifluoro-2-methylbutan-2-yl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0029] In example 11l, the present disclosure provides a compound of Formula (I), which is 1-(5-fluoro-2-methoxy-4-(1,1,3,3,3-pentafluoropropyl)phenyl)-N-(isoxazol-3-yl)-2-oxo-1,2-dihydroquinoline-6-sulfonamide, or an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or a pharmaceutically acceptable salt thereof.

[0030] In example 12, the present disclosure provides a P atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 11a to 11l.

[0031] In example 13, the present disclosure provides an M atropisomer of each individual compound, independently, or a mixture thereof, or pharmaceutically acceptable salts thereof, recited in examples 11a to 11l.

[0032] In example 14, the present disclosure provides pharmaceutical compositions comprising a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, in accordance with any one of examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 11a-11l. 12, and 13, and a pharmaceutically acceptable excipient.

[0033] In example 15, the present disclosure provides methods of treating pain, cough, or itch, the methods comprising administering to a patient in need thereof a therapeutically effective amount of a compound, an enantiomer, diastereoisomer, atropisomer thereof, or a mixture thereof, or pharmaceutically acceptable salts thereof, in accordance with any one of examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 11a-11l. 12, and 13.

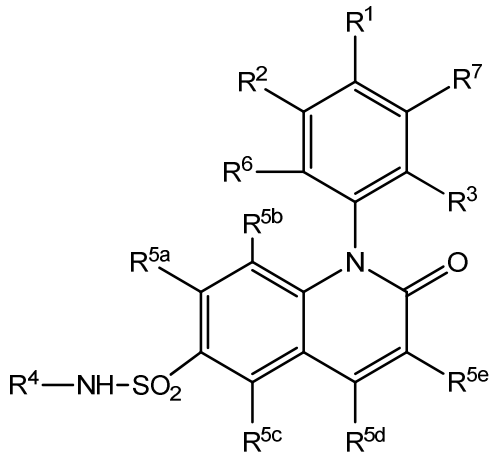
[0034] In example 16, the present disclosure provides methods of example 15 wherein the pain is selected from chronic pain, acute pain, neuropathic pain, pain associated with rheumatoid arthritis, pain associated with osteoarthritis, pain associated with cancer, cancer, or pain associated with diabetes.

[0035] In example 17, the present disclosure provides methods of example 15 wherein the cough is selected from post viral cough, viral cough, or acute viral cough. See Dib-Hajj. et. al., "The $Na_V1.7$ sodium channel: from molecule to man", *Nature Reviews Neuroscience* (2013), 14, 49-62.

CLAIMS

What is claimed is:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof,



(I);

wherein:

R^1 is selected from $-CH_2-CF_3$, $-CH_2-CH_2-CF_3$, $-CH_2-CH_2-CH_2-CF_3$, $-CH_2-CH(CH_3)-CF_3$, $-CH_2-CF_2-CF_3$, $-CH_2-C(CH_3)_2-CF_3$, $-C(CH_3)_2-CH_2-CF_3$, $-CF_2-CH_2-CF_3$, or $-CH_2-CH_2-CHF_2$;

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

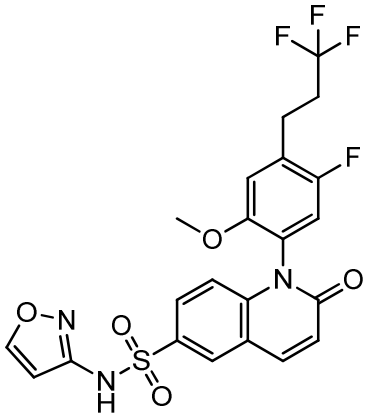
R^3 is C_{1-6}alk, C_{1-6}haloalk, $-O-C_{1-6}$alk, or –CN;

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

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

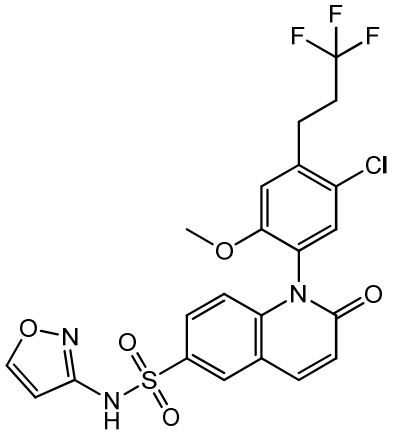
Each of R^{5a}; R^{5b};R^{5c}; $R^{5d;}$ and R^{5e} is independently hydrogen or halo.

2. The compound according to claim 1 having the formula:



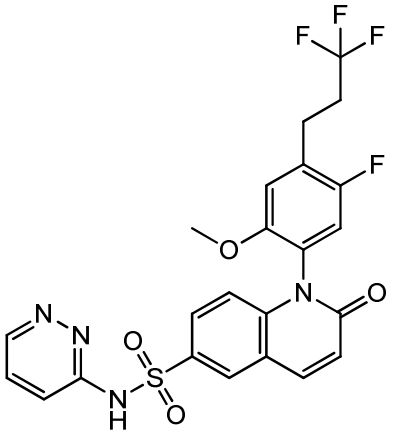
; or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 having the formula:



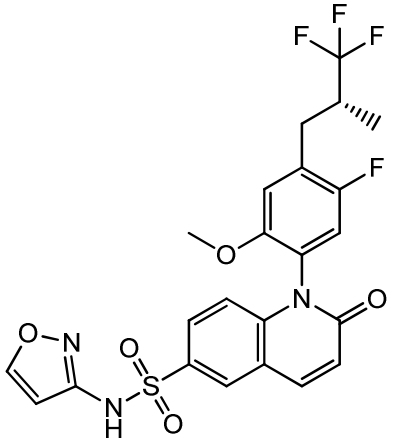
; or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 having the formula:



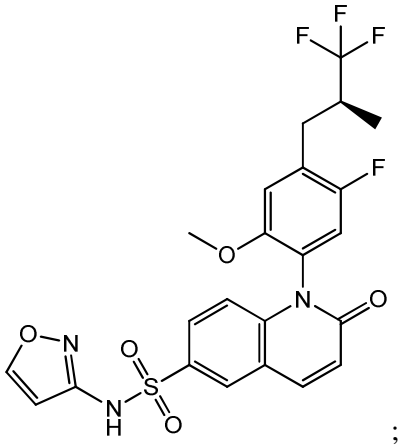
; or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 having the formula:



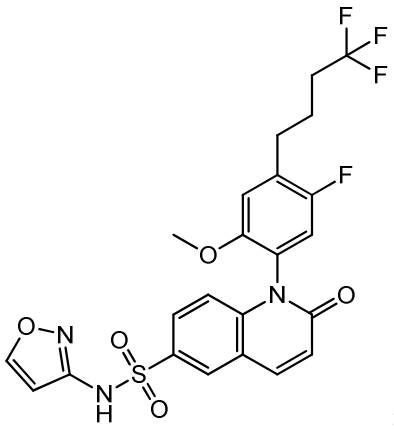
; or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1 having the formula:



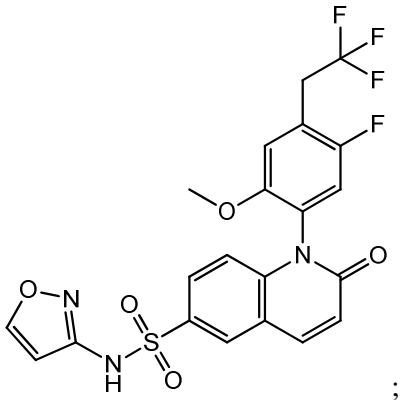
; or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1 having the formula:



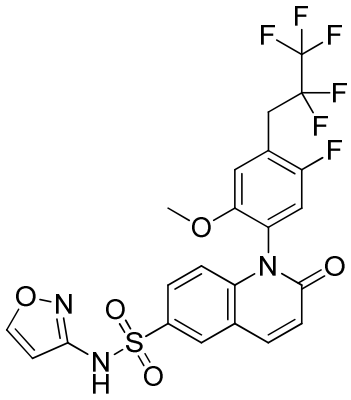
; or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1 having the formula:



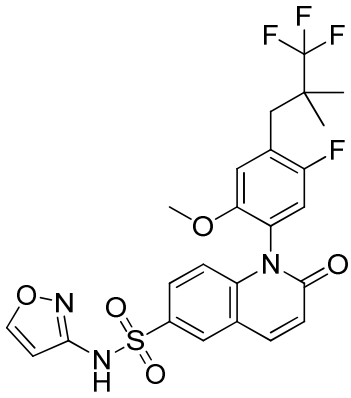
; or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1 having the formula:



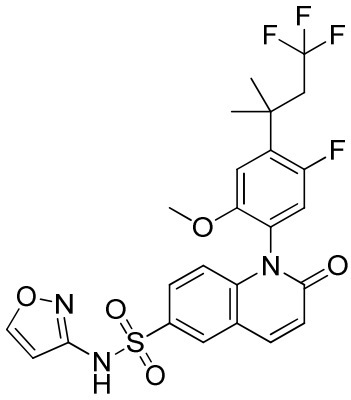
; or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1 having the formula:



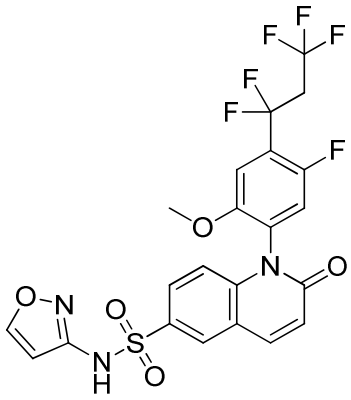
; or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1 having the formula:



; or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1 having the formula:



; or a pharmaceutically acceptable salt thereof.

13. The pharmaceutically acceptable salt of the compound according to any one of claims 2 to 12.

14. A pharmaceutical composition comprising an effective amount of the compound or the pharmaceutically acceptable salt thereof according to any one of claims 2 to 12, and a pharmaceutically acceptable excipient.

15. Use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating pain, cough, or itch.

16. The use according to claim 15; wherein the condition is pain, which is selected from chronic pain, acute pain, neuropathic pain, pain associated with rheumatoid arthritis, pain associated with osteoarthritis, or pain associated with cancer.

17. The use according to claim 15; wherein the condition is cough, which is selected from post viral cough, viral cough, or acute viral cough.