

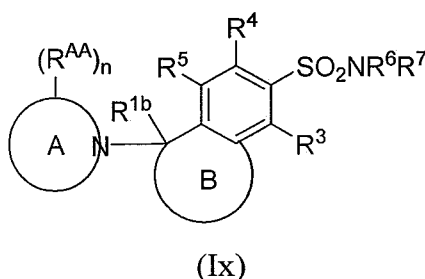
Clin. Genet. (2007);71:311-319). Conversely, gain of function mutations in NaV1.7 have been established in two human heritable pain conditions, primary erythromelalgia and familial rectal pain, (Yang, Y., et al., J. Med. Genet. (2004), 41(3):171-4). In addition, a single nucleotide polymorphism (R1150W) that has very subtle effects on the time- and voltage-dependence of channel gating has large effects on pain perception (Estacion, M., et al., 2009. Ann Neurol 66: 862-6; Reimann, F., et al., Proc Natl Acad Sci U S A (2010), 107: 5148-53). About 10% of the patients with a variety of pain conditions have the allele conferring greater sensitivity to pain and thus might be more likely to respond to block of NaV1.7. Because NaV1.7 is expressed in both sensory and sympathetic neurons, one might expect that enhanced pain perception would be accompanied by cardiovascular abnormalities such as hypertension, but no correlation has been reported. Thus, both the CIP mutations and SNP analysis suggest that human pain responses are more sensitive to changes in NaV1.7 currents than are perturbations of autonomic function.

Sodium channel blockers have been shown to be useful in the treatment of pain, (see, e.g., Wood, J.N., et al., J. Neurobiol. (2004), 61(1), 55-71. Genetic and functional studies have provided evidence to support that activity of NaV1.7 as a major contributor to pain signalling in mammals. (See Hajj, et al. Nature Reviews Neuroscience; 2013, vol 14, 49-62; and Lee, et al. Cell; 2014, vol 157; 1-12). Presently, there are a limited number of effective sodium channel blockers for the treatment of pain with a minimum of adverse side effects which are currently in the clinic. Thus there remains a need for selective voltage-gated sodium channel modulators (e.g., modulators of NaV1.7) that can provide a greater therapeutic index for treatment.

SUMMARY

The present invention provides novel compounds having sodium channel blocking activity that are useful for the treatment of pain.

In one aspect, the present invention refers to a compound of formula (Ix):



or a pharmaceutically acceptable salt thereof; wherein,

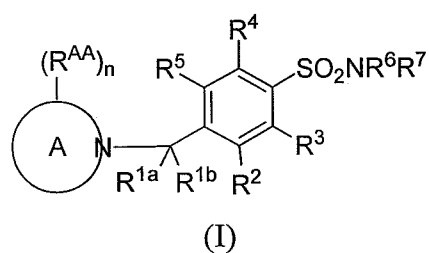
each R^{AA} is independently selected from the group consisting of F, Cl, Br, I, -CN, -C(=O)OR^{A1}, -SO₂R^{A1}, -OR^{A1}, -(X^{RA})-(3-15 membered carbocyclyl), -(X^{RA})-(6-12 membered aryl), -(X^{RA})-(5-12 membered heteroaryl), and -R^{A2}, wherein said 3-15 membered carbocyclyl, 6-12 membered aryl, and 5-12 membered heteroaryl of R^{AA} is optionally substituted with from 1 to

5 substituents R^b independently selected from the group consisting of F, Cl, Br, I, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{1-4} (halo)alkoxy, and $-C(O)N(R^c)_2$; R^{A1} is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl and benzyl; R^{A2} is selected from the group consisting of C_{1-8} alkyl that is optionally substituted with one or more substituents selected from oxo ($=O$), fluoro, hydroxy, amino, C_{1-4} alkylamino and di(C_{1-4} alkyl)amino; X^{RA} is selected from the group consisting of absent, $-C(=O)-$, and C_{1-4} alkylene; wherein any C_{1-4} alkylene, of X^{RA} is optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and phenyl that is optionally substituted with 1 to 5 substituents selected from, F, Cl, Br, I, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkoxy, C_{1-4} alkylamino and C_{1-4} dialkylamino; ring "A" is a 5-12 membered heteroaryl, or a 3-15 membered heterocyclyl; Ring B is a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl, which 5, 6, or 7 membered carbocyclyl and 5, 6, or 7 membered heterocyclyl is optionally substituted with one or more groups independently selected from C_{1-4} alkyl, halo, and halo C_{1-4} alkyl; R^{1b} is H or C_{1-4} alkyl; R^3 , R^4 , and R^5 are each independently selected from the group consisting of H, F, Cl, Br, I, $-CN$, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy; R^6 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, and aryl(C_{1-4} alkyl); and R^7 is selected from the group consisting of C_{1-8} alkyl, 3-15 membered heterocyclyl, 5-12 membered heteroaryl, $-C(O)N(R^c)_2$ and $-C(=NCN)N(R^c)_2$; or R^6 and R^7 , together with the nitrogen to which they are attached, form a 3-15 membered heterocyclyl or 5-12 membered heteroaryl; wherein any C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aralkyl, 3-15 membered heterocyclyl, and 5-12 membered heteroaryl is optionally substituted with one or more groups R^d that are independently selected from the group consisting of F, Cl, Br, I, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkoxy, C_{1-4} alkylamino and C_{1-4} dialkylamino; each R^c is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl and benzyl; and n is 0, 1, 2, 3, 4, 5, or 6.

In another aspect, the present invention refers to a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In yet another aspect, the present invention refers to a compound as described in the present invention or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a disease or disorder selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

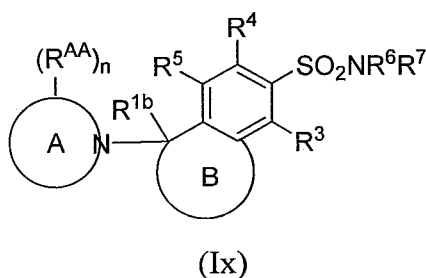
In a first example (Example 1; abbreviated as “E1”) the disclosure provides for a compound of formula (I):



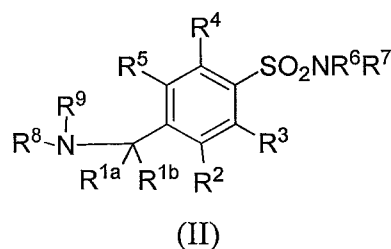
- 5 or a salt thereof; wherein,
- each R^{AA} is independently selected from the group consisting of F, Cl, Br, I, -CN, -C(=O)OR^{A1}, -SO₂R^{A1}, -OR^{A1}, -(X^{RA})-(3-15 membered carbocyclyl), -(X^{RA})-(6-12 membered aryl), -(X^{RA})-(5-12 membered heteroaryl), and -R^{A2}, wherein said 3-15 membered carbocyclyl, 6-12 membered aryl, and 5-12 membered heteroaryl of R^{AA} is optionally substituted with from 1 to

5 substituents R^b independently selected from the group consisting of F, Cl, Br, I, C_{1-4} alkyl, C_{1-4} haloalkyl, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, and C_{1-4} (halo)alkoxy; R^{A1} is selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, phenyl and benzyl; R^{A2} is selected from the group consisting of C_{1-8} alkyl that is optionally substituted with one or more substituents selected from oxo (=O), fluoro, hydroxy, amino, C_{1-4} alkylamino and di(C_{1-4} alkyl)amino; X^{RA} is selected from the group consisting of absent, $-C(=O)-$, and C_{1-4} alkylene; wherein any C_{1-4} alkylene, of X^{RA} is optionally substituted with 1 to 3 substituents selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and phenyl that is optionally substituted with 1 to 5 substituents selected from, F, Cl, Br, I, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkoxy, C_{1-4} alkylamino and C_{1-4} dialkylamino; ring "A" is a 5-12 membered heteroaryl, or a 3-15 membered heterocyclyl; R^{1a} is H or C_{1-4} alkyl; R^{1b} is H or C_{1-4} alkyl; R^2 is selected from the group consisting of H, F, Cl, Br, I, $-CN$, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy; R^3 , R^4 , and R^5 are each independently selected from the group consisting of H, F, Cl, Br, I, $-CN$, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy; R^6 is selected from the group consisting of H, C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, and aryl(C_{1-4} alkyl); and R^7 is selected from the group consisting of C_{1-8} alkyl, 3-15 membered heterocyclyl, 5-12 membered heteroaryl, $-C(O)N(R^c)_2$ and $-C(=NCN)N(R^c)_2$; or R^6 and R^7 , together with the nitrogen to which they are attached, form a 3-15 membered heterocyclyl or 5-12 membered heteroaryl; wherein any C_{1-8} alkyl, C_{3-8} cycloalkyl, aryl, aralkyl, 3-15 membered heterocyclyl, and 5-12 membered heteroaryl is optionally substituted with one or more groups R^d that are independently selected from the group consisting of F, Cl, Br, I, $-NH_2$, $-OH$, $-CN$, $-NO_2$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkoxy, C_{1-4} alkylamino and C_{1-4} dialkylamino; each R^c is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, phenyl and benzyl; and n is 0, 1, 2, 3, 4, 5, or 6.

In a second example (Example 2; abbreviated as "E2") the disclosure provides for a compound of formula IX:



In a third example (Example 3; abbreviated as “E3”) the disclosure provides for a compound of formula (II):



5 or a salt thereof; wherein,

R^{1a} is H or C₁₋₄ alkyl; or **R^{1a}** and **R²** taken together with the atoms to which they are attached form a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl, which 5, 6, or 7 membered carbocyclyl and 5, 6, or 7 membered heterocyclyl is optionally substituted with one or more groups independently selected from C₁₋₄ alkyl, halo, and haloC₁₋₄ alkyl;

10 **R^{1b}** is H or C₁₋₄ alkyl;

R² is selected from the group consisting of H, F, Cl, Br, I, -CN, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₁₋₈ haloalkyl and C₁₋₈ alkoxy; or **R²** and **R^{1a}** taken together with the atoms to which they are attached form a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl, which 5, 6, or 7 membered carbocyclyl and 5, 6, or 7 membered heterocyclyl is optionally substituted with one or more groups independently selected from C₁₋₄ alkyl, halo, and haloC₁₋₄ alkyl;

15 **R³**, **R⁴**, and **R⁵** are each independently selected from the group consisting of H, F, Cl, Br, I, -CN, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₁₋₈ haloalkyl and C₁₋₈ alkoxy;

R⁶ is selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, and aryl(C₁₋₄ alkyl); and **R⁷** is selected from the group consisting of C₁₋₈ alkyl, 3-15 membered heterocyclyl, 5-12

20 membered heteroaryl, -C(O)N(R^c)₂ and -C(=NCN)N(R^c)₂; or **R⁶** and **R⁷**, together with the nitrogen to which they are attached, form a 3-15 membered heterocyclyl or 5-12 membered heteroaryl;

wherein any C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aralkyl, 3-15 membered heterocyclyl, and 5-12 membered heteroaryl is optionally substituted with one or more groups **R^d** that are independently selected from the group consisting of F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄(halo)alkoxy, C₁₋₄ alkylamino and C₁₋₄ dialkylamino; each **R^c** is independently

25 selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, phenyl and benzyl;

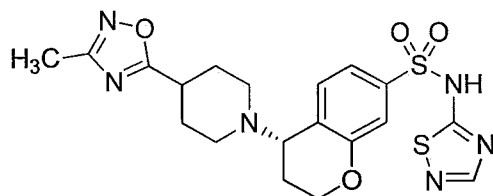
R⁸ is selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, and aryl(C₁₋₄ alkyl); and

R⁹ is selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, and aryl(C₁₋₄ alkyl),

30 wherein any C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, and aryl(C₁₋₄ alkyl) is optionally substituted with one or more halo.

Further examples of the compounds of the disclosure are described below.

and



and salts thereof.

In another example the present disclosure provides for a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another example the present disclosure provides for a method of treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof. In another example of the present disclosure said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof. In another example of the present disclosure said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

In another example the present disclosure provides for a method of treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In another example the present disclosure provides for a method of decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with a compound of formula I, or a pharmaceutically acceptable salt thereof.

5 In another example the present disclosure provides for a method of treating pruritus in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

10 In another example the present disclosure provides for a method of treating cancer in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount a compound of formula I, or a pharmaceutically acceptable salt thereof.

15 In another example the present disclosure provides for a method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof. In another example of the present disclosure the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental
20 pain, peripheral nerve injury or a combination thereof. In another example the present disclosure the pain is associated with a disease or condition selected from the group consisting of HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosaroidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia
25 syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia,
30 neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

In another example the present disclosure provides for a method for the treatment or prophylaxis of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease,

or a combinations thereof, in an animal which method comprises administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

In another example the present disclosure provides for a compound of formula I, or a pharmaceutically acceptable salt thereof for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases,
5 respiratory diseases, and psychiatric diseases, or a combination thereof.

In another example the present disclosure provides for the use of a compound of formula I, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular
10 diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

In another example the present disclosure provides for the disclosure as described herein.

DETAILED DESCRIPTION OF THE INVENTION

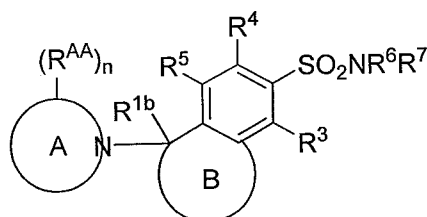
Definitions

As used herein, the term "alkyl", by itself or as part of another substituent, means, unless
15 otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (i.e., C₁₋₈ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The term "alkenyl" refers to an unsaturated alkyl radical having one or more double bonds. Similarly, the term "alkynyl" refers to an unsaturated alkyl radical having one or
20 more triple bonds. Examples of such unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers.

The term "heteroalkyl," by itself or in combination with another term, means, unless
25 otherwise stated, a stable straight or branched chain hydrocarbon radical, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms can optionally be oxidized and the nitrogen heteroatom can optionally be quaternized. The heteroatom(s) O, N and S can be placed at any interior position of the heteroalkyl group. The heteroatom Si can be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the
30 molecule. A "heteroalkyl" can contain up to three units of unsaturation, and also include mono- and poly-halogenated variants, or combinations thereof. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-CF₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃,

WE CLAIM:

1. A compound of formula (Ix):



(Ix)

or a pharmaceutically acceptable salt thereof; wherein,

each R^{AA} is independently selected from the group consisting of F, Cl, Br, I, -CN,

-C(=O)OR^{A1}, -SO₂R^{A1}, -OR^{A1}, -(X^{RA})-(3-15 membered carbocyclyl), -(X^{RA})-(6-12 membered aryl), -(X^{RA})-(5-12 membered heteroaryl), and -R^{A2}, wherein said 3-15 membered carbocyclyl,

6-12 membered aryl, and 5-12 membered heteroaryl of R^{AA} is optionally substituted with from 1 to

5 substituents R^b independently selected from the group consisting of F, Cl, Br, I, C₁₋₄ alkyl, C₁₋₄

haloalkyl, amino, C₁₋₄ alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄(halo)alkoxy, and -C(O)N(R^c)₂; R^{A1} is

selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₁₋₈ haloalkyl, C₃₋₈

cycloalkyl, phenyl and benzyl; R^{A2} is selected from the group consisting of C₁₋₈ alkyl that is

optionally substituted with one or more substituents selected from oxo (=O), fluoro, hydroxy,

amino, C₁₋₄ alkylamino and di(C₁₋₄alkyl)amino; X^{RA} is selected from the group consisting of

absent, -C(=O)-, and C₁₋₄ alkylene; wherein any C₁₋₄ alkylene, of X^{RA} is optionally substituted with

1 to 3 substituents selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ haloalkyl, and phenyl that is

optionally substituted with 1 to 5 substituents selected from, F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂,

C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄(halo)alkoxy, C₁₋₄ alkylamino and C₁₋₄ dialkylamino;

ring "A" is a 5-12 membered heteroaryl, or a 3-15 membered heterocyclyl;

Ring B is a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl, which 5, 6, or 7

membered carbocyclyl and 5, 6, or 7 membered heterocyclyl is optionally substituted with one or

more groups independently selected from C₁₋₄ alkyl, halo, and haloC₁₋₄ alkyl;

R^{1b} is H or C₁₋₄ alkyl;

R³, R⁴, and R⁵ are each independently selected from the group consisting of H, F, Cl, Br, I, -CN,

C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₁₋₈ haloalkyl and C₁₋₈ alkoxy;

R⁶ is selected from the group consisting of H, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, and aryl(C₁₋₄ alkyl);

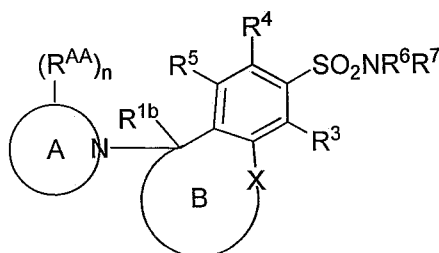
and R⁷ is selected from the group consisting of C₁₋₈ alkyl, 3-15 membered heterocyclyl, 5-12

membered heteroaryl, -C(O)N(R^c)₂ and -C(=NCN)N(R^c)₂; or R⁶ and R⁷, together with the nitrogen

to which they are attached, form a 3-15 membered heterocyclyl or 5-12 membered heteroaryl;

wherein any C₁₋₈ alkyl, C₃₋₈ cycloalkyl, aryl, aralkyl, 3-15 membered heterocyclyl, and 5-12 membered heteroaryl is optionally substituted with one or more groups **R^d** that are independently selected from the group consisting of F, Cl, Br, I, -NH₂, -OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄(halo)alkoxy, C₁₋₄ alkylamino and C₁₋₄ dialkylamino; each **R^c** is independently
 5 selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, phenyl and benzyl; and **n** is 0, 1, 2, 3, 4, 5, or 6.

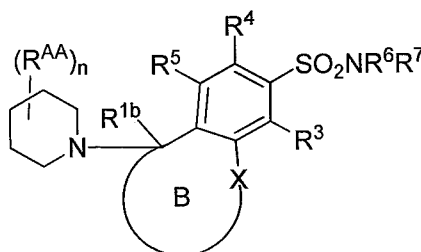
2. The compound of claim 1, which is a compound of formula Ib:



(Ib)

wherein the ring B, including **X**, is a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl; or a pharmaceutically acceptable salt thereof.

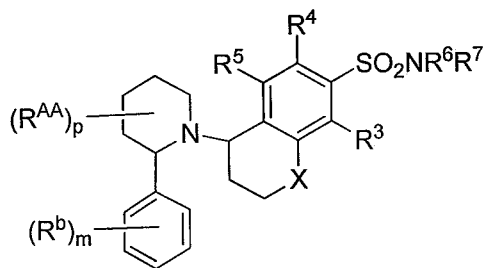
3. The compound of claim 2, which is a compound of formula Ic:



(Ic)

or a pharmaceutically acceptable salt thereof.

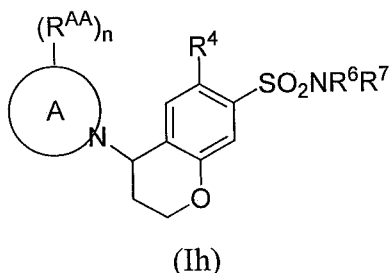
4. The compound of claim 2, which is a compound of formula Id:



(Id)

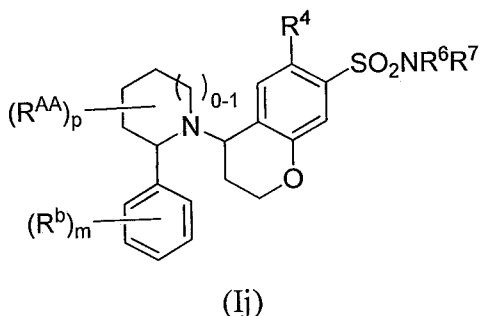
wherein **X** is O, S, SO, or SO₂; **m** is 0, 1, 2, 3, 4 or 5; and **p** is 0, 1, 2, 3, 4, or 5; or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4, which is a compound of formula Ih:



or a pharmaceutically acceptable salt thereof.

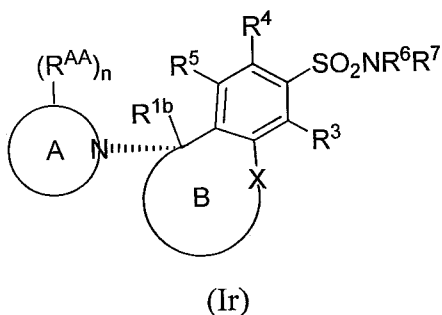
6. The compound of any one of claims 1-4, which is a compound of formula Ij:



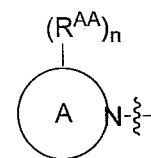
wherein **m** is 0, 1, 2, 3, 4 or 5; and **p** is 0, 1, 2, 3, 4, or 5; or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6, wherein **R**⁷ is a 5-12 membered heteroaryl; or a pharmaceutically acceptable salt thereof.

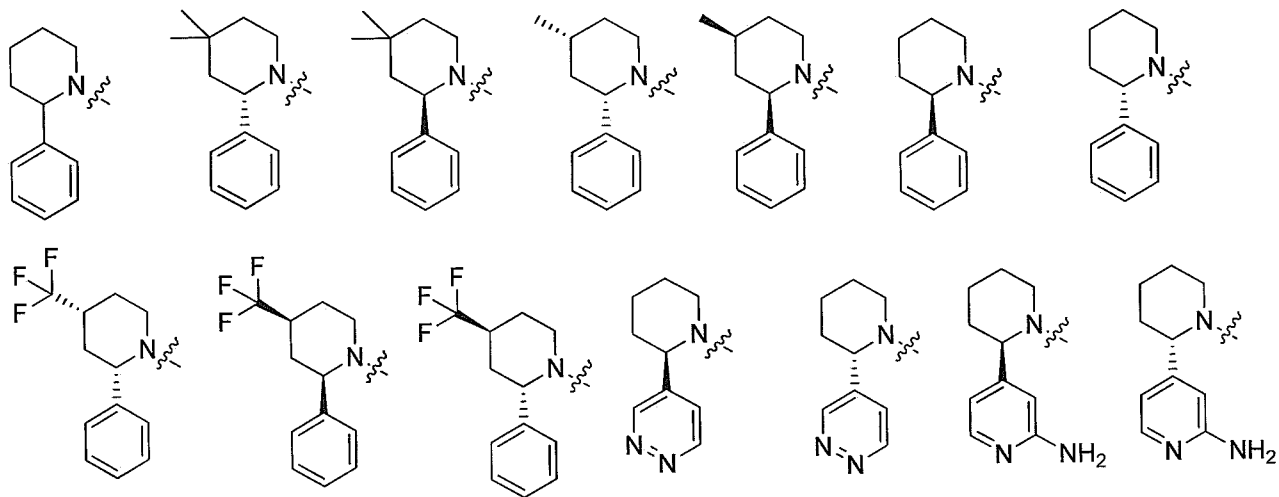
8. The compound of any one of claims 1-4, which is a compound of formula Ir:



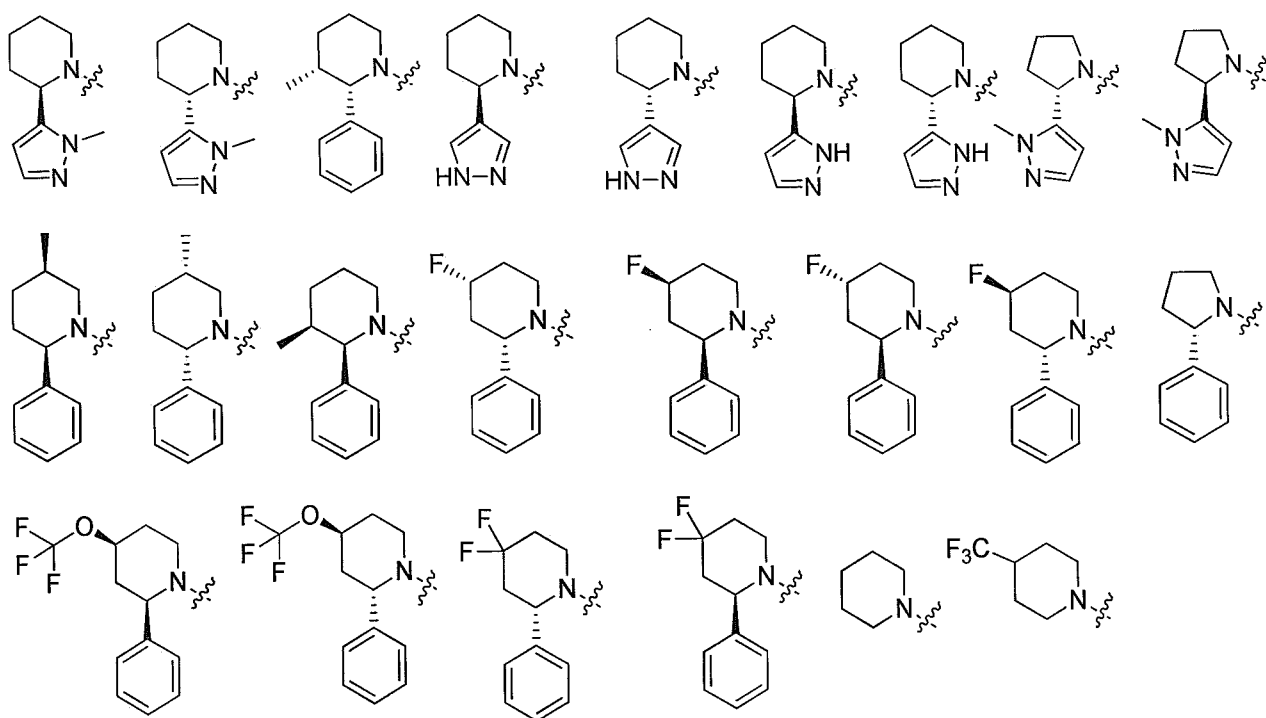
wherein the ring B, including **X**, is a 5, 6, or 7 membered carbocyclyl or a 5, 6, or 7 membered heterocyclyl; or a pharmaceutically acceptable salt thereof.



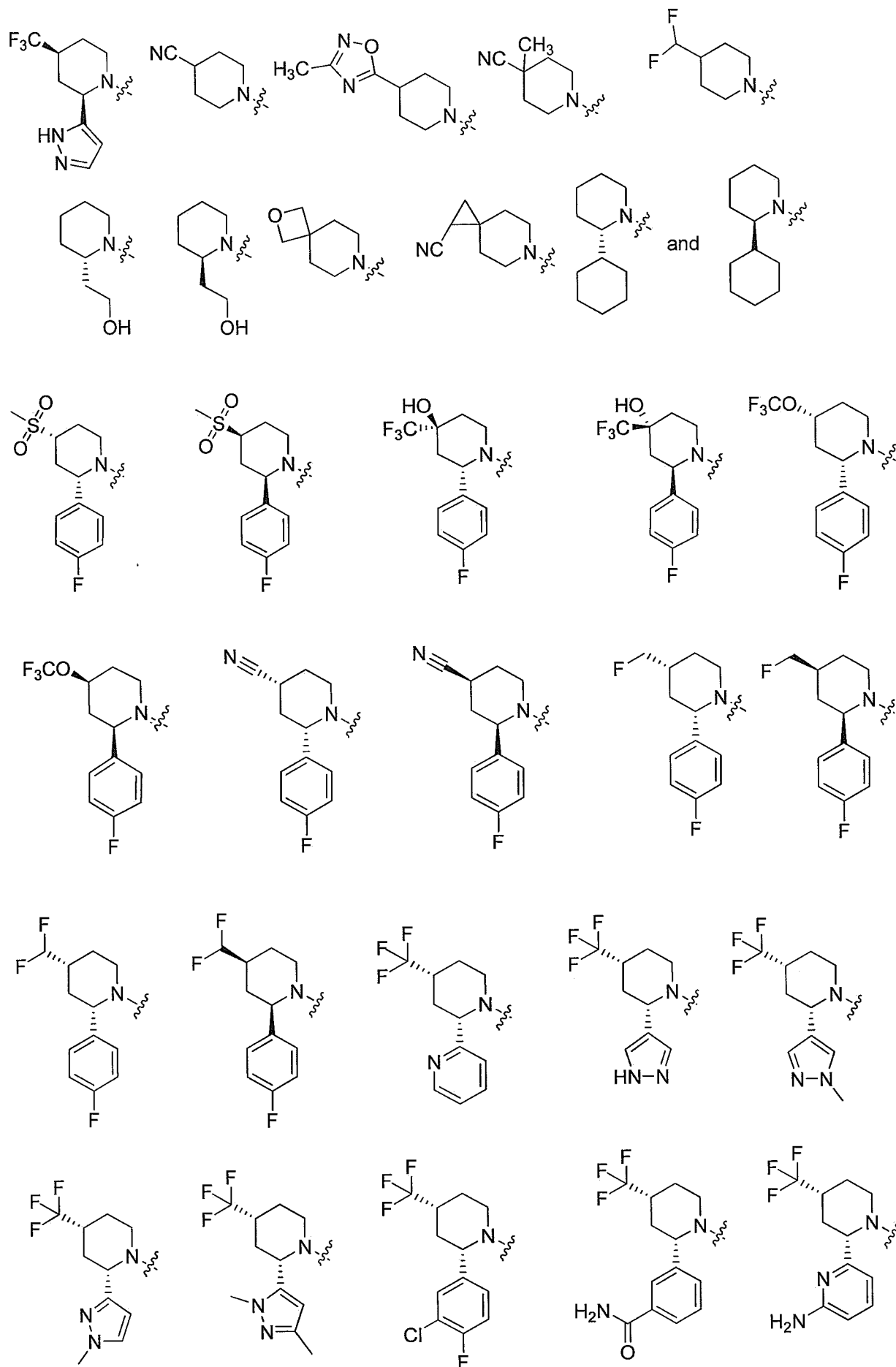
9. The compound of any one of claims 1-8, wherein the group  is selected from the group consisting of:



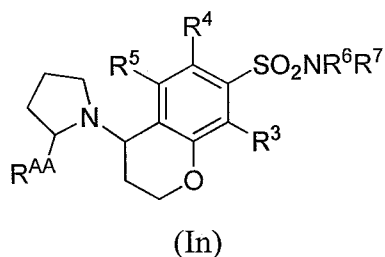
5





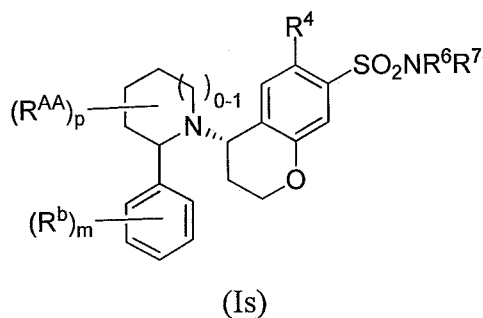


11. The compound of claim 1, which is a compound of formula In:



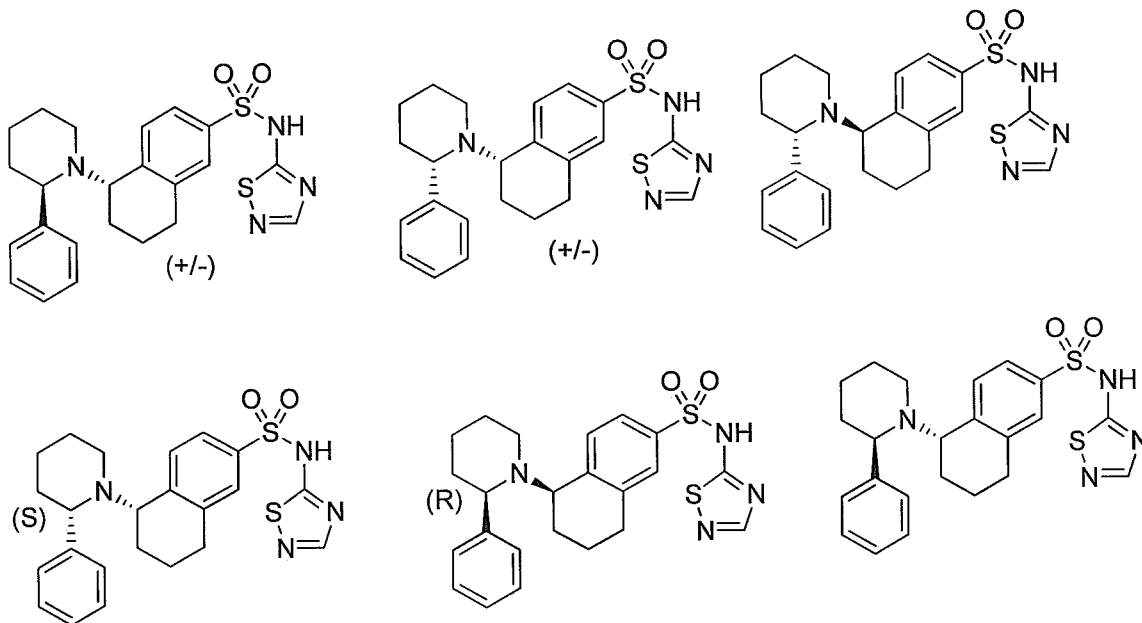
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, which is a compound of formula Is:

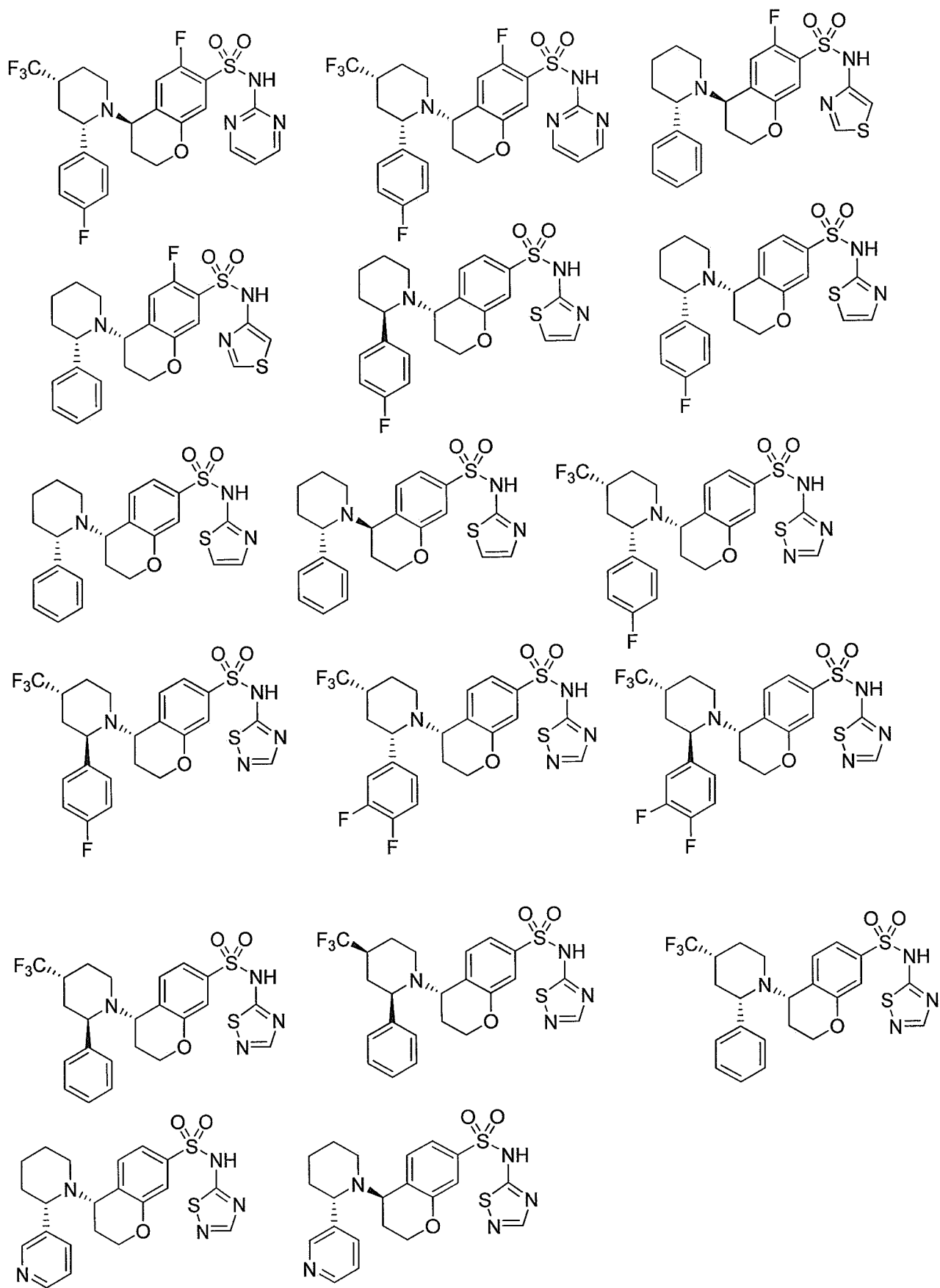


wherein **m** is 0, 1, 2, 3, 4 or 5; and **p** is 0, 1, 2, 3, 4, or 5; or a pharmaceutically acceptable salt thereof.

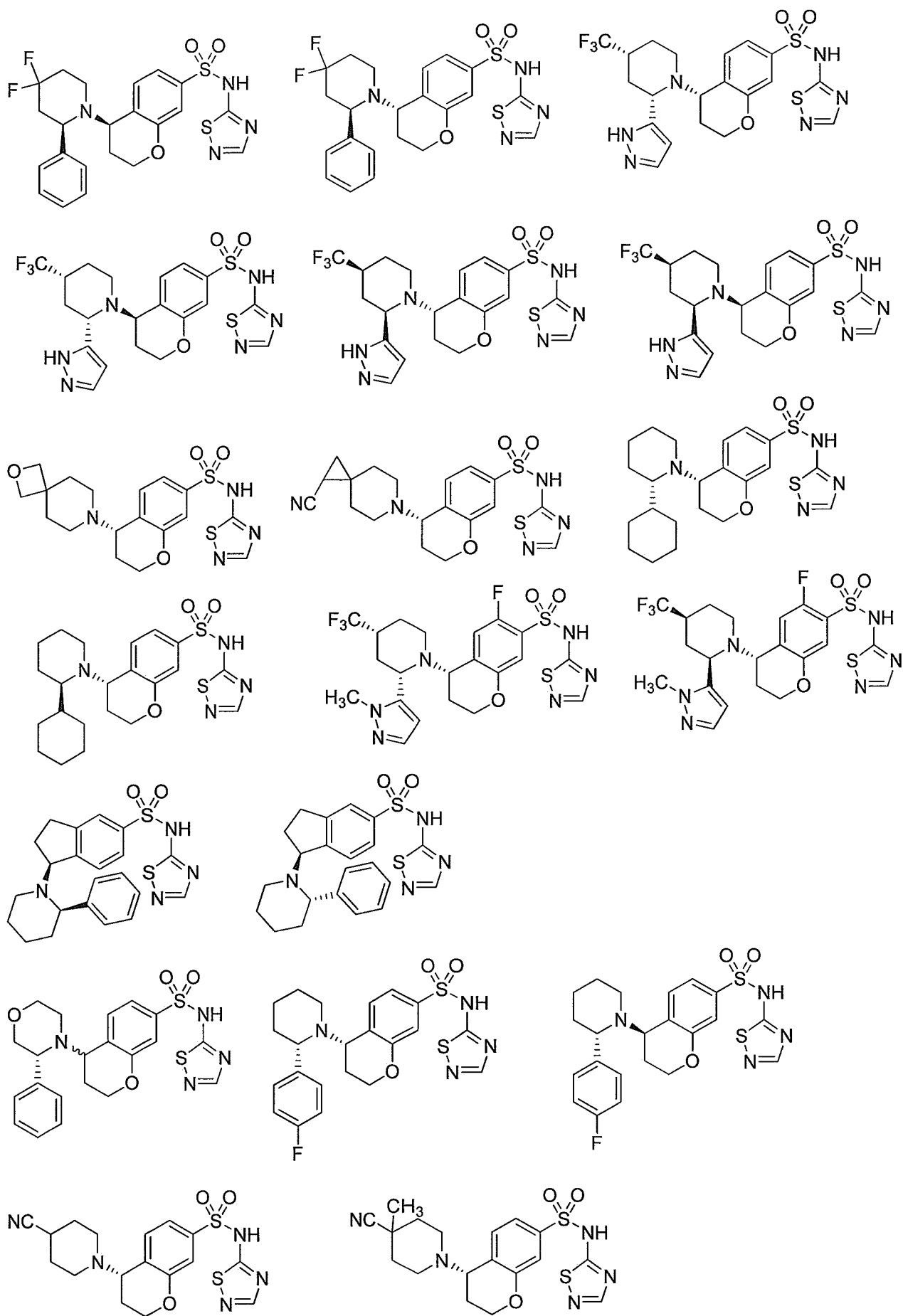
13. The compound of claim 2, which is selected from the group consisting of:

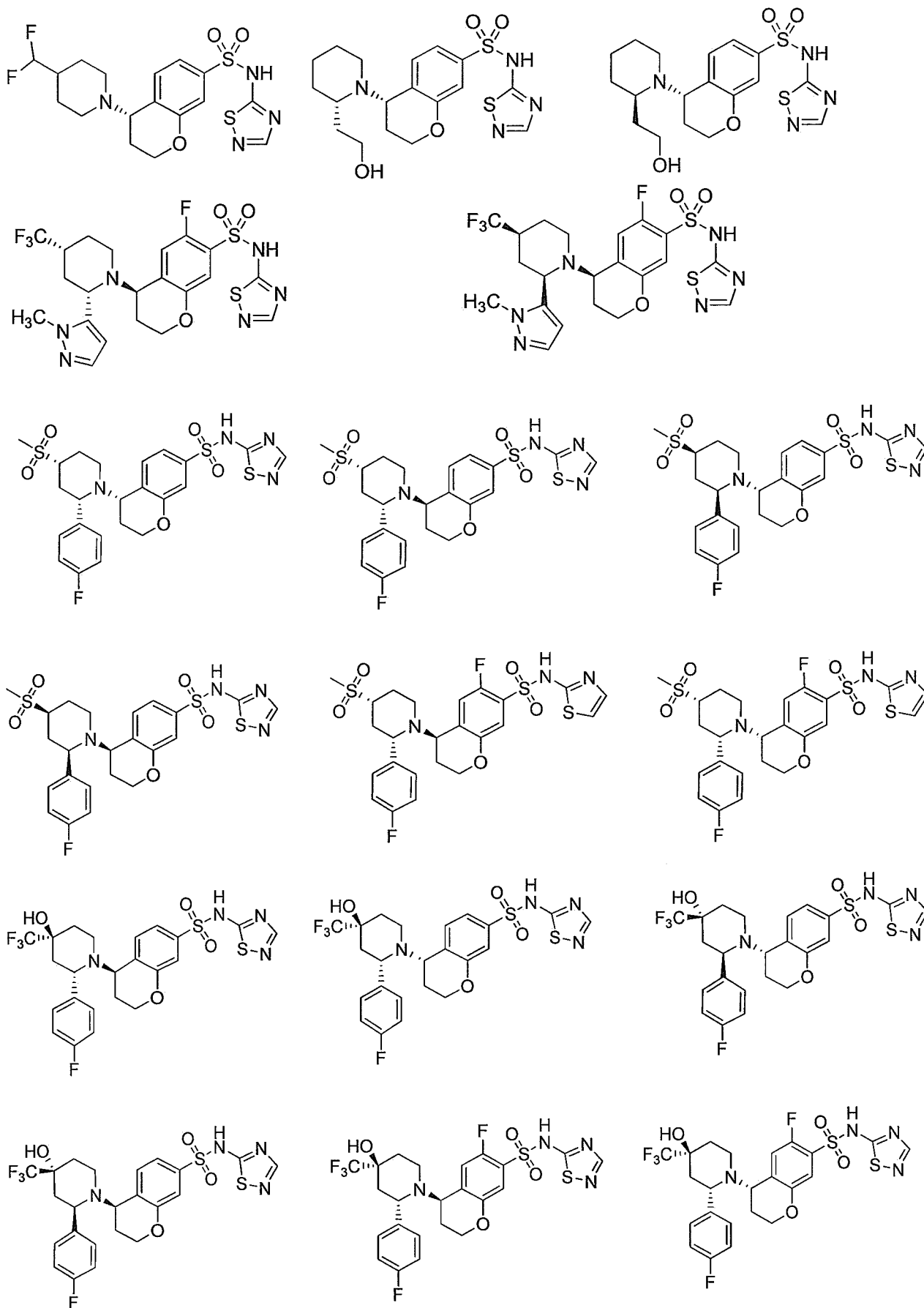


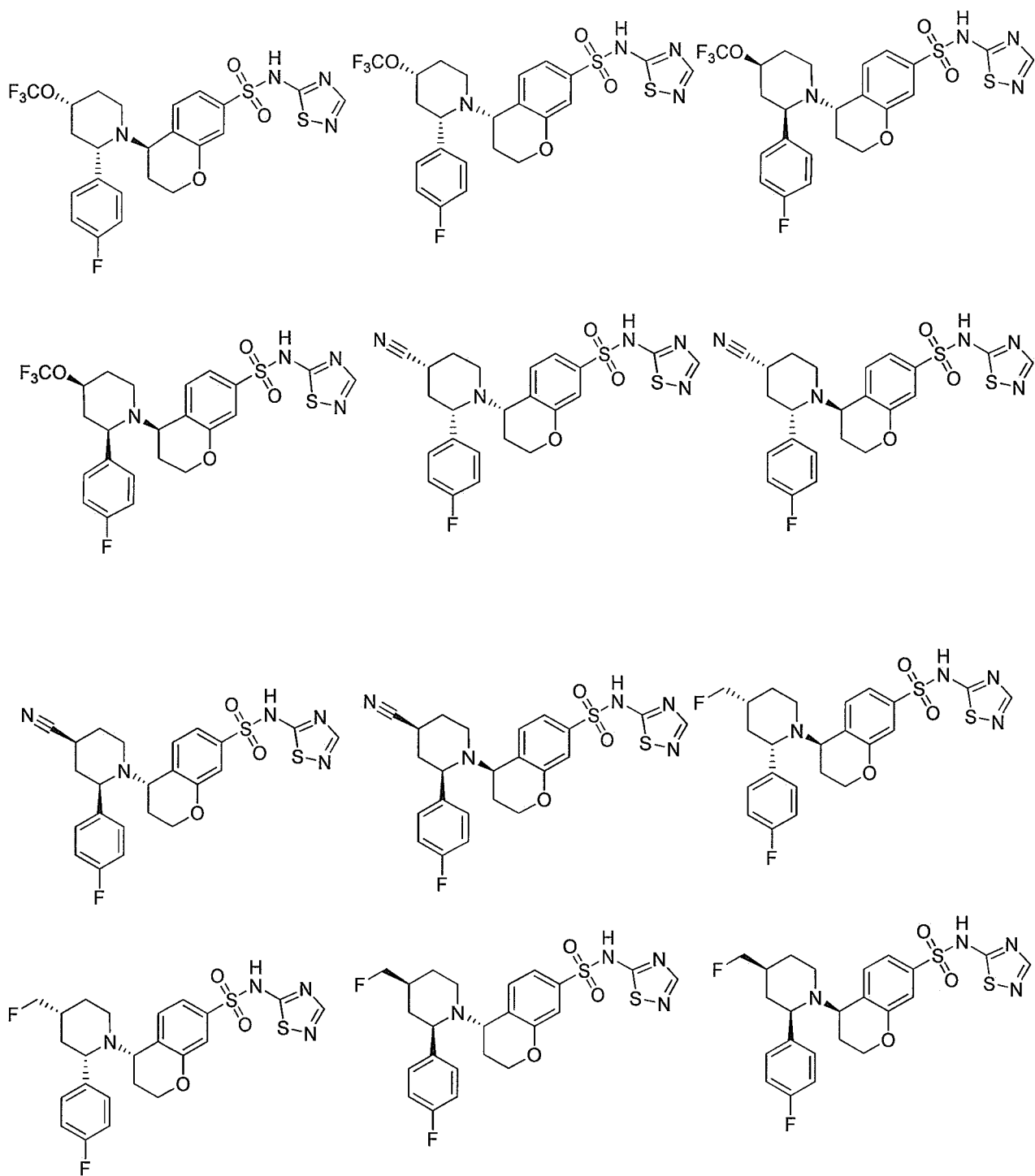


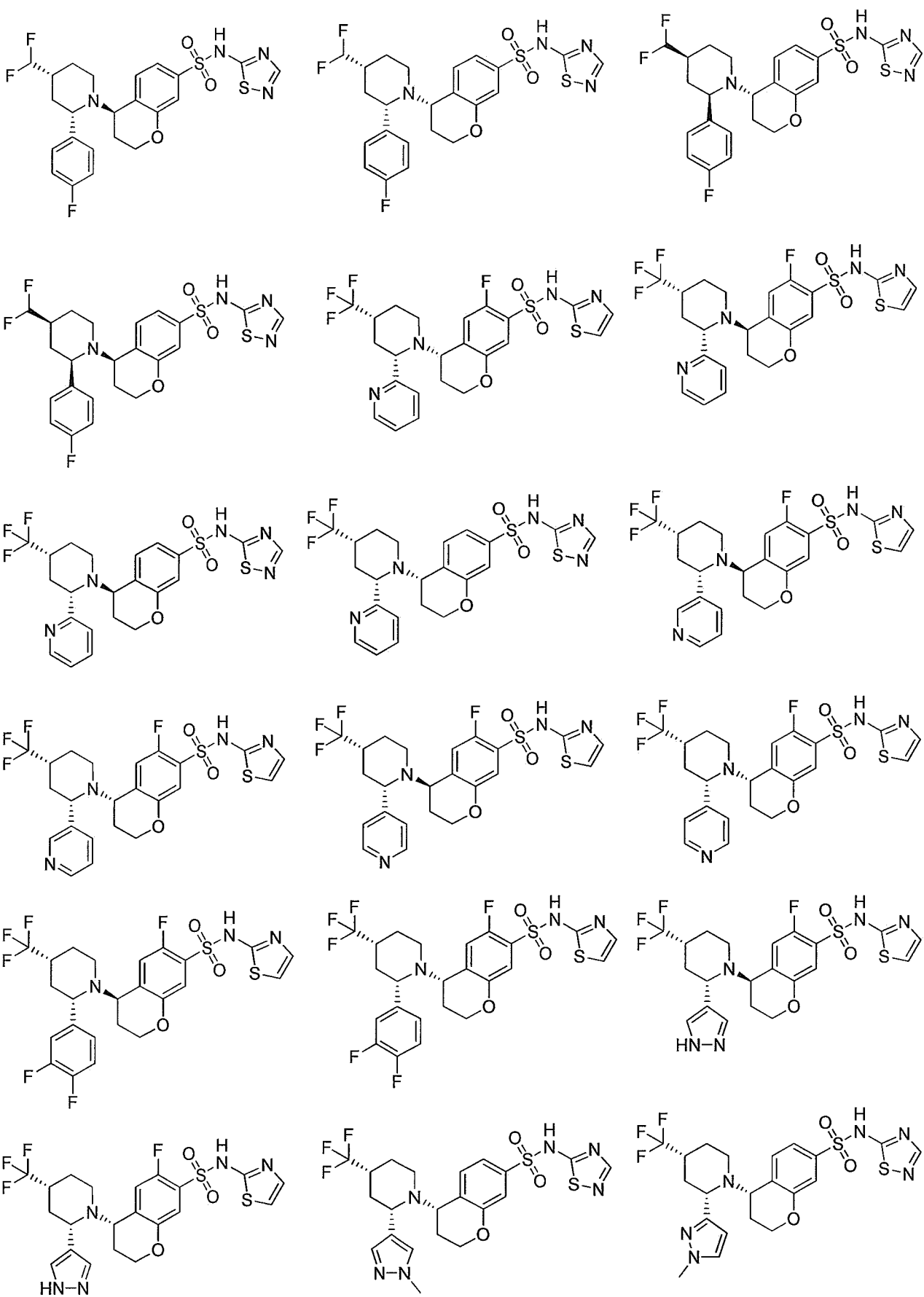


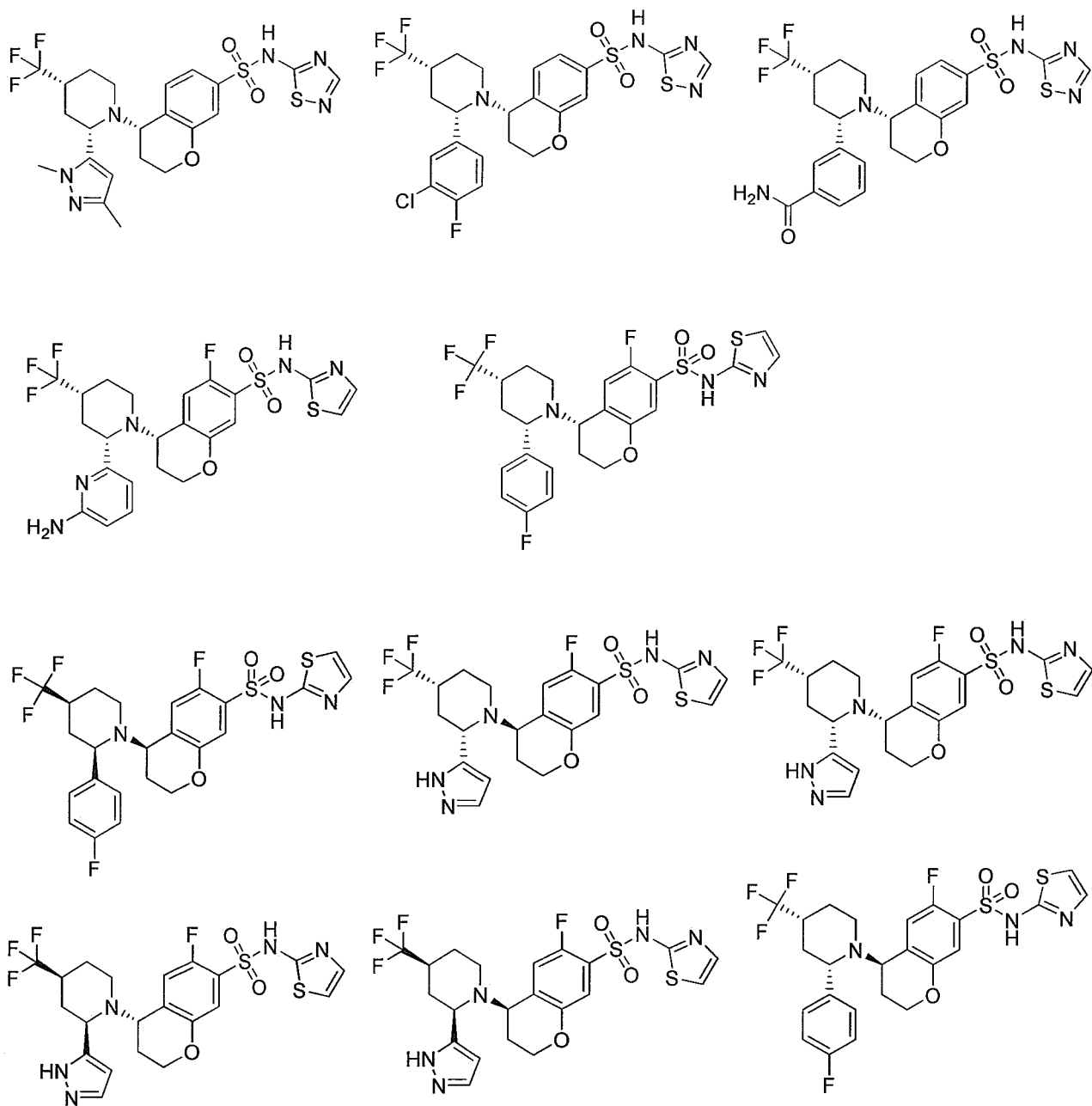


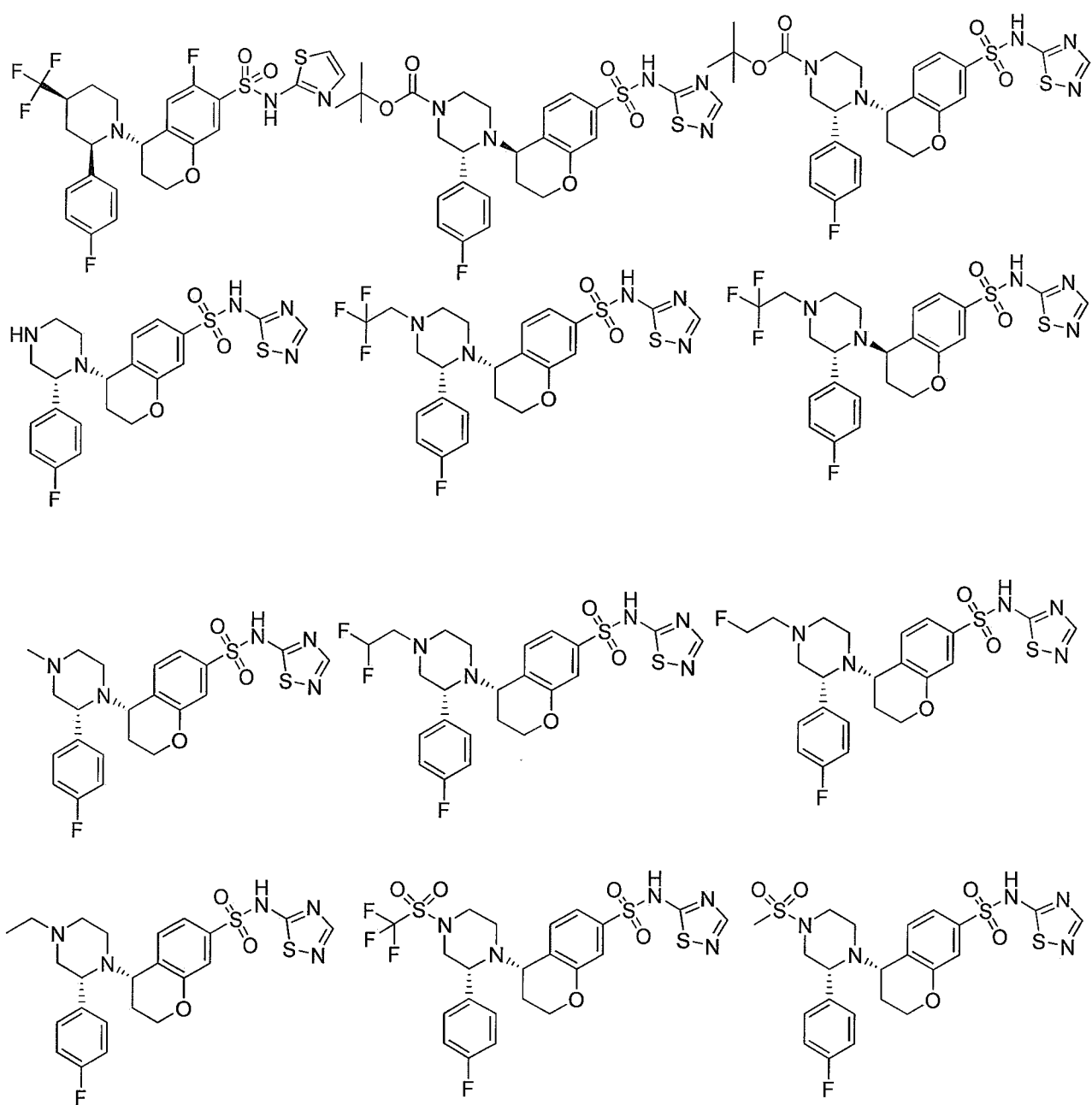


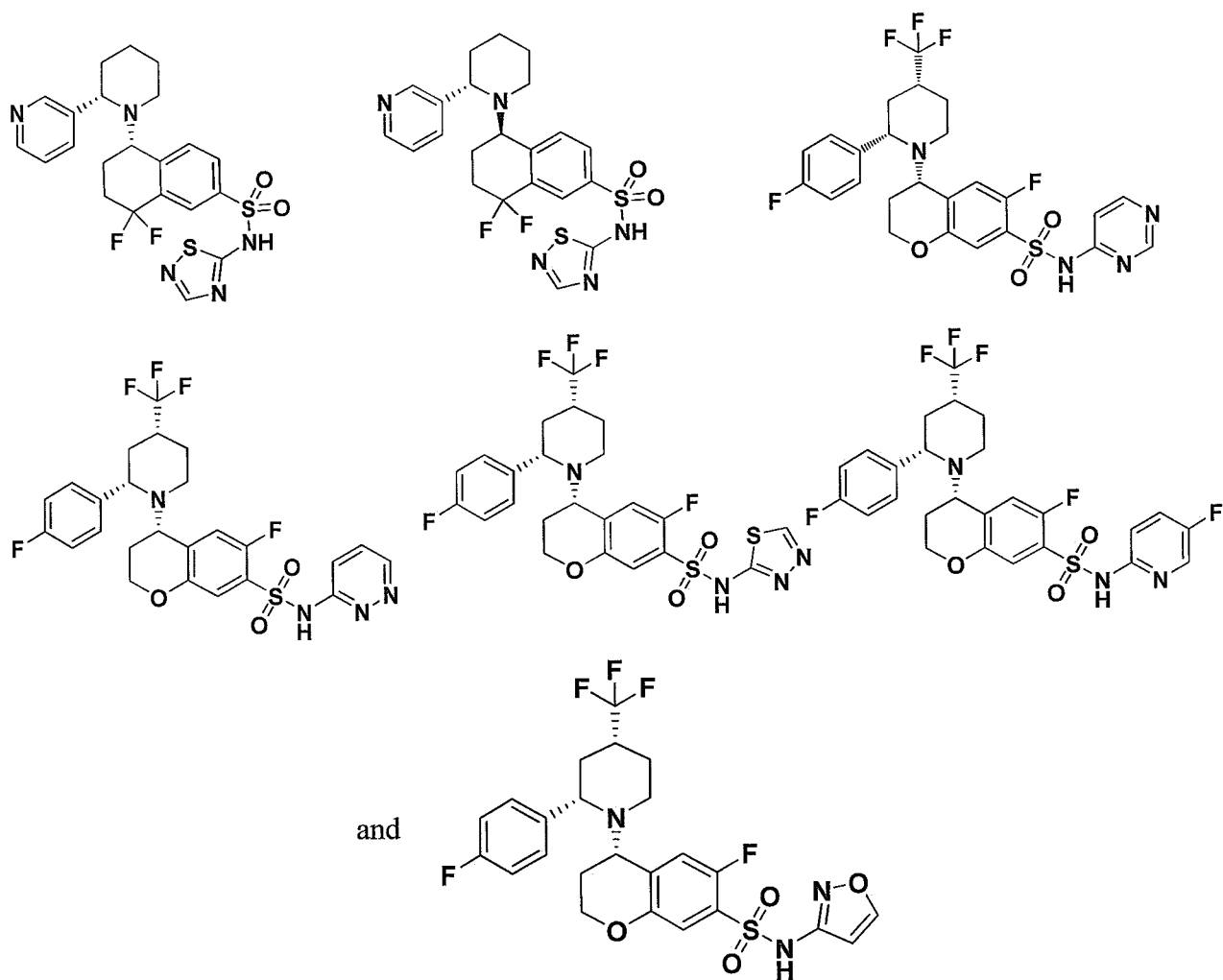












or a pharmaceutically acceptable salt thereof.

- 5 14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

- 10 15. A compound as described in any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a disease or disorder selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.