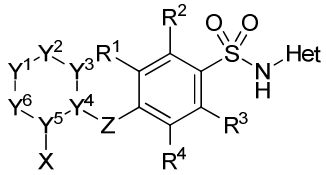
cardiovascular abnormalities such as hypertension, but no correlation has been reported. Thus, both the CIP mutations and SNP analysis suggest that human pain responses are more sensitive to changes in NaV1.7 currents than are perturbations of autonomic function.

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

In one example the present disclosure provides novel compounds having sodium channel blocking activity that are useful for the treatment of pain.

In one aspect, the present disclosure refers to a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein :

R^1, R^2, R^3, and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, hydroxy, C_1-C_6 alkoxy, nitro, and halo,wherein any C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, and phenyl; and Z is selected from $-N(R^5)-$, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

or

R^1, R^2, and R^3 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl; and R^4 and Z together with the benzene ring to which they are both attached form a 9- or 10-membered heterobicycle;

Het is 5- or 6-membered heteroaryl optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl;

X is selected from $-N(R^6)_2$ and $-N(R^7)_3{}^+ {}^-W$, and amine oxides thereof;

Y^1 is $-C(R^8)_2-$; and Y^2 is selected from $-(C(R^8)_2)_n-$, $-N(R^9)-$, $-O-$, $-C(R^8)_2-N(R^9)-$, $-N(R^9)-C(R^8)_2-$, $-C(R^8)_2-O-$, and $-O-C(R^8)_2-$;

or

Y^1 is selected from $-N(R^9)-$ and $-O-$; and Y^2 is $-(C(R^8)_2)_n-$;

n is selected from 0, 1, and 2;

Y^3 and Y^6 are each $-C(R^8)_2-$;

Y^4 and Y^5 are each $-C(R^8)-$;

R^5 is selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl, wherein any C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, $-NR^aR^b$, $-C(=O)NR^aR^b$, R^c, and phenyl, wherein any C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkanoyl is optionally substituted with C_3-C_6 cycloalkyl; or two R^6 groups together with the nitrogen to which they are both attached form a 4- to 10-membered heterocycle that is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, which C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from hydroxy and halo;

each R^7 is independently selected from C_1-C_6 alkyl; or two R^7 groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

each R^8 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, benzyl, 5-15 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, hydroxy, halo, cyano, and $-L$-C_6-C_{12} aryl; wherein each C_3-C_6 cycloalkyl, -L-C_6-C_{12} aryl, benzyl, 5-15 membered heteroaryl, and C_1-C_6 alkoxy, is optionally substituted with one to three substituents R^x each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, $-S(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-S(O)_2(C_1$-C_6 alkyl), $-NH_2$ $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl or two R^8 that are on adjacent carbons taken together form a double bond; and R^9 is selected from hydrogen, C_1-C_6 alkyl and C_6-C_{12} aryl, which C_6-C_{12} aryl is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_3-C_6

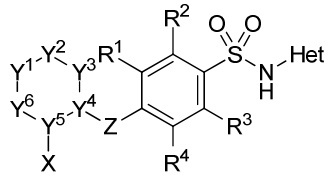
cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, and C_1-C_6 haloalkyl; or one R^8 or R^9 taken together with another R^8 or R^9 and the atoms to which they are attached form a 3-8 membered fused, bridged or spirocyclic ring, which 3-8 membered ring is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, halo, and C_1-C_6 haloalkyl; and L is selected from a bond, −O−, −S−, −S(O)−, and −S(O)$_2$−;

each R^a and R^b is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkanoyl;

each R^c is independently selected from 4-7 membered heterocycle that is optionally substituted with one or more groups independently selected from halo, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

W^- is a counterion.

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



I

or a pharmaceutically acceptable salt thereof, wherein :

R^1, R^2, R^3, and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, hydroxy, C_1-C_6 alkoxy, nitro, and halo,wherein any C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, and phenyl; and Z is selected from −N(R^5)−, −O−, −S−, −S(O)−, and −S(O)$_2$−;

or

R^1, R^2, and R^3 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl; and R^4 and Z together with the benzene ring to which they are both attached form a 9- or 10-membered heterobicycle;

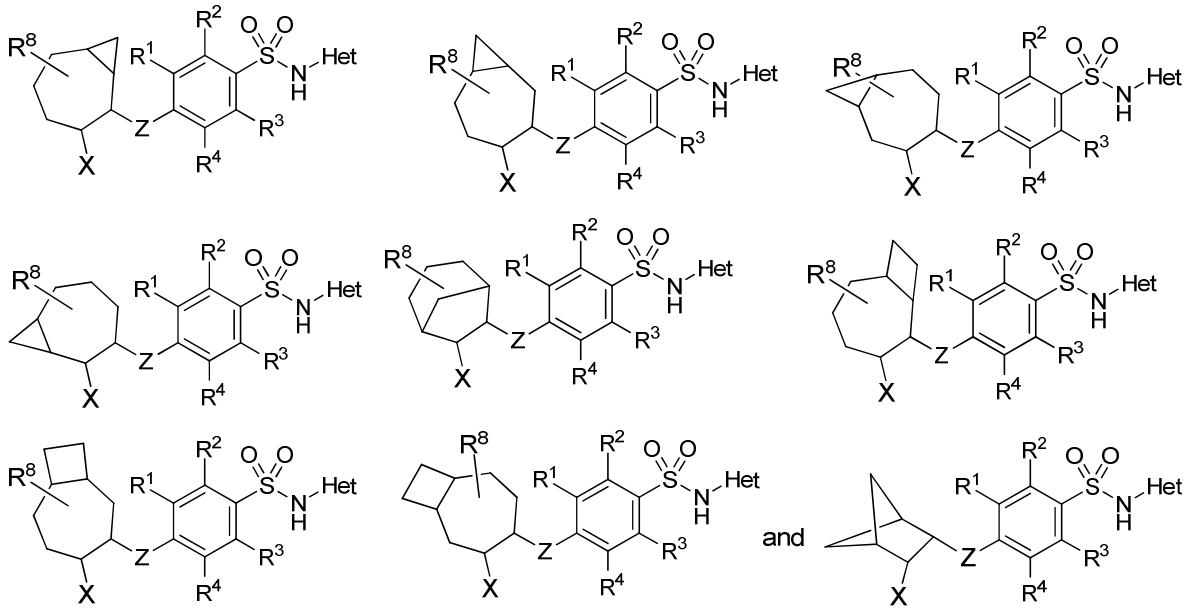
Het is 5- or 6-membered heteroaryl optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl;

X is selected from −N(R^6)$_2$ and −N(R^7)$_3^+$ $^-$W, and amine oxides thereof;

Y^1 is −C(R^8)$_2$−; and Y^2 is selected from −($C(R^8)_2$)$_n$−, −N(R^9)−, −O−, −C(R^8)$_2$−N(R^9)−, −N(R^9)−C(R^8)$_2$−, −C(R^8)$_2$−O−, and −O−C(R^8)$_2$−;

or

E55. A compound of E1 or E2 selected from:



or a pharmaceutically acceptable salt thereof.

E56. The compound of E1, E2, E3, E4, E5, E28, E29, E30, E31, E32, E33, E34, E35, E36, E37, E38, E39, E40, E41, or E42, wherein R^8 or R^9 taken together with another R^8 or R^9 and the atoms to which they are attached form a 3-8 membered fused ring, which is a benzo ring.

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 one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, 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 one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating neuropathic pain in a mammal.

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 one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal.

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. In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal.

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. In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating pruritus in a mammal.

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.

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 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, 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 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, 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 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

Definitions

As used herein, the term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (i.e., $C_{1\text{-}8}$ 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 terms "alkoxy," "alkylamino" and “alkylthio”, are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom (“oxy”), an amino group (“amino”) or thio group. Additionally, for dialkylamino groups, the alkyl portions can be the same or different.

The terms "halo" by itself or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

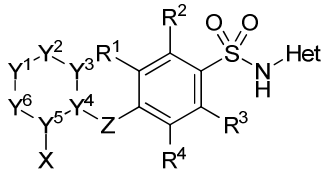
The term “haloalkyl” refers to an alkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) halo groups. For example the term includes an alkyl group having 1-6 carbon atoms that is substituted with one or more halo groups. Non-limiting examples of the term C_1-C_6 haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, and 2,2,2-trifluoroethyl.

The term “halocycloalkyl” refers to a cycloalkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) halo groups. For example the term includes a cycloalkyl group having 3-6 carbon atoms that is substituted with one or more halo groups. Non-limiting examples of the term C_1-C_6 halocycloalkyl include 1-fluorocyclopropyl.

The term “hydroxyalkyl” refers to an alkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) hydroxy groups. For example the term includes C_1-C_6 hydroxyalkyl, which is an alkyl group having 1-6 carbon atoms that is substituted with one or more hydroxy groups. Non-limiting examples of the term C_1-C_6 hydroxyalkyl include hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl.

WE CLAIM:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein :

R^1, R^2, R^3, and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, hydroxy, C_1-C_6 alkoxy, nitro, and halo,wherein any C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, and phenyl; and Z is selected from $-N(R^5)-$, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

or

R^1, R^2, and R^3 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl; and R^4 and Z together with the benzene ring to which they are both attached form a 9- or 10-membered heterobicycle;

Het is 5- or 6-membered heteroaryl optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl;

X is selected from $-N(R^6)_2$ and $-N(R^7)_3{}^+ {}^-W$, and amine oxides thereof;

Y^1 is $-C(R^8)_2-$; and Y^2 is selected from $-(C(R^8)_2)_n-$, $-N(R^9)-$, $-O-$, $-C(R^8)_2-N(R^9)-$, $-N(R^9)-C(R^8)_2-$, $-C(R^8)_2-O-$, and $-O-C(R^8)_2-$;

or

Y^1 is selected from $-N(R^9)-$ and $-O-$; and Y^2 is $-(C(R^8)_2)_n-$;

n is selected from 0, 1, and 2;

Y^3 and Y^6 are each $-C(R^8)_2-$;

Y^4 and Y^5 are each $-C(R^8)-$;

R^5 is selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl, wherein any C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered

heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, -NR^aR^b, -$C(=O)NR^aR^b$, R^c, and phenyl, wherein any C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkanoyl is optionally substituted with C_3-C_6 cycloalkyl; or two R^6 groups together with the nitrogen to which they are both attached form a 4- to 10-membered heterocycle that is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, which C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from hydroxy and halo;

each R^7 is independently selected from C_1-C_6 alkyl; or two R^7 groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

each R^8 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, benzyl, 5-15 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, hydroxy, halo, cyano, and –L-C_6-C_{12} aryl; wherein each C_3-C_6 cycloalkyl, -L-C_6-C_{12} aryl, benzyl, 5-15 membered heteroaryl, and C_1-C_6 alkoxy, is optionally substituted with one to three substituents R^x each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -$S(C_1$-C_6 alkyl), -$S(O)(C_1$-C_6 alkyl), -$S(O)_2(C_1$-C_6 alkyl), -NH_2 -$NH(C_1$-C_6 alkyl), -$N(C_1$-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl or two R^8 that are on adjacent carbons taken together form a double bond; and R^9 is selected from hydrogen, C_1-C_6 alkyl and C_6-C_{12} aryl, which C_6-C_{12} aryl is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, and C_1-C_6 haloalkyl; or one R^8 or R^9 taken together with another R^8 or R^9 and the atoms to which they are attached form a 3-8 membered fused, bridged or spirocyclic ring, which 3-8 membered ring is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, halo, and C_1-C_6 haloalkyl; and L is selected from a bond, −O−, −S−, −S(O)−, and −$S(O)_2$−;

each R^a and R^b is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkanoyl;

each R^c is independently selected from 4-7 membered heterocycle that is optionally substituted with one or more groups independently selected from halo, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

W^- is a counterion.

2. The compound of claim 1 wherein:

R^1, R^2, R^3, and R^4 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, halo, and C_1-C_6 haloalkyl; and Z is selected from $-N(R^5)-$, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

or

R^1, R^2, and R^3 are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl; and R^4 and Z together with the benzene ring to which they are both attached form a 9- or 10-membered heterobicycle;

Het is 5- or 6-membered heteroaryl optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl;

X is selected from $-N(R^6)_2$ and $-N(R^7)_3^+ \ ^-W$;

Y^1 is $-C(R^8)_2-$; and Y^2 is selected from $-(C(R^8)_2)_n-$, $-N(R^9)-$, $-O-$, $-C(R^8)_2-N(R^9)-$, $-N(R^9)-C(R^8)_2-$, $-C(R^8)_2-O-$, and $-O-C(R^8)_2-$;

or

Y^1 is selected from $-N(R^9)-$ and $-O-$; and Y^2 is $-(C(R^8)_2)_n-$;

n is selected from 0, 1, and 2;

Y^3 and Y^6 are each $-C(R^8)_2-$;

Y^4 and Y^5 are each $-C(R^8)-$;

R^5 is selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

each R^6 is independently selected from hydrogen, C_2-C_6 alkoxyalkyl, C_1-C_6 alkyl, benzyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, and phenyl; or two R^6 groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

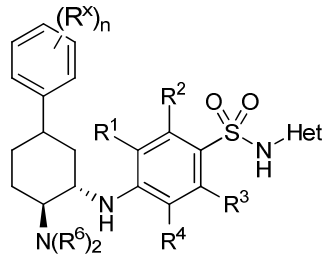
each R^7 is independently selected from C_1-C_6 alkyl; or two R^7 groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

each R^8 is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, hydroxyl, halo, cyano, benzyl and phenyl; wherein each benzyl or phenyl is optionally substituted with one to three

substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl or two R^8 that are on adjacent carbons taken together form a double bond; and R^9 is selected from hydrogen and C_1-C_6 alkyl; or one R^8 or R^9 taken together with another R^8 or R^9 and the atoms to which they are attached form a 3-8 membered fused, bridged or spirocyclic ring; and

W is a counterion; or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 which is a compound of formula (Ik):



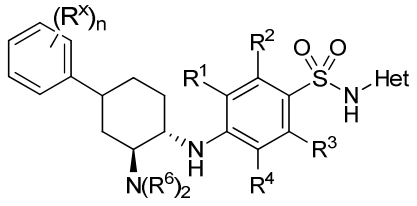
(Ik)

wherein:

n is 1, 2, or 3; and

each R^x is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 which is a compound of formula (Im):



(Im)

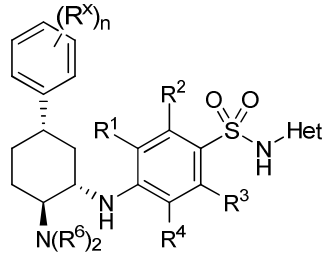
wherein:

n is 1, 2, or 3; and

each R^x is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy,

C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is a compound of formula (In):



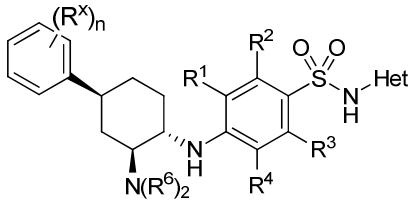
(In)

wherein:

n is 1, 2, or 3; and

each R^x is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 which is a compound of formula (Ip):



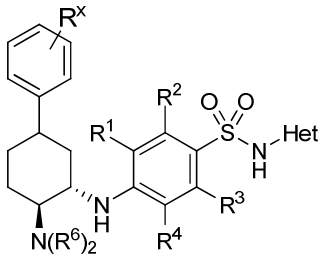
(Ip)

wherein:

n is 1, 2, or 3; and

each R^x is independently selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof

7. The compound of claim 1 which is a compound of formula (Ir):

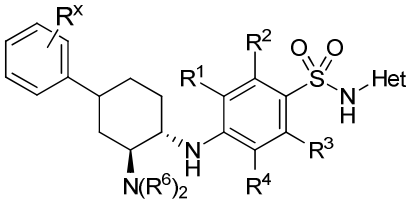


(Ir)

wherein:

R^x is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof

8. The compound of claim 1, which is a compound of formula (Is):

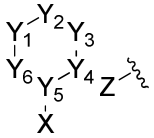


(Is)

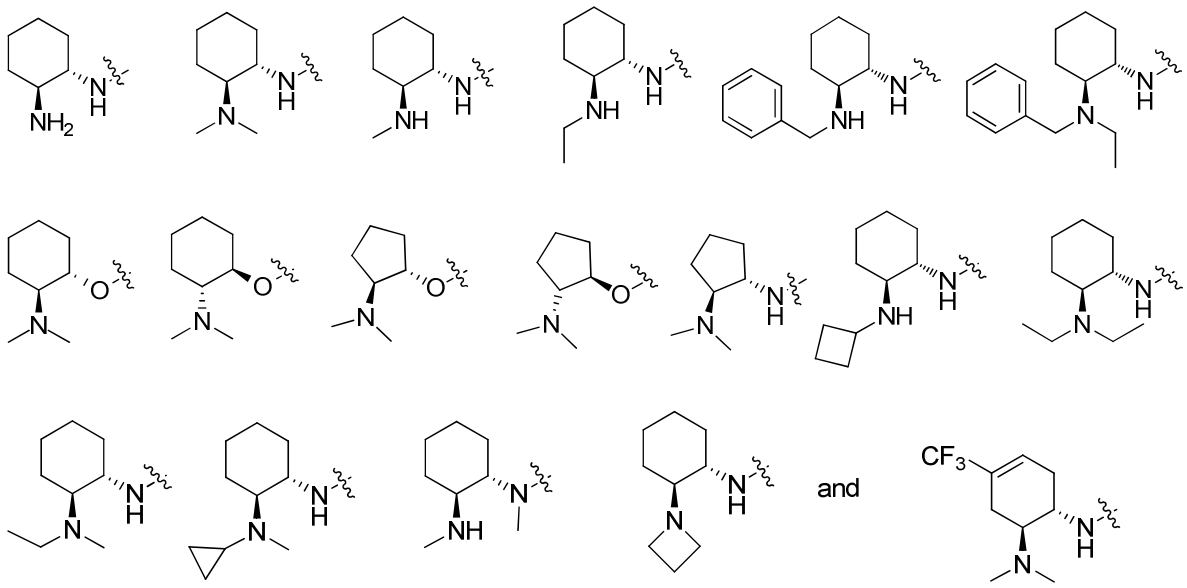
wherein:

R^x is selected from the group consisting of C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the group

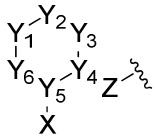


is selected from the group consisting of:

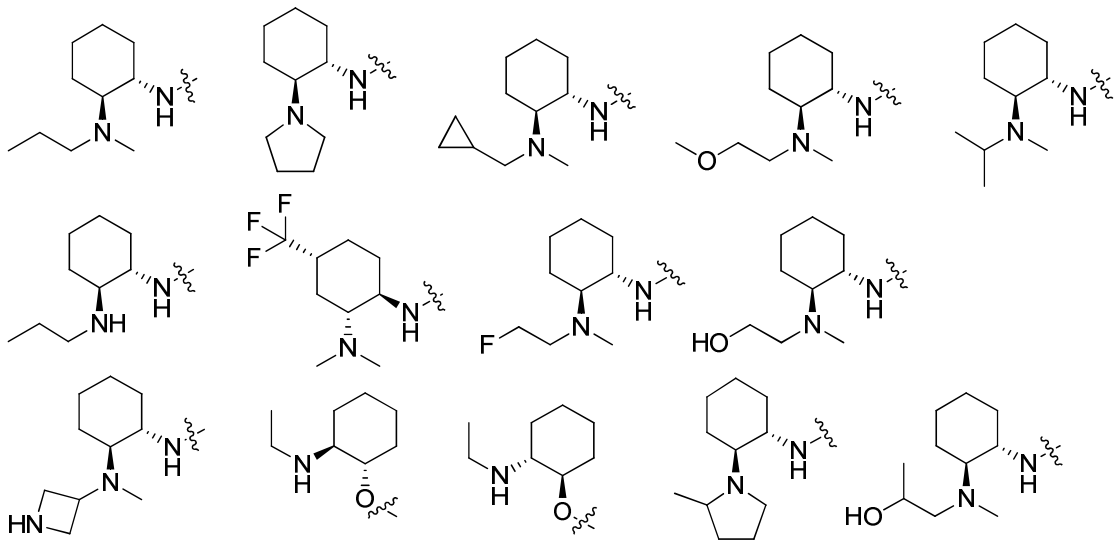


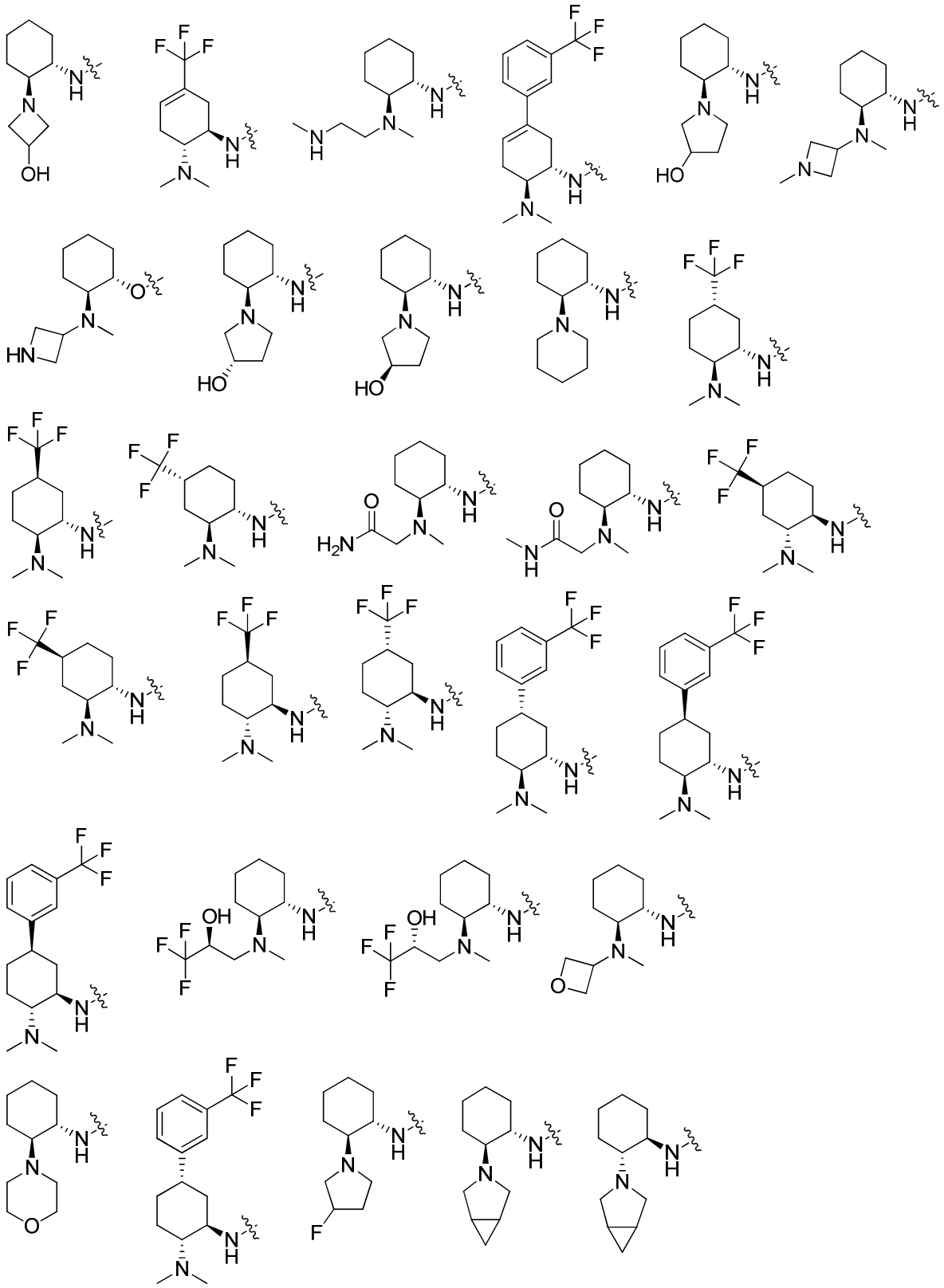
or a pharmaceutically acceptable salt thereof.

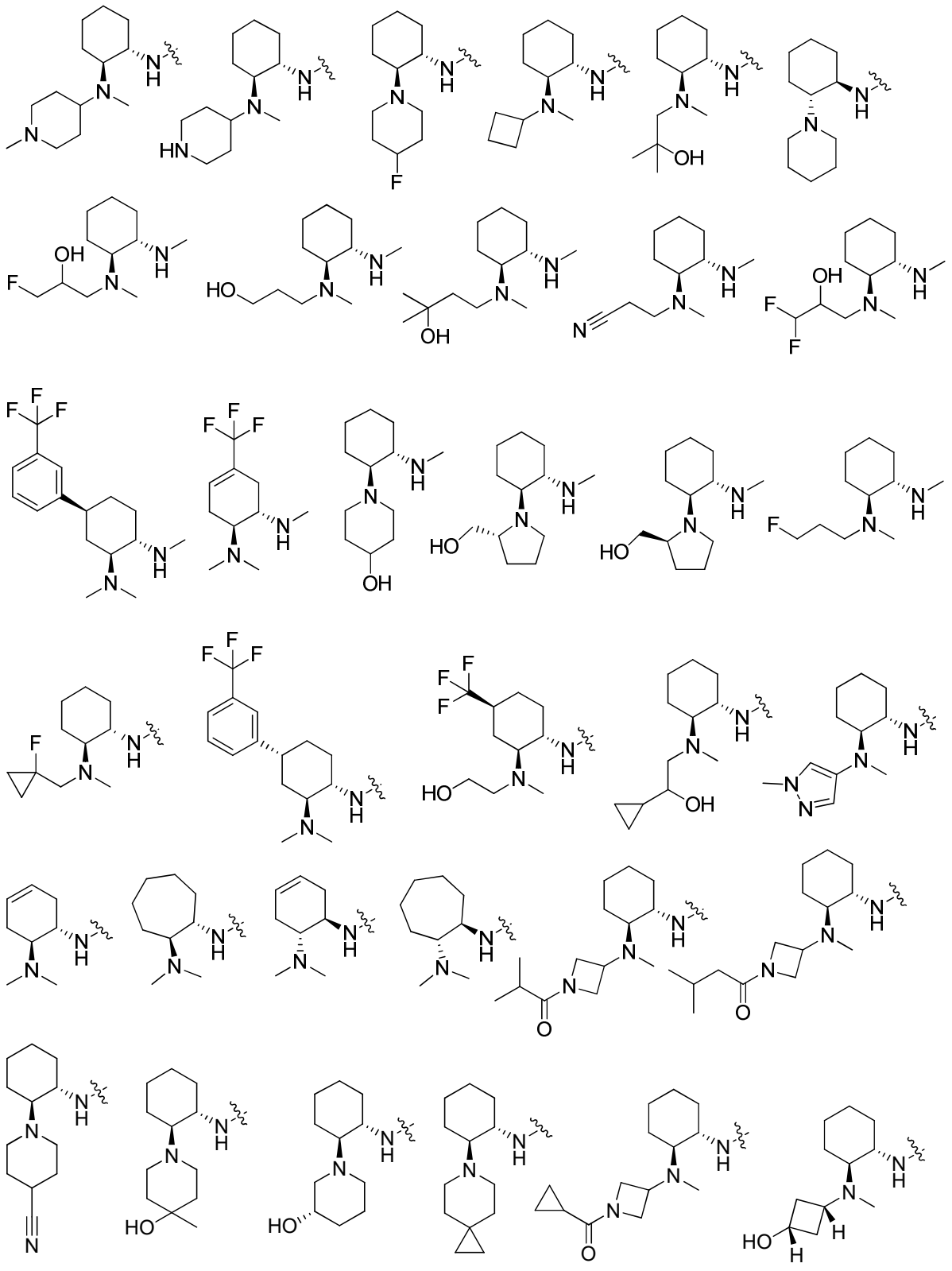
10. The compound of claim 1 wherein the group

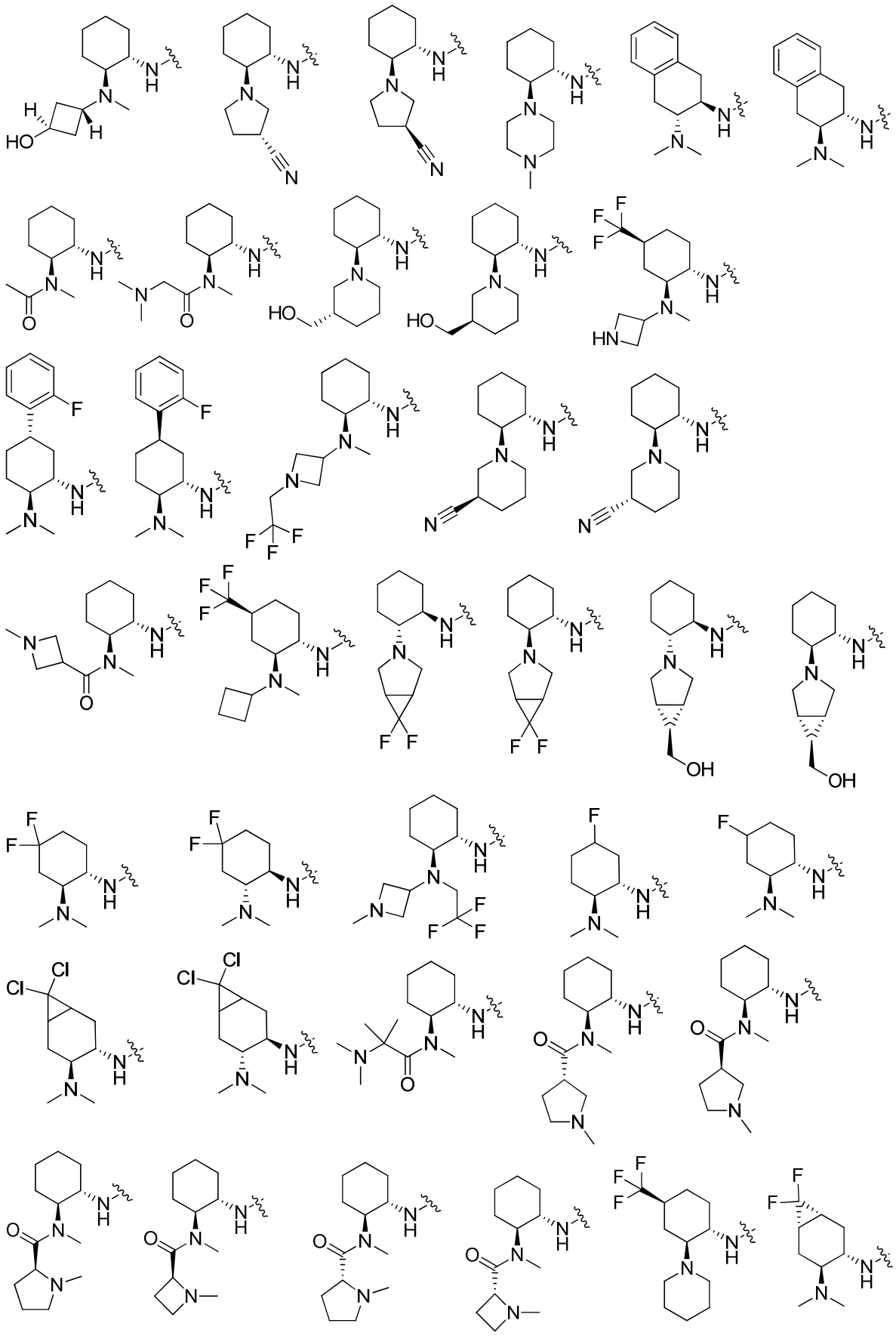


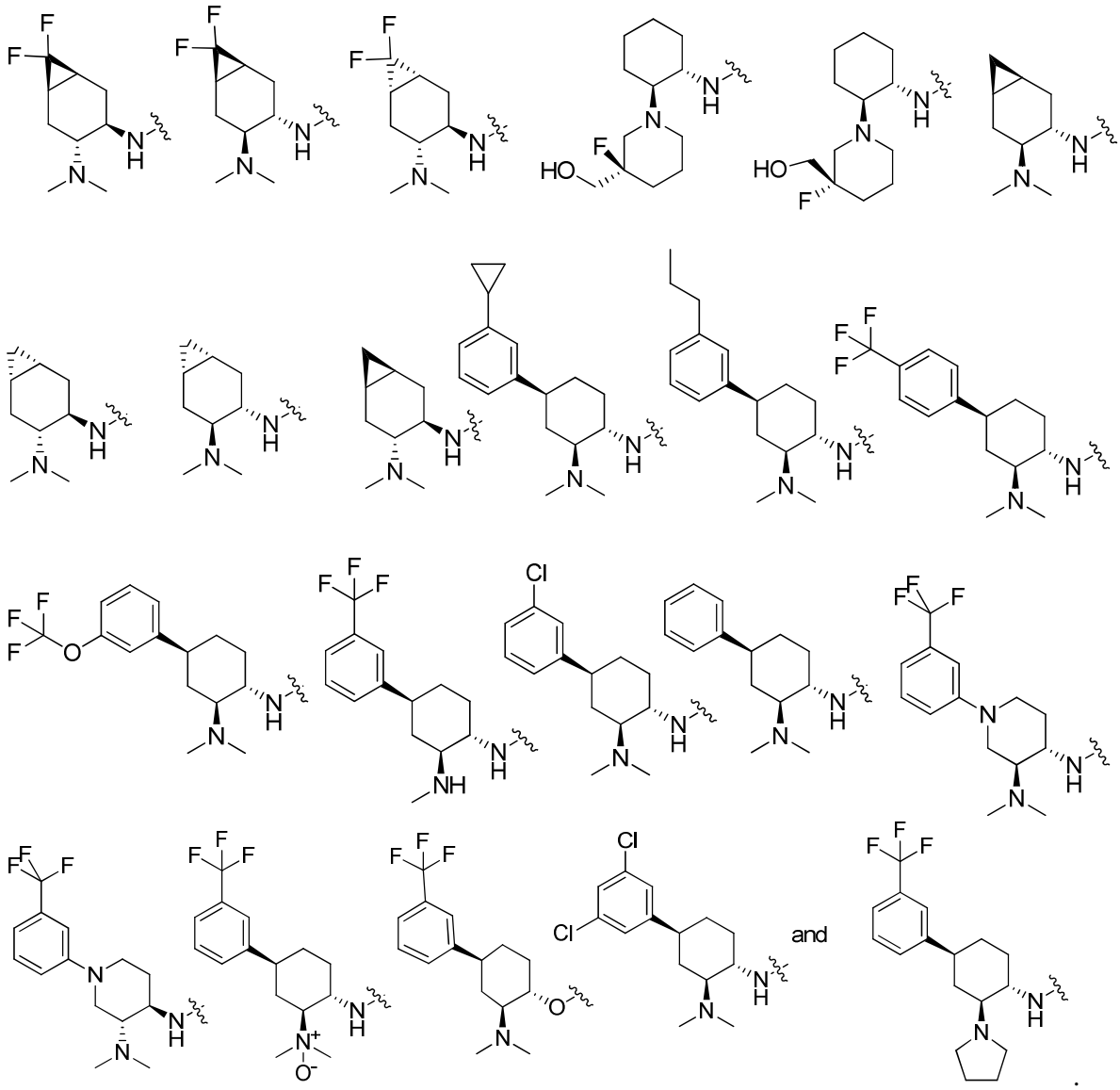
is selected from the group consisting of:





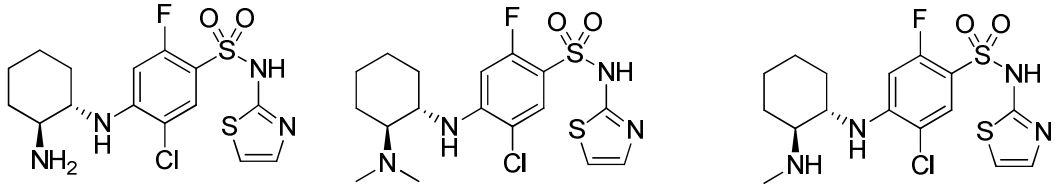


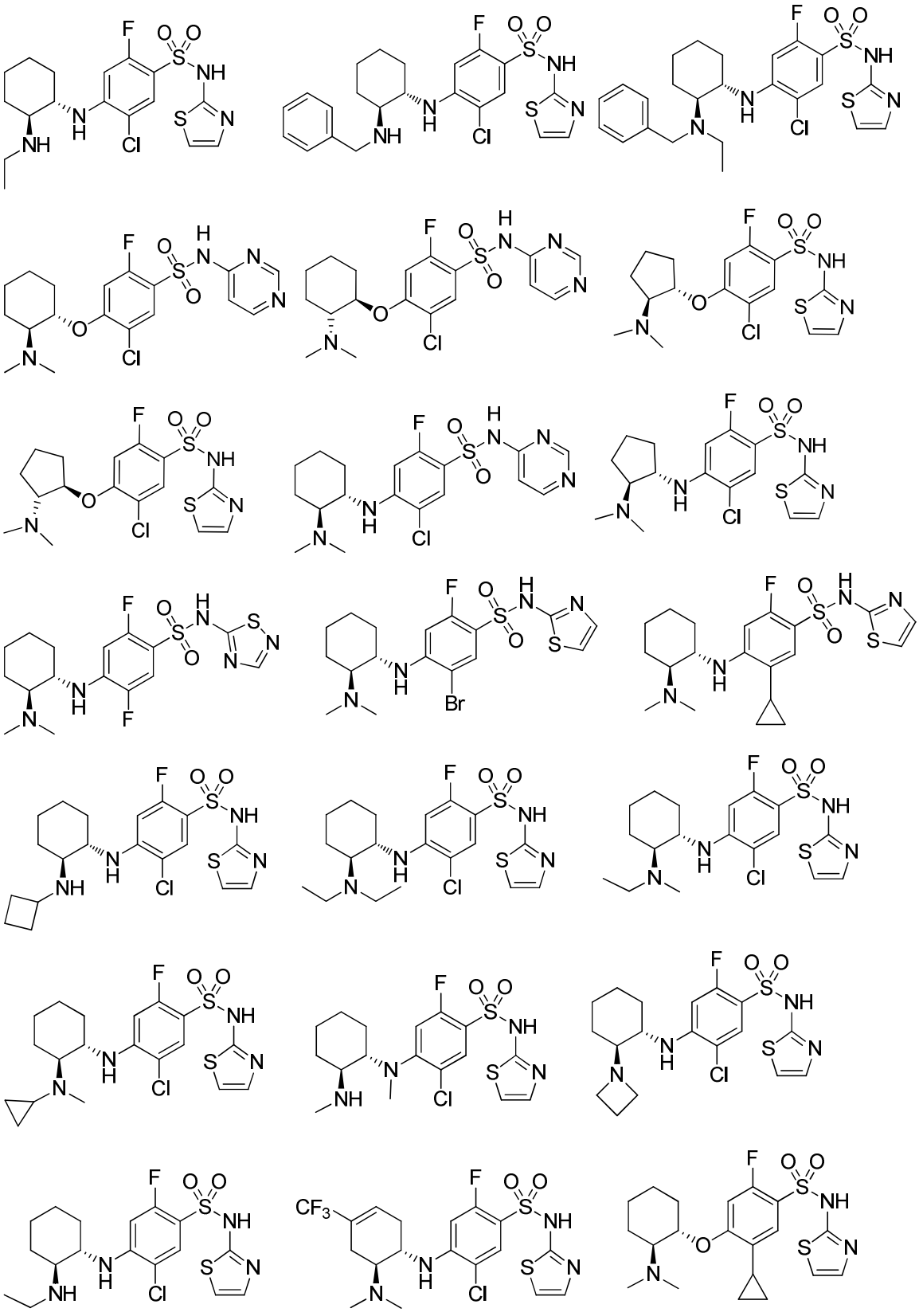


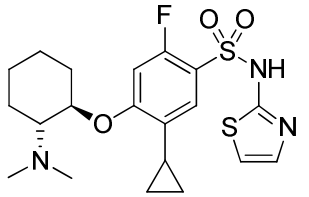
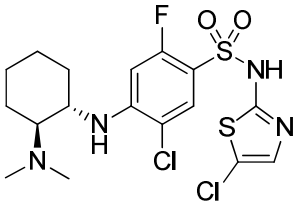
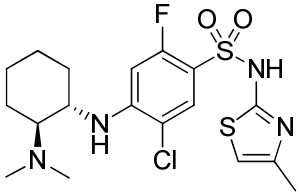


or a pharmaceutically acceptable salt thereof.

11. The compound of clam 1, which is selected from the group consisting of:

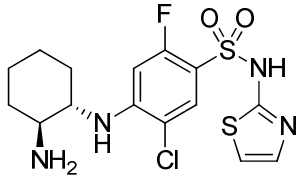
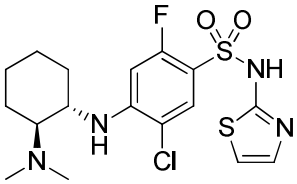
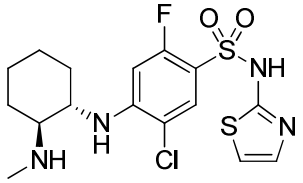
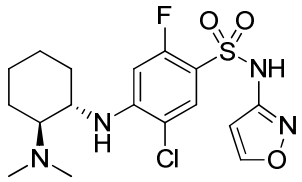
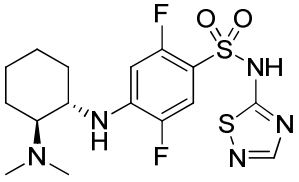
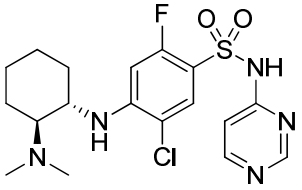
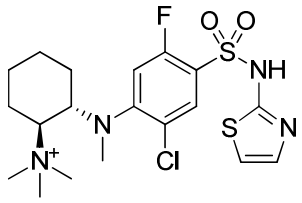
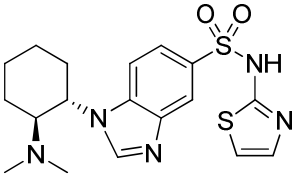
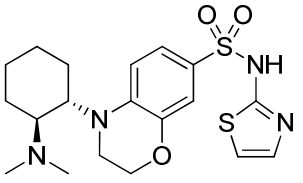
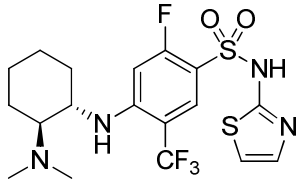
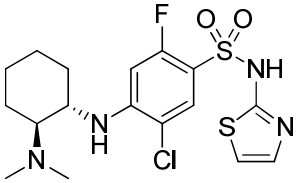
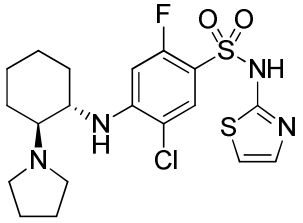
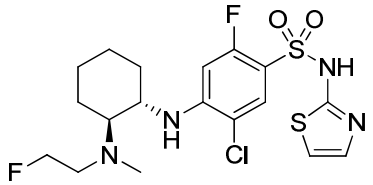
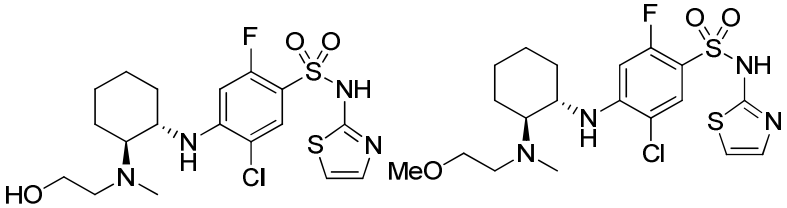
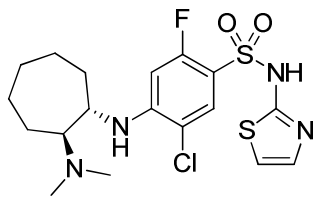
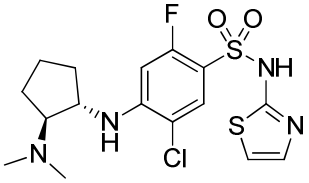
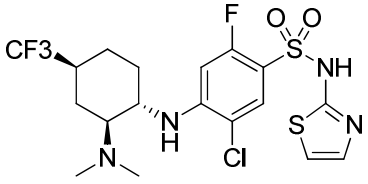


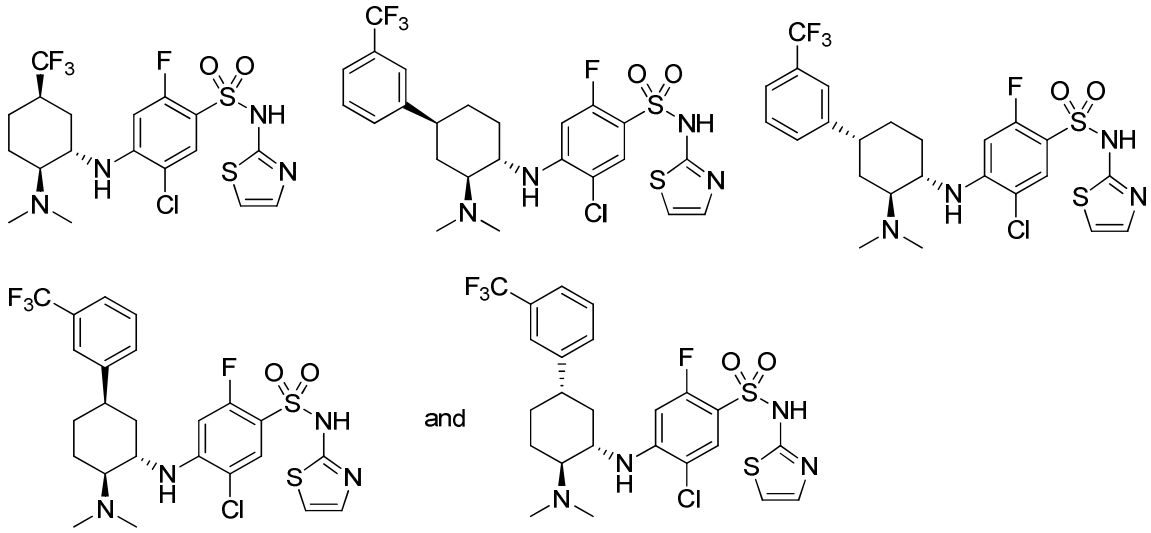




and


or a pharmaceutically acceptable salt thereof.

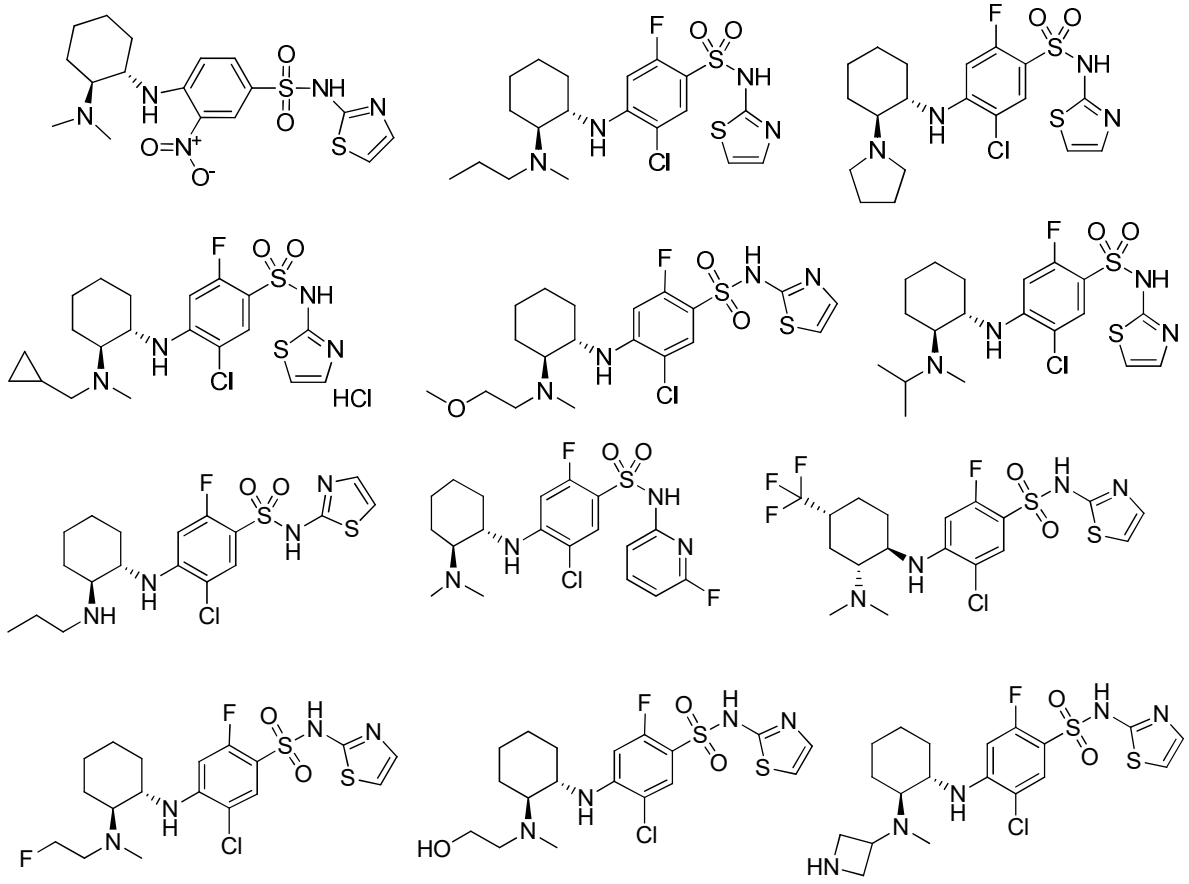
12. The compound of claim 1, which is selected from the group consisting of:

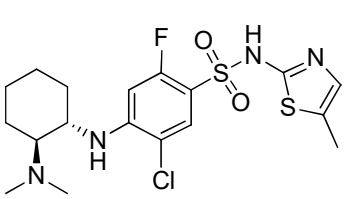
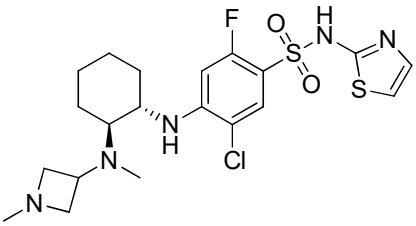
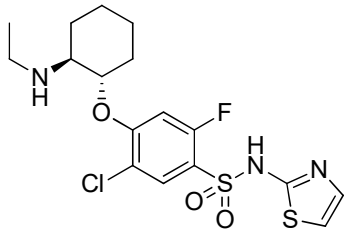
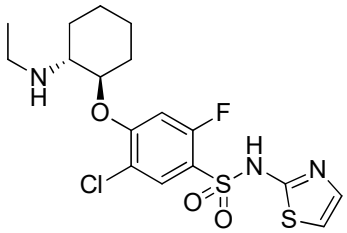
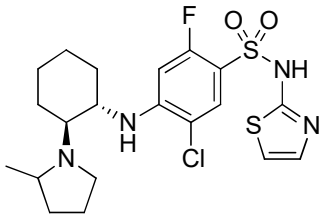
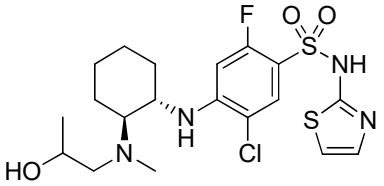
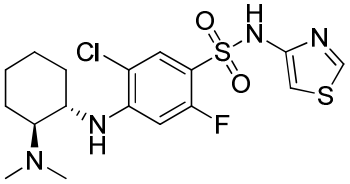
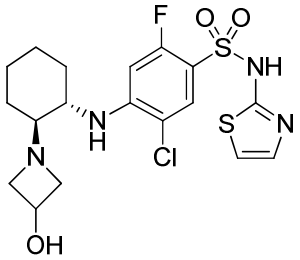
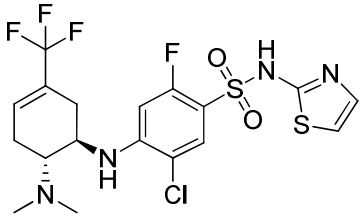
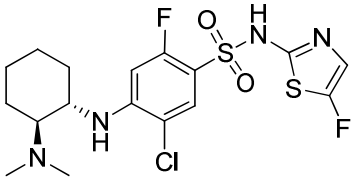
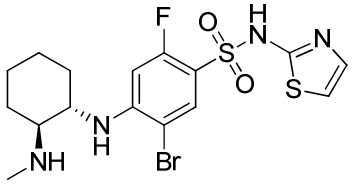
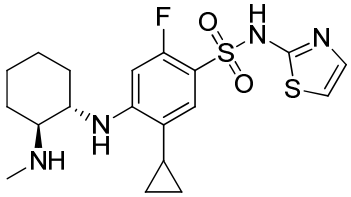
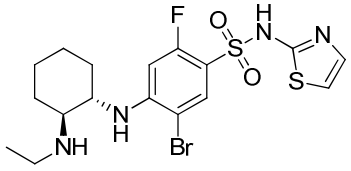
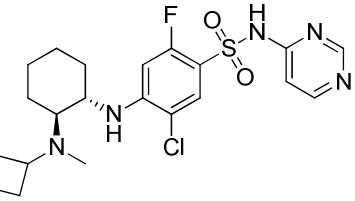
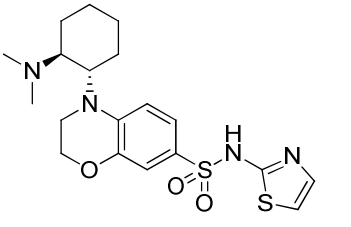


















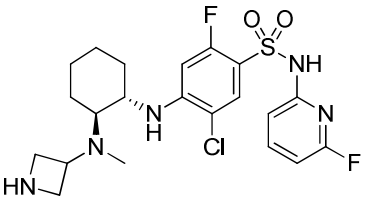
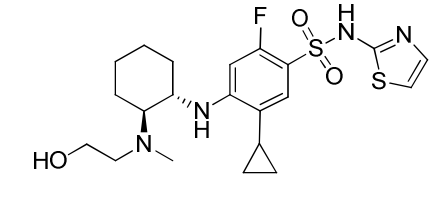
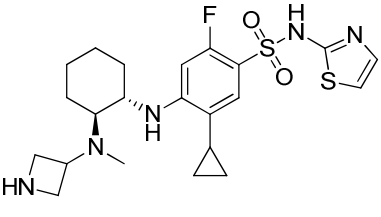


or a pharmaceutically acceptable salt thereof.

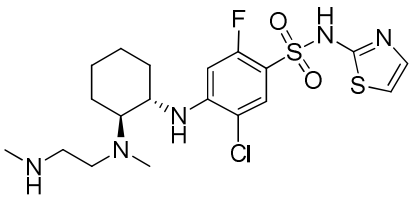
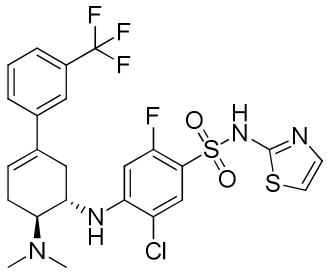
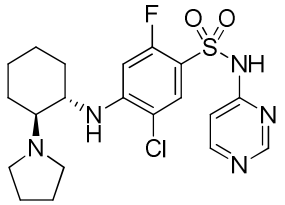
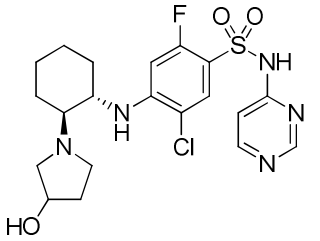
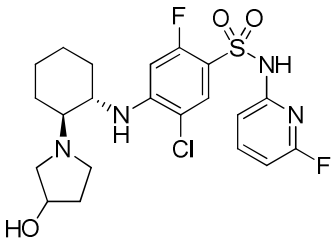
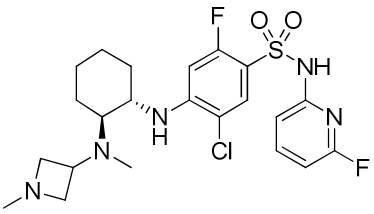
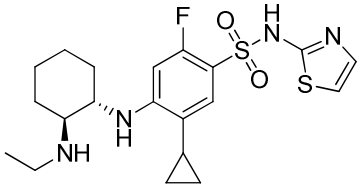
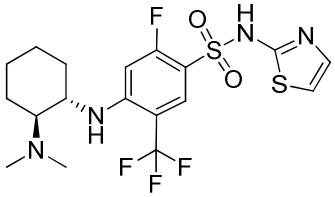
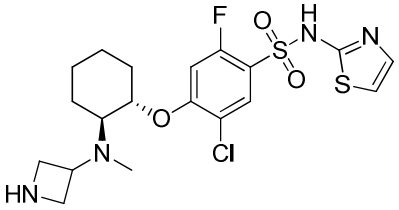
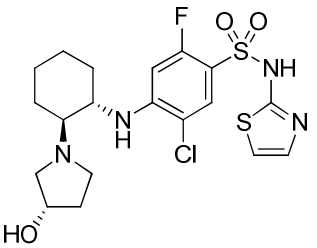
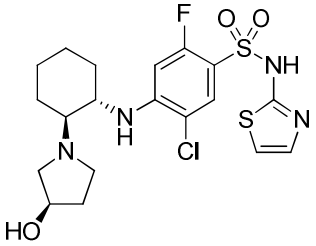
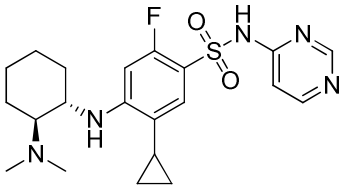
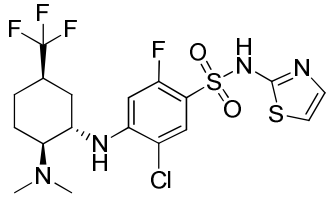
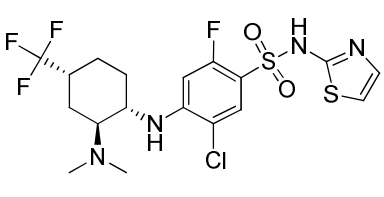
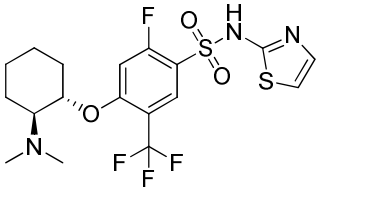
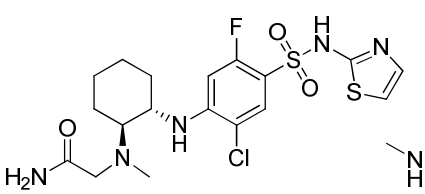
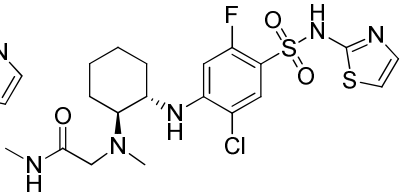
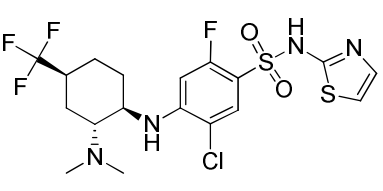
13. The compound of claim 1, which is selected from the group consisting of:

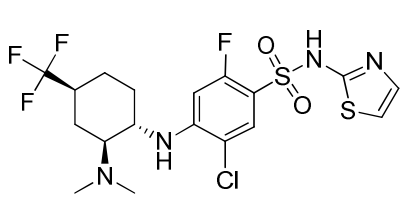
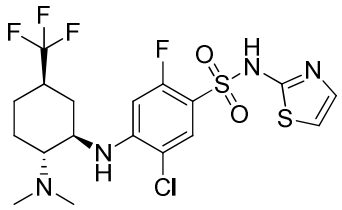
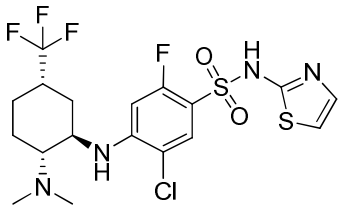
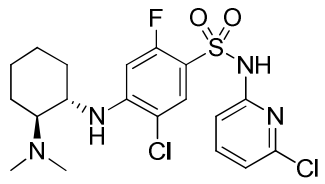
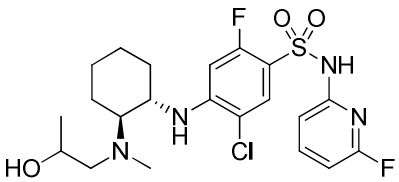
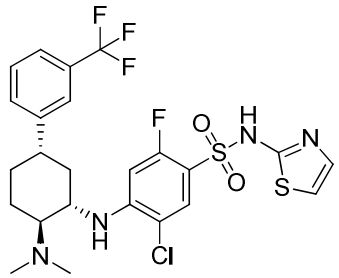
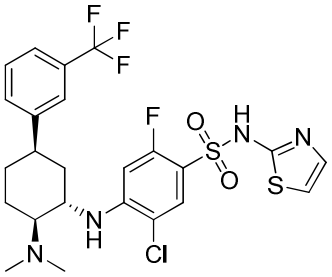
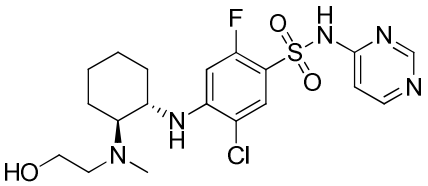
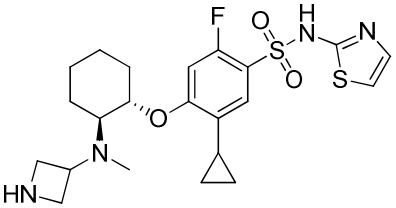
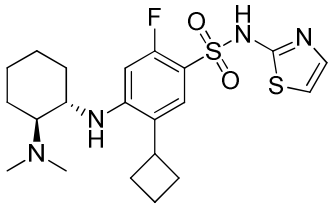
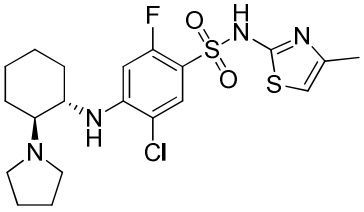
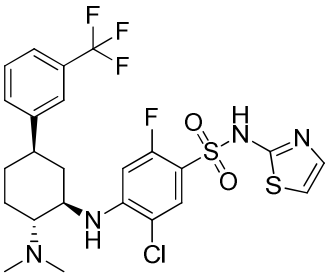
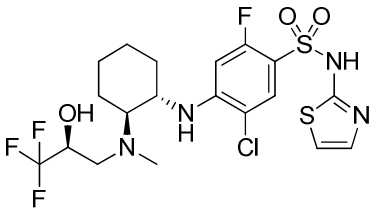
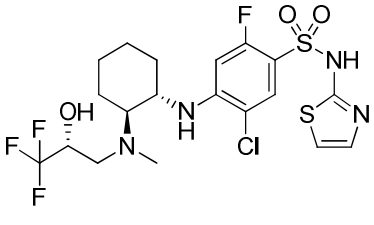
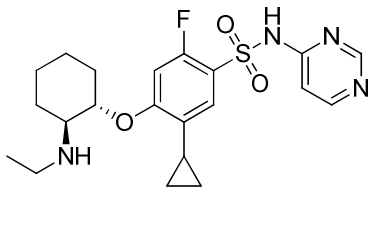


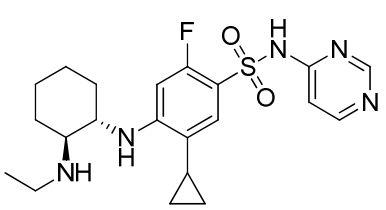
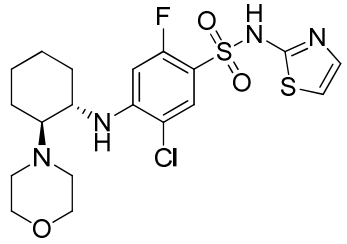
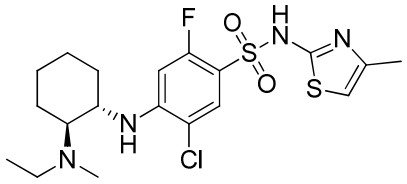
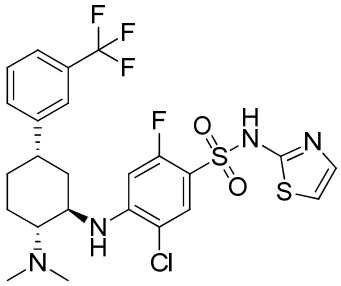
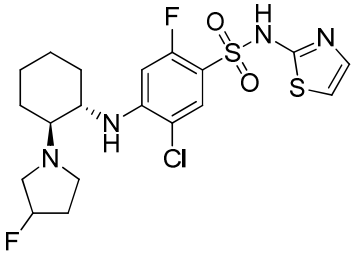
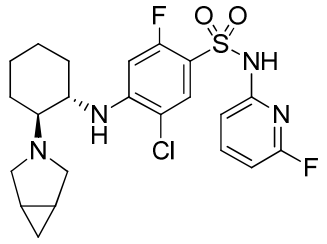
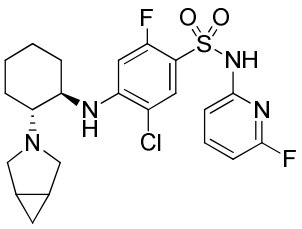
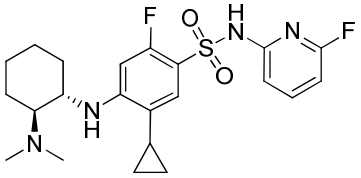
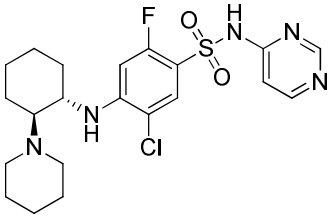
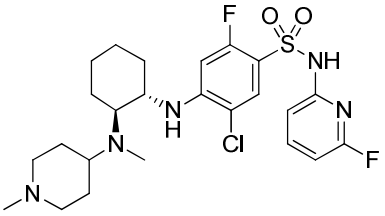
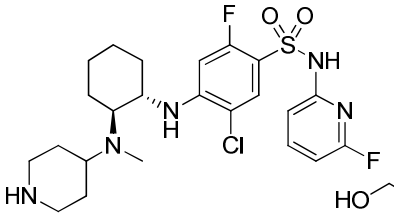
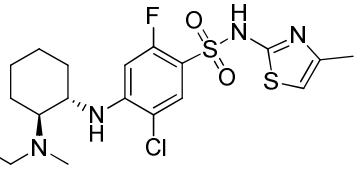
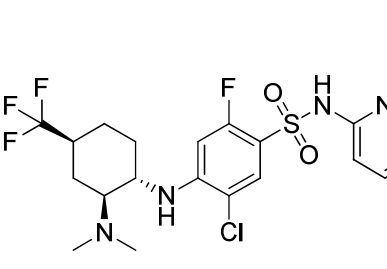
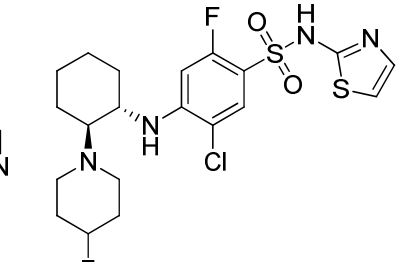
















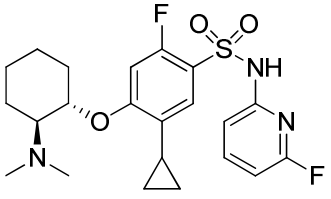
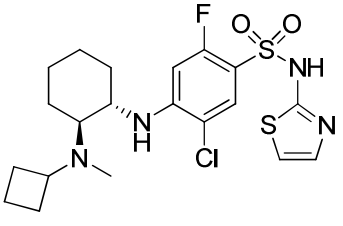
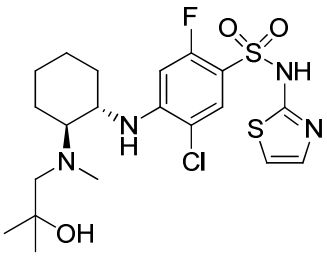
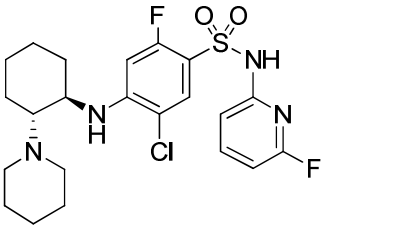




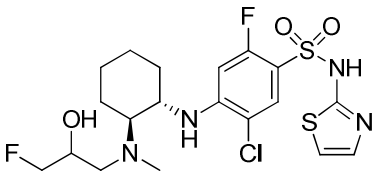
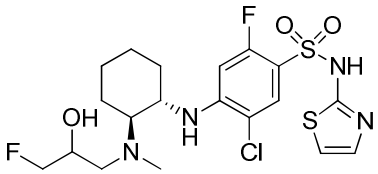
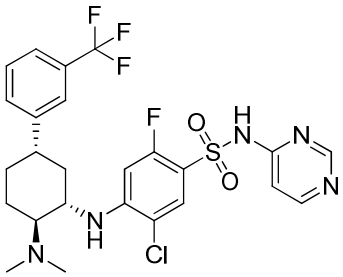
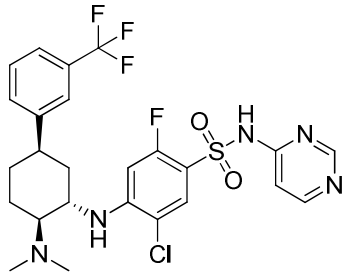
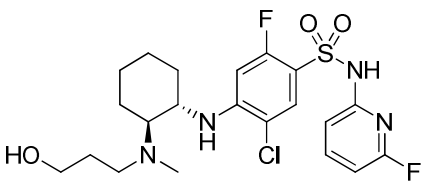
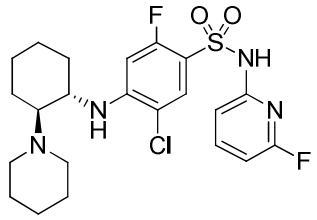
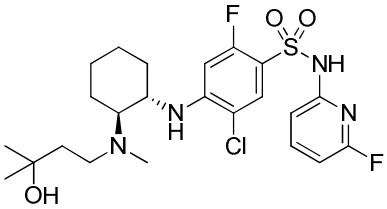
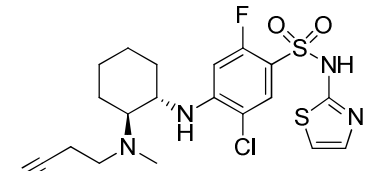
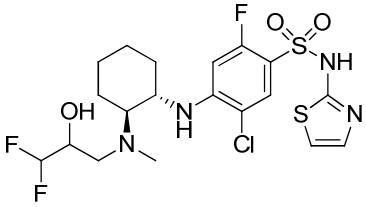
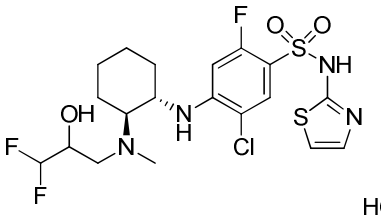
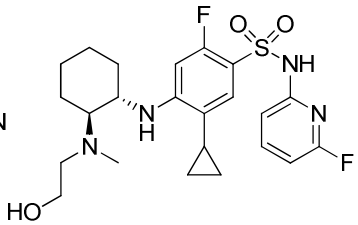
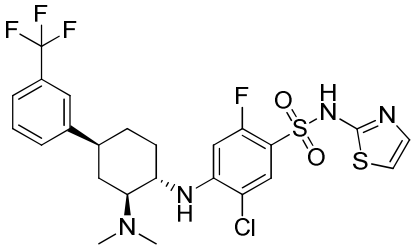
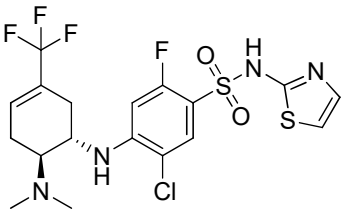
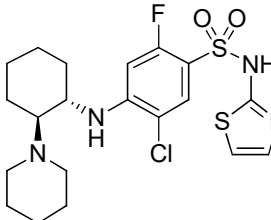
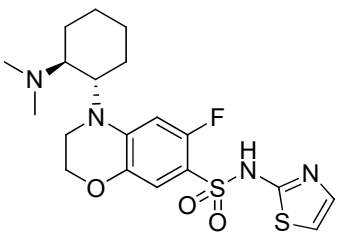


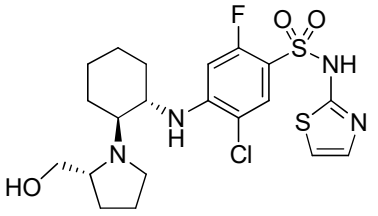
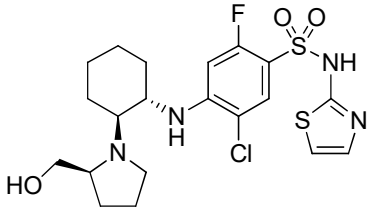
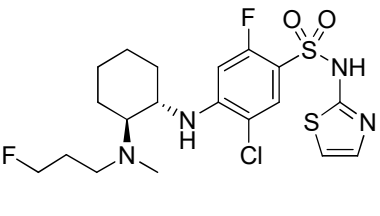



















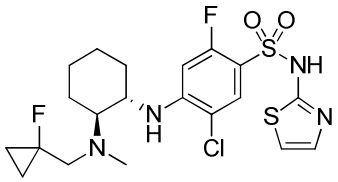
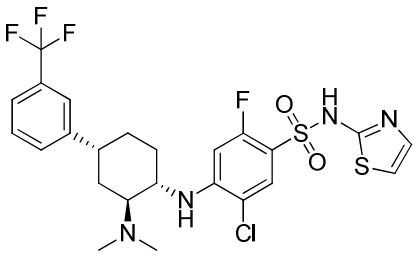
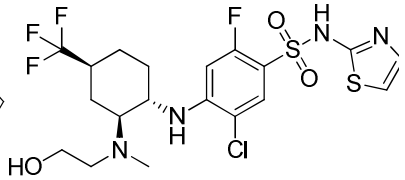
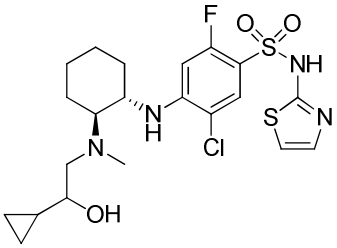
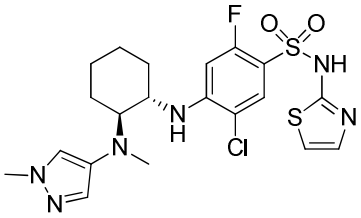
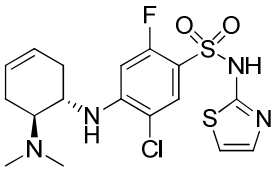
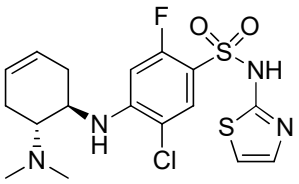
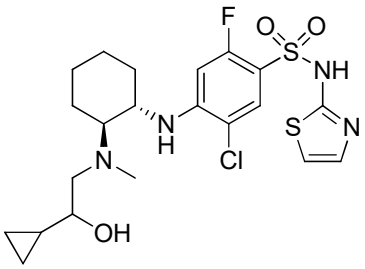
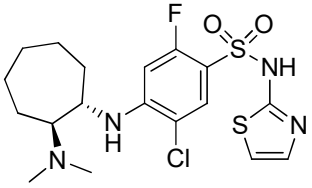
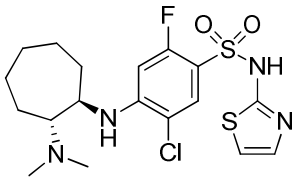
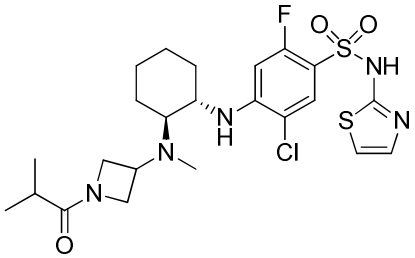
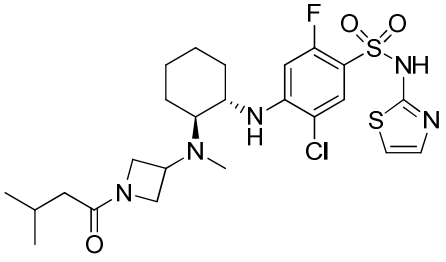
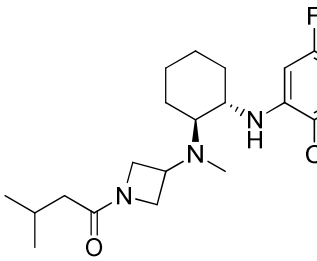
















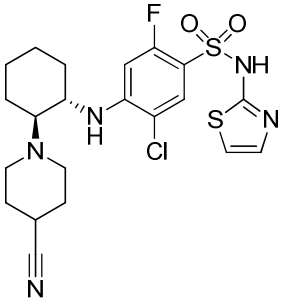















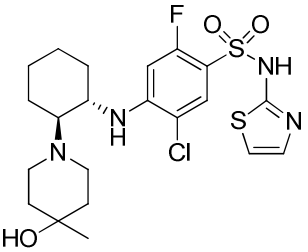
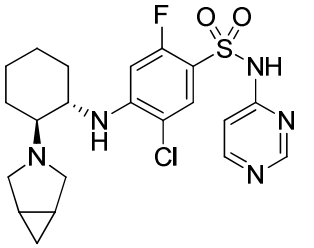
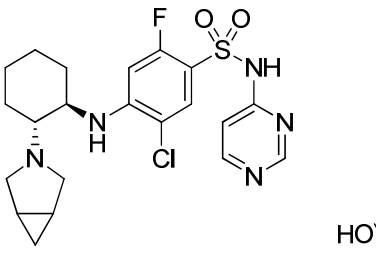





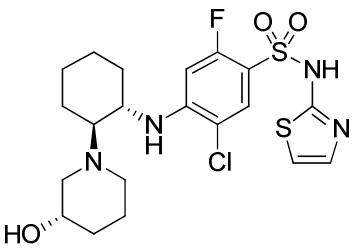
















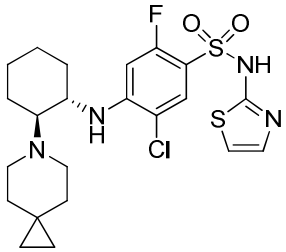
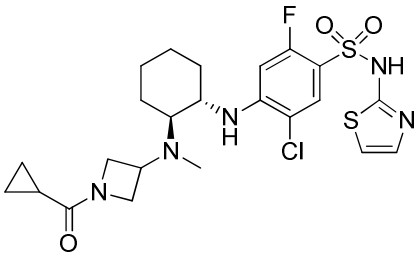
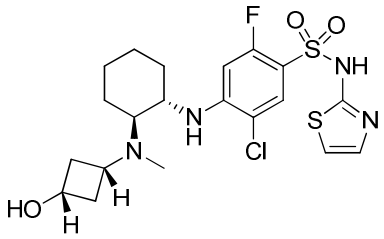
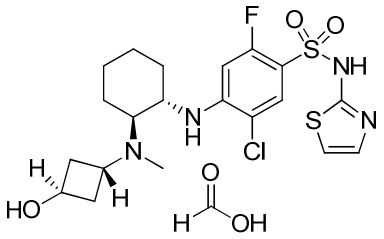
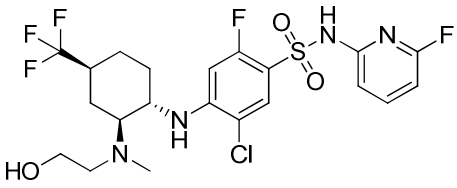
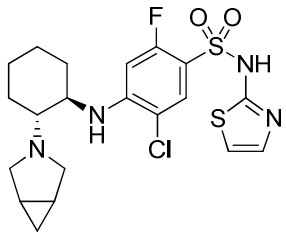
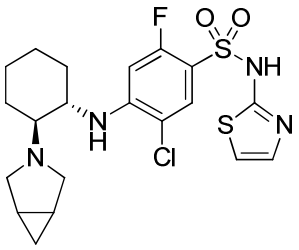
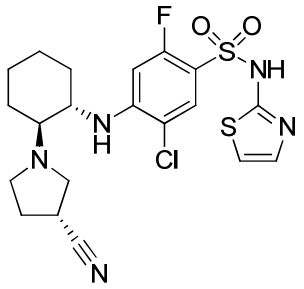
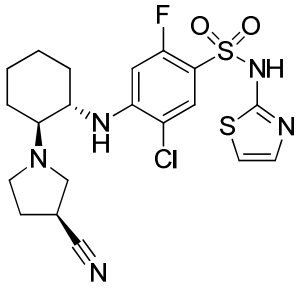
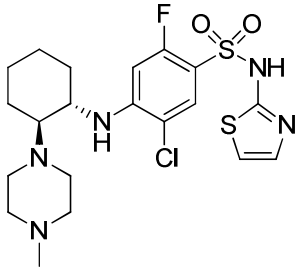
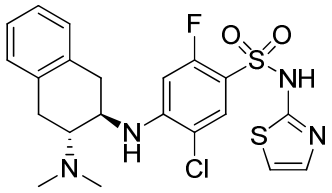
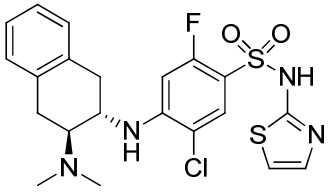
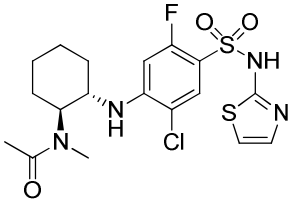
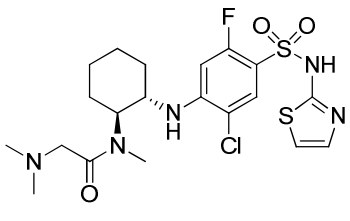
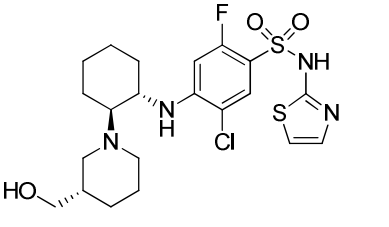
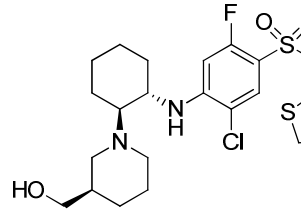
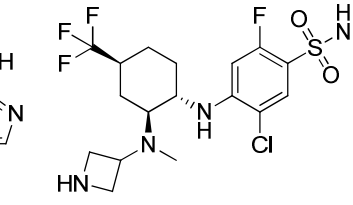
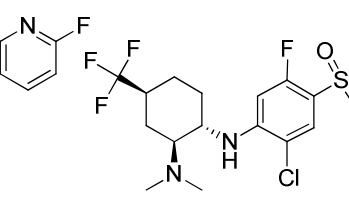





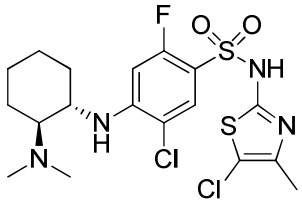
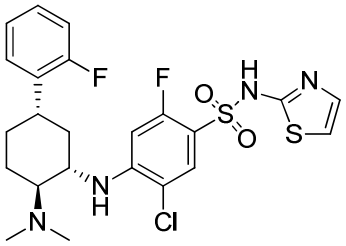
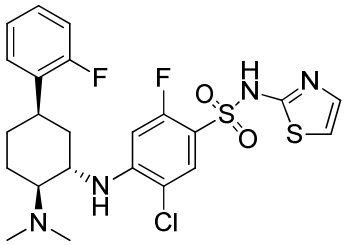
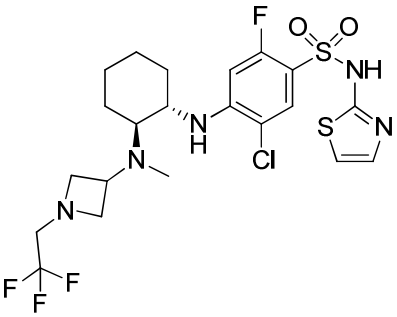
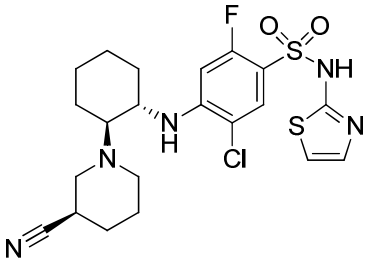
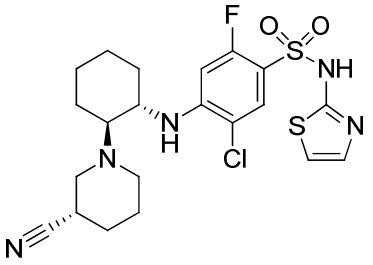
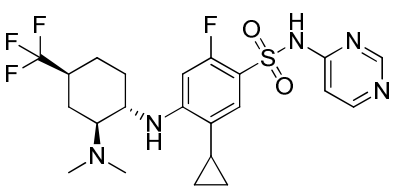
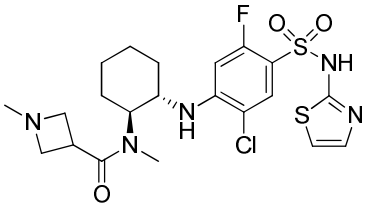
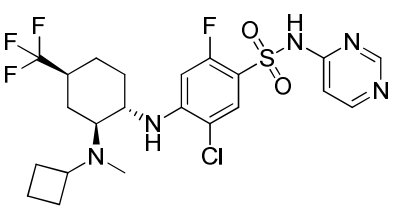
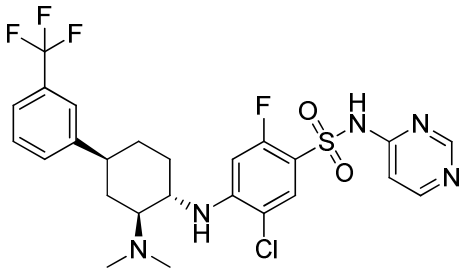
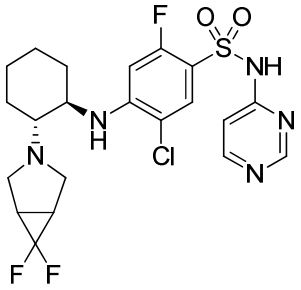
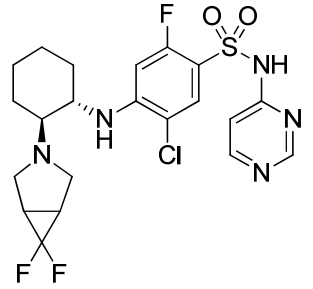
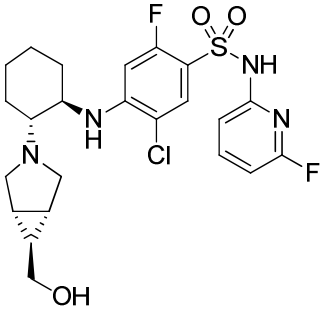
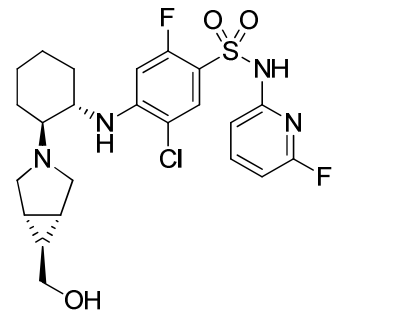


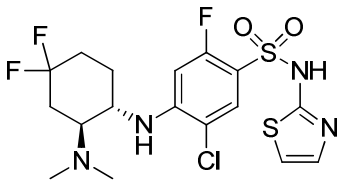
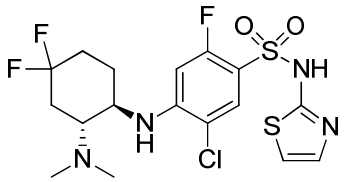


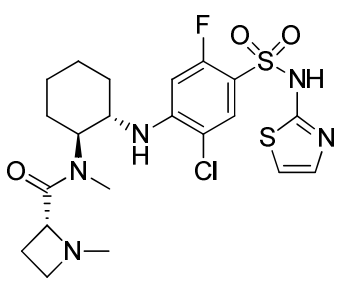
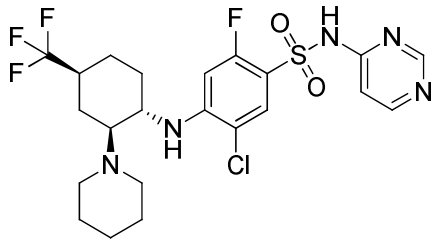



















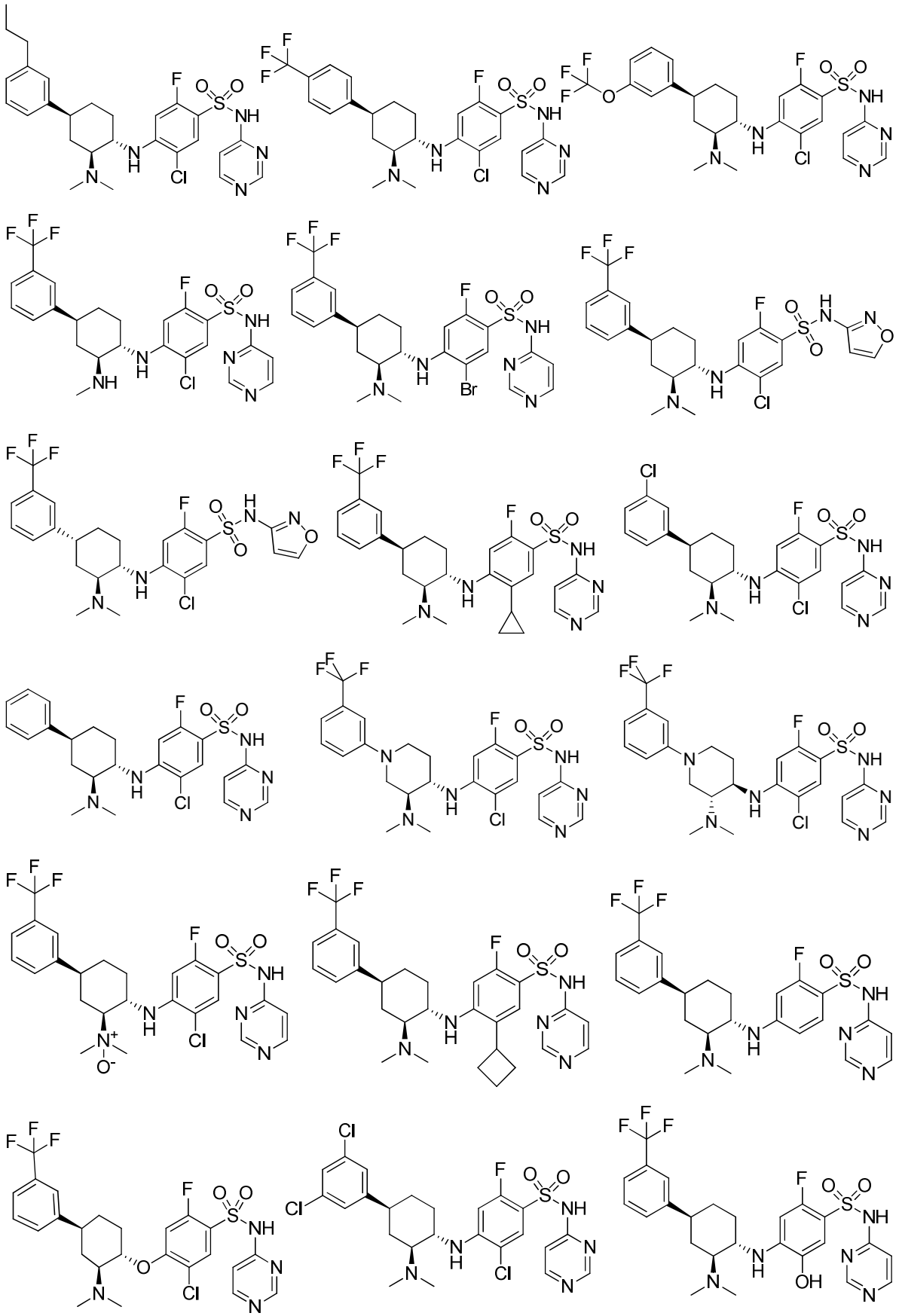


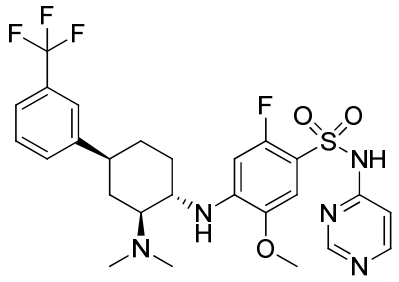





















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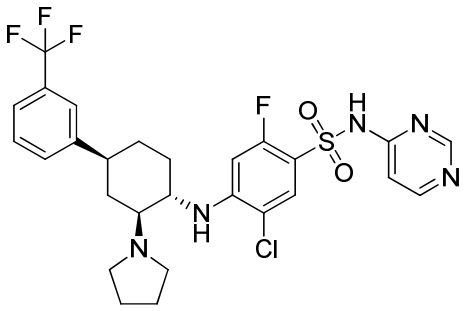

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

15. Use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating neuropathic pain in a mammal.

16. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal.

17. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal.

18. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating pruritus in a mammal.

19. Use of a compound of Claim 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating neuropathic pain in a mammal.