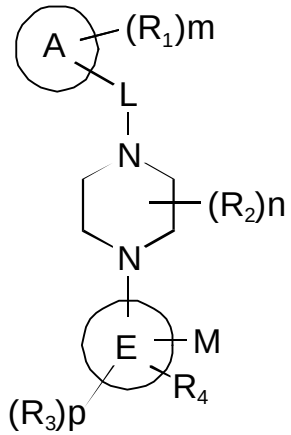
CLAIMS

What is claimed is:

1. A compound represented by Formula I, or a tautomer, stereoisomer, or pharmaceutically acceptable salt thereof:



I, wherein:

ring A is selected from a 5- to 6-membered heterocyclic ring;

R_1 is selected from halogen, hydroxyl, amino, cyano, oxo (=O), C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl, wherein the C_1 to C_6 alkyl, the C_1 to C_6 alkoxy, and the C_3 to C_7 cycloalkyl are optionally substituted with one to four substituents selected from halogen, hydroxyl, amino, cyano, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_3 to C_7 cycloalkyl, and oxo;

m is selected from 0, 1, 2, 3, or 4, and when a plurality of substituents R_1 are present, the plurality of substituents R_1 are the same or different;

L is absent or selected from C_0 to C_6 alkyl-O-C_0 to C_6 alkyl, C_0 to C_6 alkyl-NH-C_0 to C_6 alkyl, and C_1 to C_6 alkyl, wherein the C_1 to C_6 alkyl-O-C_1 to C_6 alkyl, the C_0 to C_6 alkyl-NH-C_0 to C_6 alkyl, and the C_1 to C_6 alkyl are optionally substituted with one to four substituents selected from deuterium, oxo (=O), methyl, ethyl, halogenated methyl, and halogenated ethyl;

R_2 is selected from oxo (=O), C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_3 to C_7 cycloalkyl, a 5- to 10-membered heterocyclic ring, and a 6- to 10-membered aromatic ring, wherein the C_1 to C_6 alkyl, the C_1 to C_6 alkoxy, and the C_3 to C_7 cycloalkyl are optionally substituted with one, two, three, or four substituents selected from halogen, hydroxyl, cyano, amino, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl;

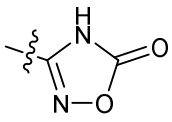
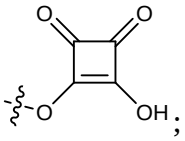
n is selected from 0, 1, 2, 3, 4, 5, 6, 7, or 8, and when a plurality of substituents R_2 are

present, the plurality of substituents R_2 are the same or different;

ring E is selected from a benzene ring or a 5- to 6-membered heteroaromatic ring;

R_3 is selected from halogen, hydroxyl, cyano, dimethylamino, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl, wherein the C_1 to C_6 alkyl, the C_1 to C_6 alkoxy, and the C_3 to C_7 cycloalkyl are optionally substituted with one to four substituents selected from halogen, hydroxyl, cyano, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl;

p is selected from 0, 1, 2, 3, or 4, and when a plurality of substituents R_3 are present, the plurality of substituents R_3 are the same or different;

M is selected from carboxylic group, $-CONHSO_2R_5$, $-SO_2NHCOR_5$, tetrazole, or a tetrazole bioisostere, wherein the tetrazole bioisostere comprises phosphoric acid,  , and  ;

R_4 is selected from $-CHF_2$, $-CH_2F$, -(C_0 to C_6 alkyl)-O-(halogenated C_1 to C_6 alkyl), and -(C_0 to C_6 alkyl)-O-(C_3 to C_4 cycloalkyl), wherein the -(C_0 to C_6 alkyl)-O-(halogenated C_1 to C_6 alkyl) and the -(C_0 to C_6 alkyl)-O-(C_3 to C_4 cycloalkyl) are optionally substituted with one to four substituents selected from hydroxyl, amino, C_3 to C_7 heterocycloalkyl, C_1 to C_3 alkyl, C_3 to C_6 cycloalkyl, and C_1 to C_3 alkoxy;

M and R_4 are on the ring E in an ortho relationship; and

R_5 is selected from C_1 to C_8 alkyl, C_3 to C_8 cycloalkyl, C_1 to C_8 alkoxy, and a 5- to 6-membered heterocyclic ring, wherein the C_1 to C_8 alkyl, the C_3 to C_8 cycloalkyl, the C_1 to C_8 alkoxy, and the 5- to 6-membered heterocyclic ring are optionally substituted with one to four substituents selected from halogen, amino, C_3 to C_7 heterocycloalkyl, C_1 to C_3 alkyl, C_3 to C_6 cycloalkyl, and C_1 to C_3 alkoxy.

2. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, satisfying one or more of the following conditions 1a) to 1j):

1a) the ring A is a 5- to 6-membered heteroaromatic ring, 5- to 6-membered heterocycloalkenyl, or 5- to 6-membered heterocycloalkyl, wherein the 5- to 6-membered heteroaromatic ring, the 5- to 6-membered heterocycloalkenyl, or the 5- to 6-membered

heterocycloalkyl comprises one, two, or three identical or different heteroatoms, and preferably, the one, two, or three identical or different heteroatoms are selected from N, O, and S;

1b) the ring A is selected from: furanyl, pyrrolyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridazinyl, triazinyl, dihydropyrrolyl, dihydropyrazolyl, dihydroimidazolyl, dihydrotriazolyl, dihydrotetrazolyl, dihydrotriazolyl, dihydrotetrazolyl, tetrahydropyridinyl, dihydropyridinyl, tetrahydropyrazinyl, dihydropyrazinyl, tetrahydropyrimidinyl, dihydropyrimidinyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyridazinyl, and hexahydropyrimidinyl; and

1c) the ring A is selected from pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, and thiadiazolyl;

1d) the ring E is a benzene ring or a 5- to 6-membered heteroaromatic ring, wherein the 5- to 6-membered heteroaromatic ring comprises one, two, or three identical or different heteroatoms, the one, two, or three identical or different heteroatoms being selected from N, O, and S;

1e) the ring E is selected from a benzene ring, pyridine, pyrimidine, and pyridazine; and

1f) Ring E is selected from a benzene ring;

1g) R_1 is selected from halogen, hydroxyl, amino, cyano, oxo (=O), C_1 to C_3 alkyl, halogenated C_1 to C_3 alkyl, C_1 to C_3 alkoxy, halogenated C_1 to C_3 alkoxy, C_3 to C_7 cycloalkyl, C_1 to C_3 alkyl-C_1 to C_3 alkoxy, and C_1 to C_3 alkyl-C_3 to C_7 cycloalkyl; and

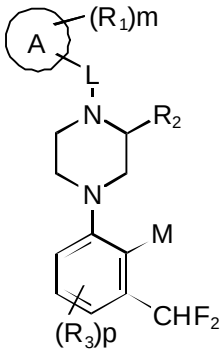
1h) R_1 is selected from halogen, methyl, halogenated methyl, and methoxy; or

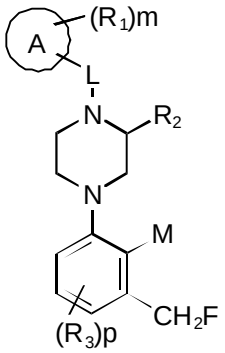
1i) m is selected from 0, 1, 2, 3, or 4; and

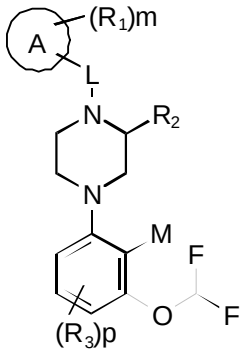
1j) m is selected from 0 or 1.

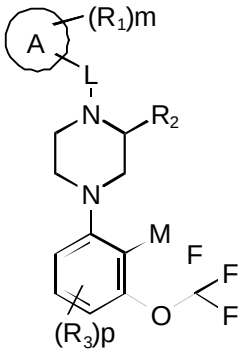
3. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein:

the compound has a structure selected from:



II-1 ,


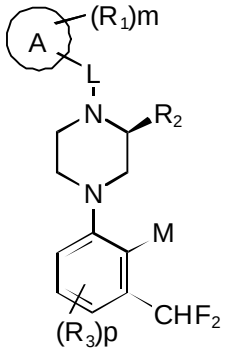
II-2 ,


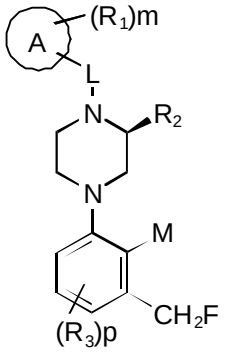
II-3 , and


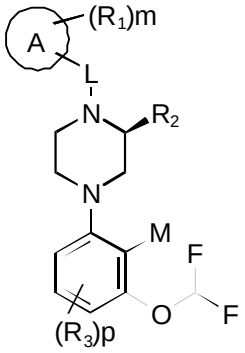
II-4 ,

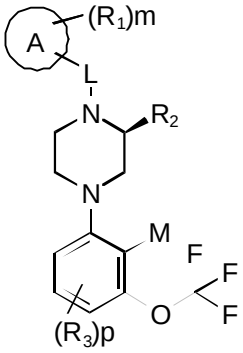
where ring A, M, L, R_1, R_2, R_3, m, and p are as defined in claim 1; and/or

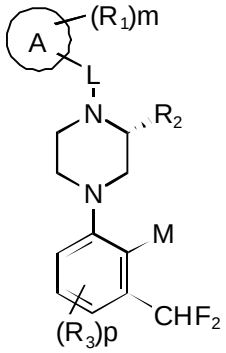
the compound has a structure selected from:

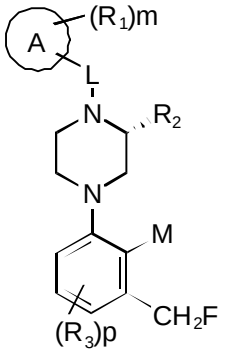


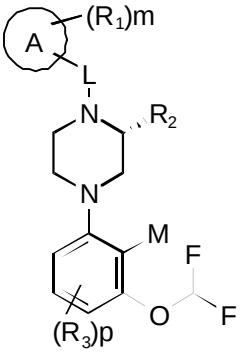
III-1 ,


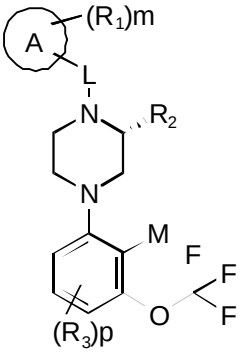
III-2 ,


III-3 ,


III-4 ,


III-5 ,


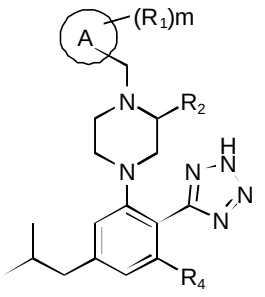
III-6 ,


III-7 , and


III-8 , where

ring A, M, L, R_1, R_2, R_3, m, and p are as defined in claim 1.

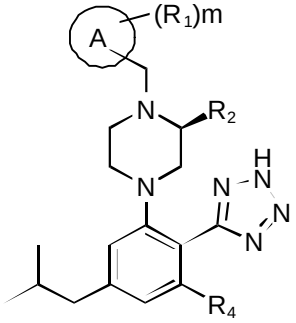
4. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has a structure represented by:



IV ,

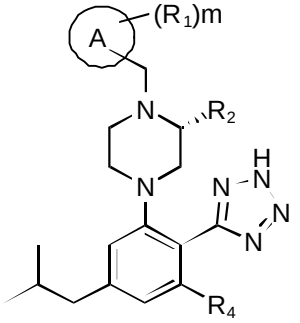
where ring A, R_1, m, R_2, and R_4 are as defined in claim 1; and/or

wherein the compound has a structure represented by:



IVa

or

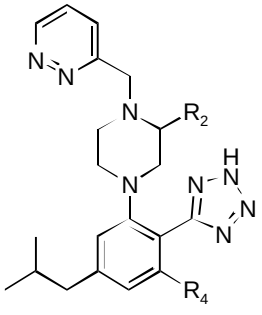


IVb ,

where ring A, R_1, R_2, R_4, and m are as defined in claim 1.

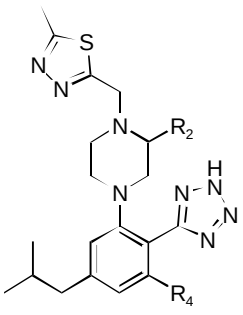
5. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1 or 4, wherein:

the compound has a structure represented by:



II

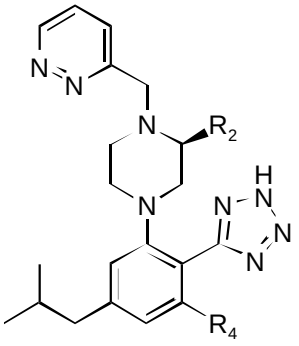
or



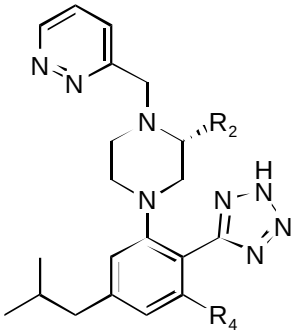
V ,

where R_2 and R_4 are as defined in claim 1, and/or

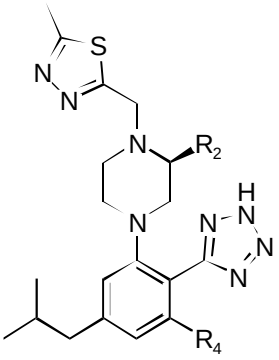
the compound has a structure represented by Formula IIa, Formula IIb, Formula Va, or Formula Vb:



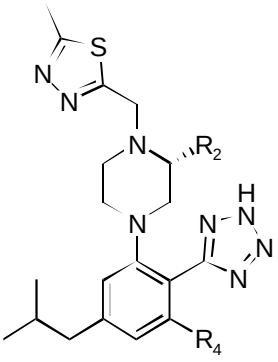
IIa ,



IIb ,



Va , or



Vb ,

where R_2 and R_4 are as defined in claim 1.

6. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to any one of claims 1, 4, and 5, satisfying one or more of the following conditions 2a) to 2e):

2a) R_4 is selected from $-CHF_2$, $-CH_2F$, and -(C_0 to C_3 alkyl)-O-(halogenated C_1 to C_3 alkyl), wherein the -(C_0 to C_3 alkyl)-O-(halogenated C_1 to C_3 alkyl), if present, is optionally substituted with one to four substituents selected from hydroxyl, amino, C_3 to C_7 heterocycloalkyl, C_1 to C_3 alkyl, C_3 to C_6 cycloalkyl, and C_1 to C_3 alkoxy;

2b) R_4 is selected from $-CHF_2$, $-CH_2F$, and -O-(halogenated C_1 to C_3 alkyl);

2c) R_4 is selected from $-CHF_2$, $-CH_2F$, and -O-(C_1 to C_3 fluoroalkyl);

2d) R_4 is selected from $-CHF_2$, $-CH_2F$, and -O-fluoromethyl; and

2e) R_4 is selected from $-CHF_2$, $-CH_2F$, $-O-CHF_2$, and $-O-CF_3$.

7. The compound, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to any one of claims 1, 3, 4, and 5, satisfying one or more of the following conditions 3a) to 3c):

3a) R_2 is selected from oxo (=O), C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_3 to C_6 cycloalkyl, a 5-

to 6-membered heterocyclic ring, and a benzene ring, wherein the C_1 to C_3 alkyl, the C_1 to C_3 alkoxy, the C_3 to C_6 cycloalkyl, the 5- to 6-membered heterocyclic ring, and the benzene ring are optionally substituted with one, two, three, or four substituents selected from halogen, hydroxyl, cyano, amino, C_1 to C_3 alkyl, C_1 to C_3 alkoxy, and C_3 to C_6 cycloalkyl, and n is selected from 0, 1, 2, 3, 4, 5, 6, 7, or 8;

3b) R_2 is selected from oxo (=O), C_1 to C_3 alkyl, and halogenated C_1 to C_4 alkyl, and n is selected from 0, 1, 2, 3, and 4; and

3c) R_2 is selected from methyl and halogenated methyl, and n is selected from 0 or 1.

8. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, satisfying one or more of the following conditions 4a) to 4i):

4a) R_3 is selected from halogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl, wherein the C_1 to C_6 alkyl, the C_1 to C_6 alkoxy, and the C_3 to C_7 cycloalkyl are optionally substituted with one to four substituents selected from halogen, hydroxyl, cyano, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, and C_3 to C_7 cycloalkyl, and p is selected from 0, 1, 2, 3, or 4;

4b) R_3 is selected from F, C_1 to C_5 alkyl, halogenated C_1 to C_5 alkyl, and methyl-cyclopropyl, and p is selected from 1, 2, and 3; and

4c) R_3 is selected from F, methyl, trifluoromethyl, isobutyl, fluorinated isobutyl, and methyl-cyclopropyl, and p is selected from 1;

4d) M is selected from carboxylic group, $-CONHSO_2R_5$, $-SO_2NHCOR_5$, tetrazole, or a tetrazole bioisostere;

4e M is selected from carboxylic group, $-CONHSO_2R_5$, $-SO_2NHCOR_5$, and tetrazole, R_5 being selected from C_1 to C_3 alkyl and C_3 to C_5 cycloalkyl; and

4f M is selected from tetrazole; or

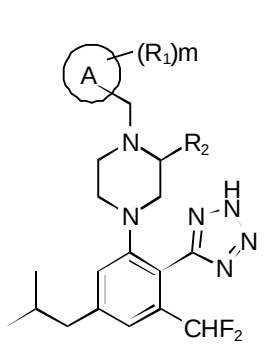
4g) L is absent or selected from methylene, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)-$, $-O-CH_2-$, and $-NH-CH_2-$;

4h) L is selected from methylene, $-CH_2CH_2-$, $-CH(CH_3)-$, and $-O-CH_2-$; and

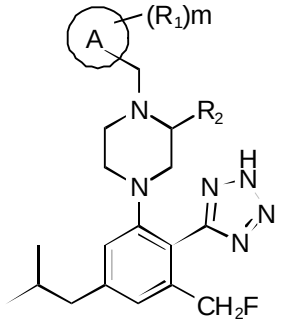
4i) L is selected from methylene.

9. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has a

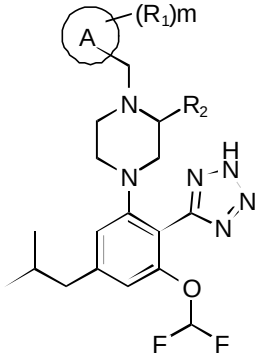
structure selected from:



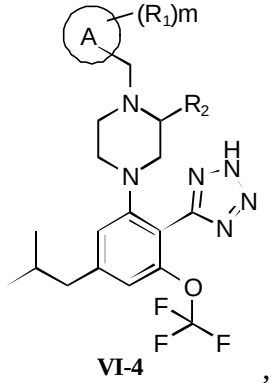
VI-1 ,



VI-2 ,



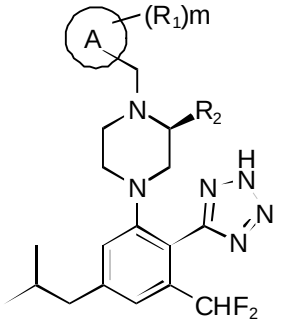
VI-3 , and



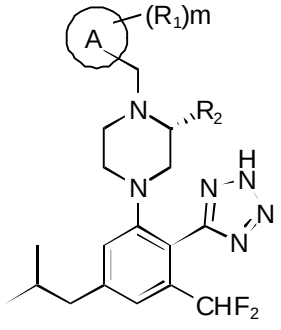
VI-4 ,

where ring A, R_1, R_2, and m are as defined in claim 1.

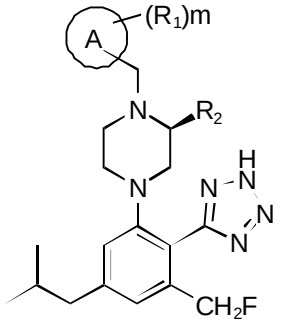
10. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has a structure represented by Formula VI-1a, Formula VI-1b, Formula VI-2a, Formula VI-2b, Formula VI-3a, Formula VI-3b, Formula VI-4a, or Formula VI-4b:



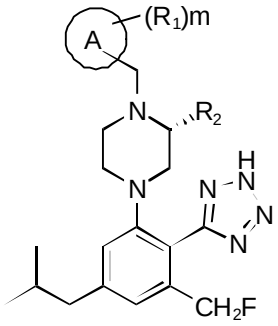
VI-1a ,



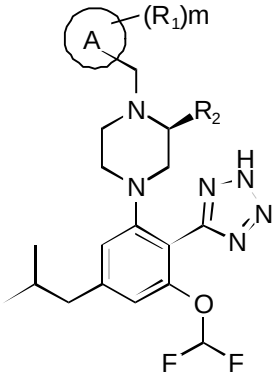
VI-1b ,



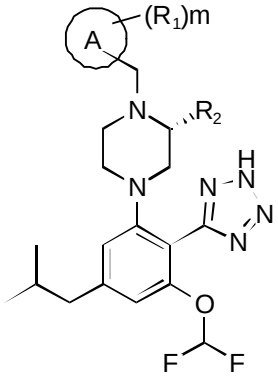
VI-2a ,



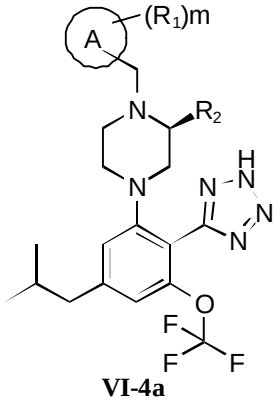
VI-2b ,



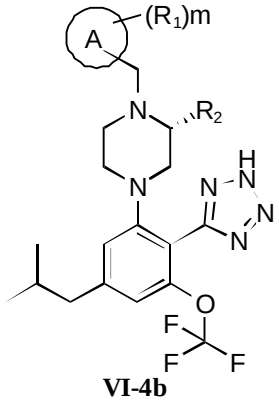
VI-3a ,



VI-3b ,

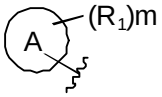


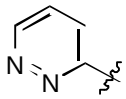
VI-4a , or

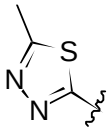


VI-4b ,

where ring A, R_1, R_2, and m are as defined in claim 1.

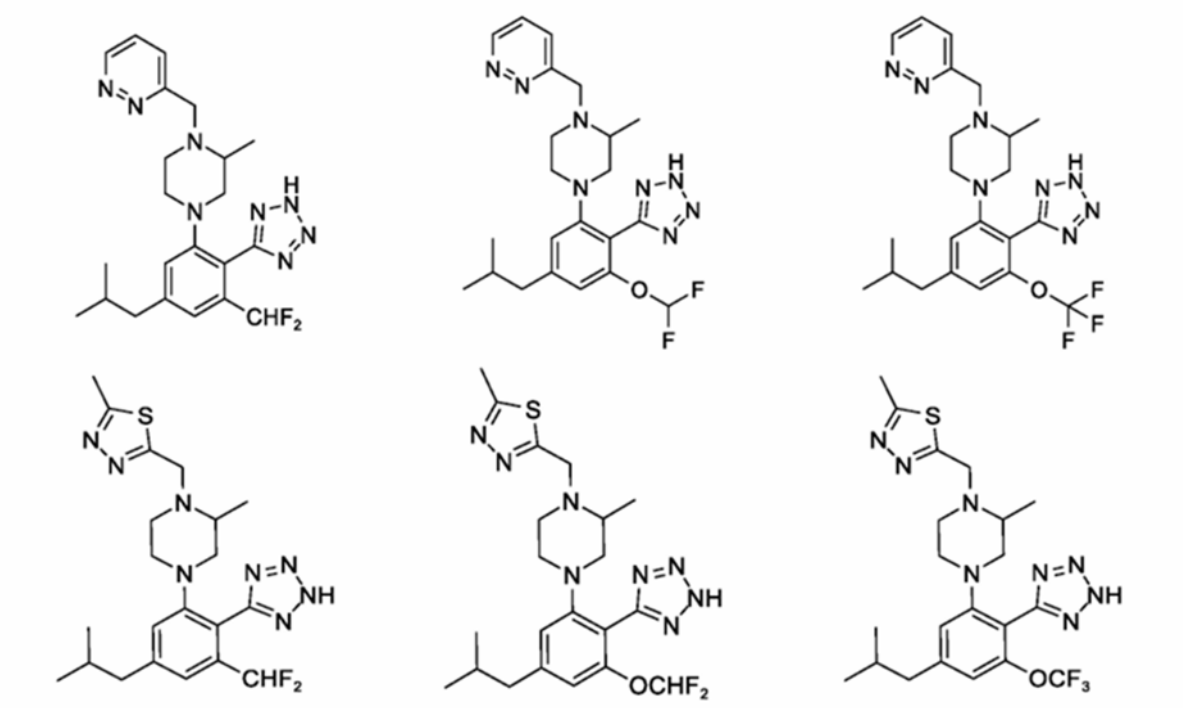
11. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to any one of claims 1, 3, 4, 9, and 10, wherein 

is 

or 

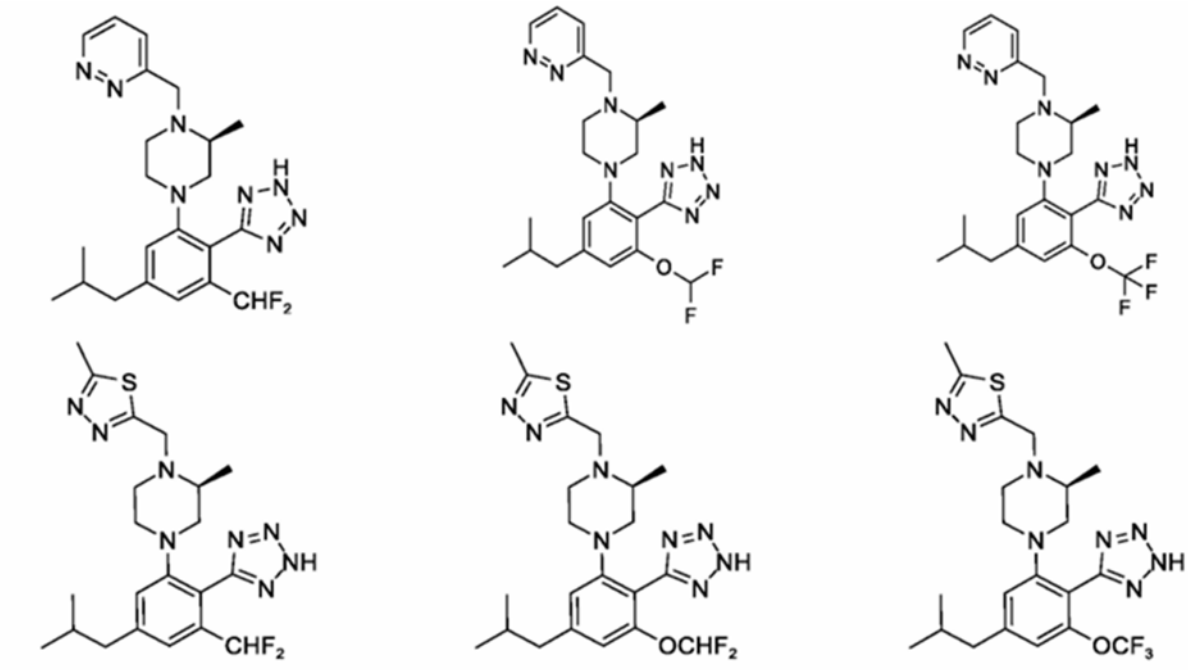
.

12. The compound, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound comprises:



.

13. The compound represented by Formula I, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound comprises:



.

14. A pharmaceutical composition, comprising:

the compound, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 13; and

a pharmaceutically acceptable carrier.

15. Use of the compound, or the tautomer, stereoisomer, or pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, or the pharmaceutical composition according to claim 14, the use comprising:

acting as an AT2R antagonist; and/or

preventing and/or treating an AT2R-mediated disease; and/or

preventing and/or treating a disease where a reduced effect of Ang II is desired or required; and/or

preventing and/or treating a disease where AT2R is expressed and an inhibition of AT2R is desired or necessary; and/or

preparing a medicament, pharmaceutical composition, or formulation as an AT2R antagonist; and/or

preparing a medicament, pharmaceutical composition, or formulation for preventing and/or treating a disease where AT2R is expressed and an inhibition of AT2R is desired or necessary;

preferably, the disease is neuropathy or neuropathic pain; and

preferably, the disease is primary neuropathy, secondary neuropathy, peripheral neuropathy, neuropathy caused by mechanical nerve injury or biochemical nerve injury, postherpetic neuralgia, diabetic neuropathic pain, or a diabetes-related neuropathic disease.