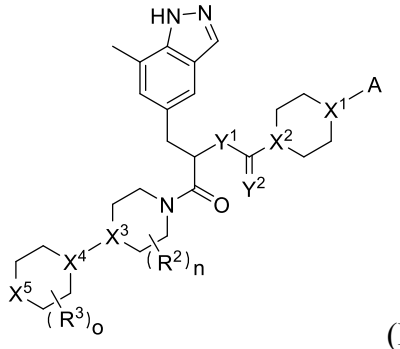
Claims

1. A compound as represented by the following formula I, or an isomer, pharmaceutically acceptable salt or solvate thereof:



(I)

wherein,

X^1 and X^2 are respectively independently CH or N, and X^2 is preferably N;

X^3 and X^4 are respectively independently C, CH or N;

X^5 is C, CH, CH_2, NH or N;

Y^1 is CH_2, O or NH, and Y^1 is preferably O or NH;

Y^2 is O or S, and Y^2 is preferably O;

R^2 is independently -H, -(C_1-C_6)alkyl or -(C_3-C_8)cycloalkyl when occurring each time, and n is 0, 1, 2, 3, 4, 5 or 6,

or, two R^2 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^2 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

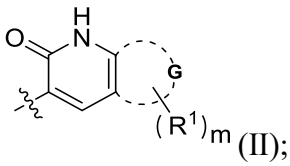
or, -$(R^2)_n$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -$(R^2)_n$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

R^3 is independently -H, -(C_1-C_6)alkyl or -(C_3-C_8)cycloalkyl when occurring each time, and o is 0, 1, 2, 3, 4, 5 or 6,

or, two R^3 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^3 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, -$(R^3)_o$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -$(R^3)_o$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

A has a structure as represented by the following formula II:


(II);

a G-chain group forms a 5-7 membered aliphatic ring or aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, and ring-forming heteroatoms in the aliphatic heterocyclic ring are -O-, -S- or ;

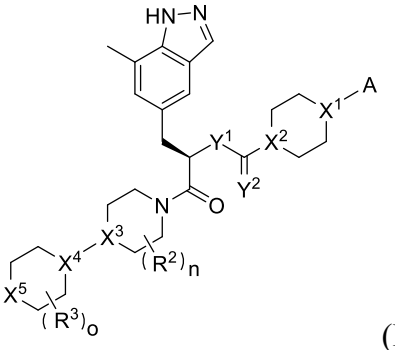
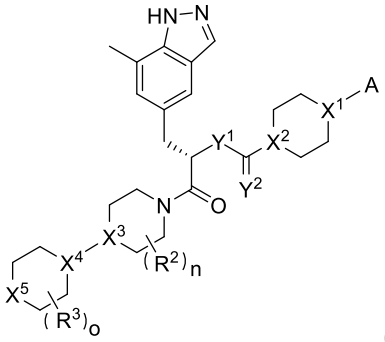
R^1 is independently -H, -(C_1-C_6)alkyl or -(C_3-C_8)cycloalkyl when occurring each time, and m is 0, 1, 2, 3, 4, 5 or 6,

or, two R^1 form a 3-8 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, $-(R^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S.

2. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1:

wherein, the compound is as represented by formula I-2 or I-3:


(I-2) and 
(I-3).

3. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, in A:

in a case that the G-chain group forms a 5 or 6 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds;

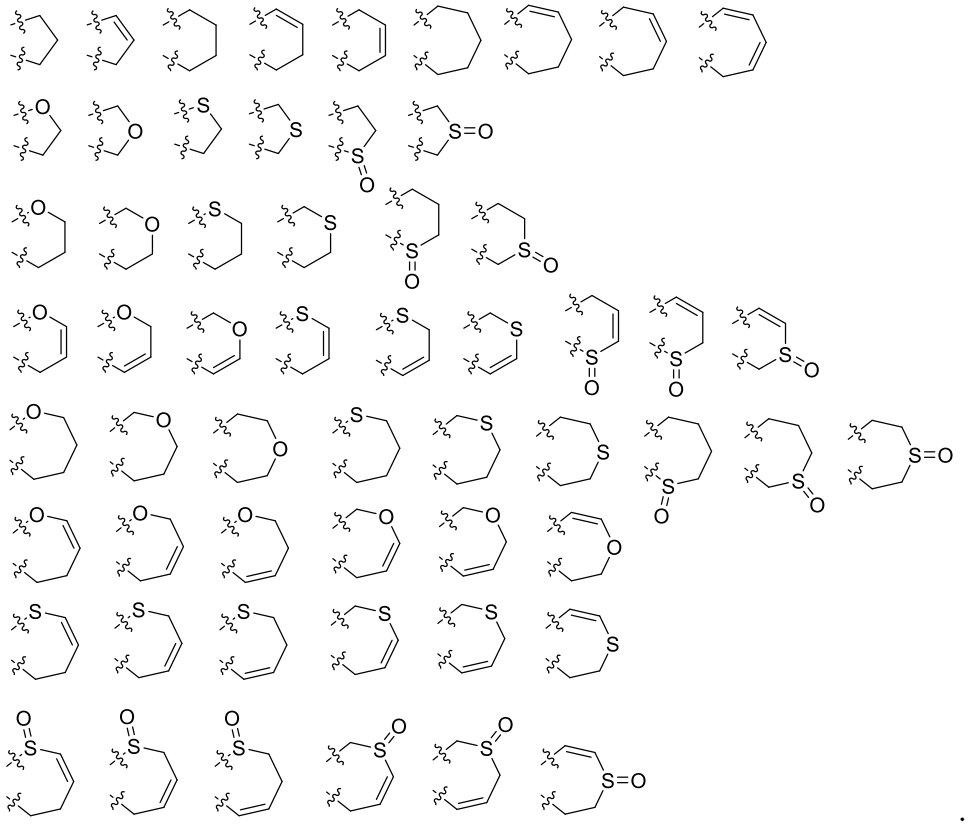
in a case that the G-chain group forms a 7 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0, 1 or 2 double bonds, and the remaining bonds are all single bonds;

in a case that the G-chain group forms a 5 membered aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, bonds on the G-chain group are all single bonds; and

in a case that the G-chain group forms a 6 or 7 membered aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds;

or

wherein, in A, the G-chain group is selected from:



.

4. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, in A,

R^1 is independently -H, -(C_1-C_3)alkyl or -(C_3-C_6)cycloalkyl when occurring each time, and m is 0, 1, 2 or 3,

or, two R^1 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attaches, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, -$(R^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -$(R^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

preferably, wherein, in A,

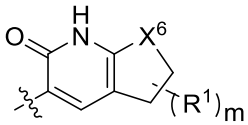
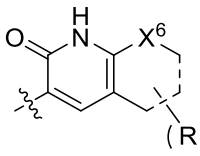
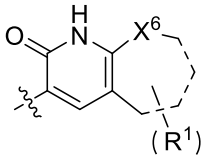
R^1 is independently -H, methyl, ethyl or cyclopropyl when occurring each time, and m is 0, 1 or 2,

or, two R^1 form cyclopropane, cyclobutane or cyclopentane together with atoms linked to the R^1, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach,

or, -$(R^1)_m$ forms cyclopropane, cyclobutane or cyclopentane together with atoms to which -$(R^1)_m$ attach, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -$(R^1)_m$ attach.

5. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1, 2, or 4:

wherein, A has a structure as represented by the following formula II-1, II-2 or II-3:


(II-1),

(II-2) and

(II-3);

in the formulas II-1, II-2 and II-3, X^6 is -O-, -S- or ;

in the formula II-2, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond; and

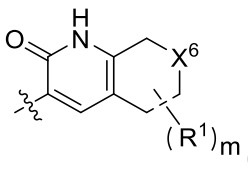
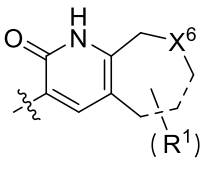
in the formula II-3, three "---" all refer to single bonds, or any one of the three "---" is a double bond and the other two are both single bonds.

6. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 5:

wherein, Y^2 is S, and X^6 is -S-.

7. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1, 2, or 4:

wherein, A has a structure as represented by the following formula II-4 or II-5:


(II-4) and

(II-5);

in the formula II-4 or II-5, X^6 is -O-, -S- or ;

in the formula II-4, "---" refers to a single bond or a double bond; and

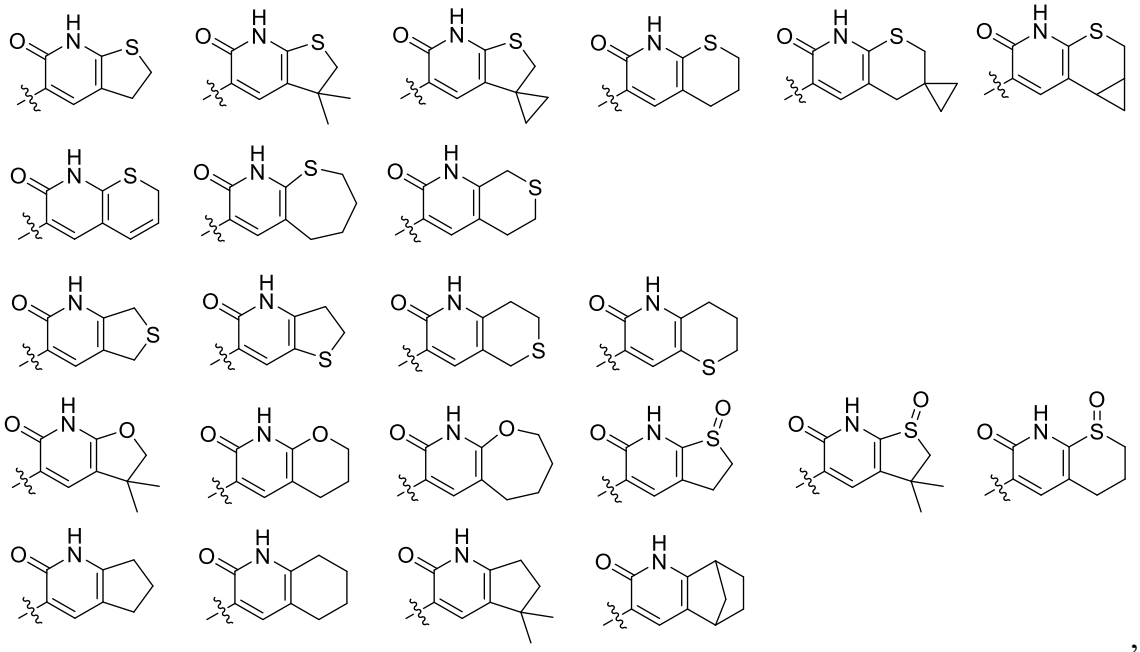
in the formula II-5, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond.

8. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, the G-chain group in A forms a 5-7 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, and m is 0.

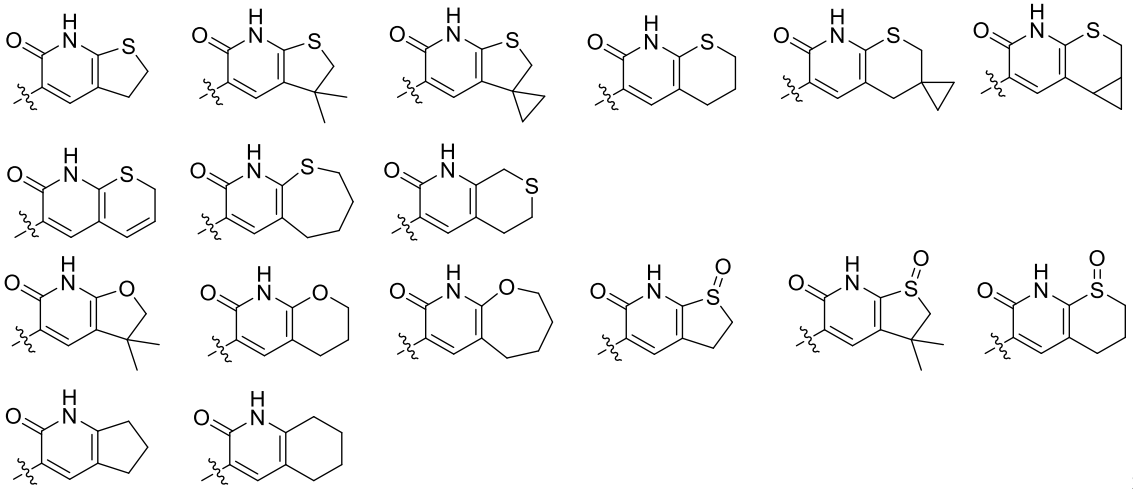
9. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, A is selected from:



, and

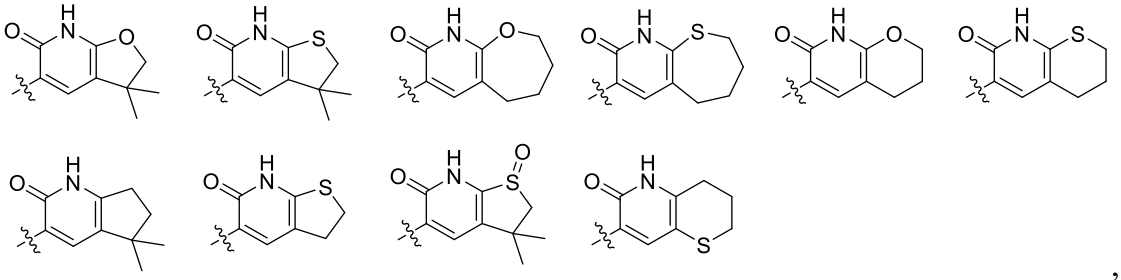
A is further preferably selected from:



;

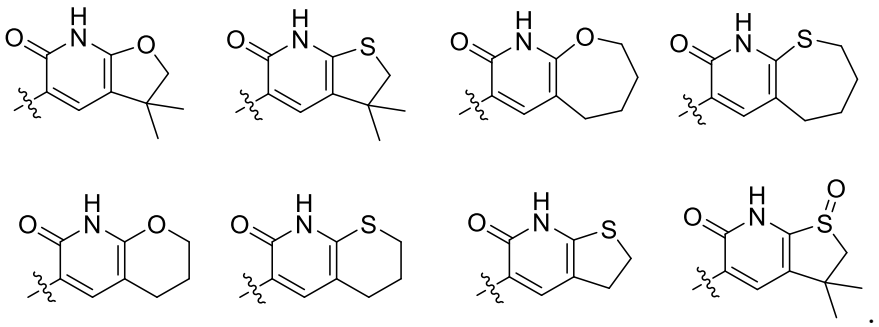
or

wherein, A is selected from:



, and

A is further preferably selected from:



10. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, R^2 is independently -H, -(C_1-C_3)alkyl or -(C_3-C_6)cycloalkyl when occurring each time, and n is 0, 1, 2 or 3,

or, two R^2 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms,

or, -$(R^2)_n$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -$(R^2)_n$ attach, and ring-carried atoms provided by -$(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms;

R^3 is independently -H, -(C_1-C_3)alkyl or -(C_3-C_6)cycloalkyl when occurring each time, and o is 0, 1, 2 or 3,

or, two R^3 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms,

or, -$(R^3)_o$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to wihch -$(R^3)_o$ attach, and ring-carried atoms provided by the -$(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms;

preferably, wherein, R^2 is independently -H, methyl, ethyl, cyclopropyl or cyclobutyl when occurring each time, and n is 0, 1 or 2,

or, two R^2 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms,

or, -$(R^2)_n$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -$(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which -$(R^2)_n$ attach, and ring-carried atoms provided by -$(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms;

R^3 is independently -H, -(C_1-C_3)alkyl or -(C_3-C_6)cycloalkyl when occurring each time, and o is 0, 1, 2 or 3,

or, two R^3 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms,

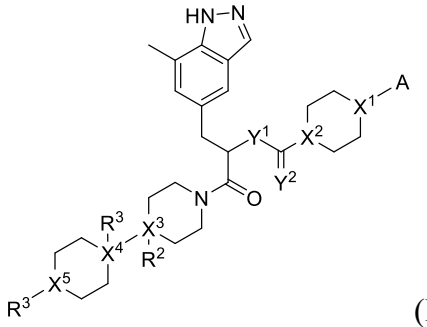
or, $-(R^3)_o$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which $-(R^3)_o$ attach, and ring-carried atoms provided by the $-(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms.

11. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1 or 2:

wherein, X^3 and X^4 are not N at the same time.

12. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1:

the compound is as represented by the following formula I-1:



(I-1),

wherein, X^1, X^2, X^3, X^4, X^5, Y^1 and Y^2 are as defined in claim 1, and A is as defined in claim 4 or 9; and

R^2 and R^3 are independently -H, $-CH_3$ or absent when occurring each time.

13. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1, 2 or 12:

wherein, more than one H in the compound are substituted by D.

14. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 13:

wherein, more than one H in R^3 are substituted by D;

or

wherein, R^3 attached to X^5 is $-CD_3$.

15. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1, 2 or 12:

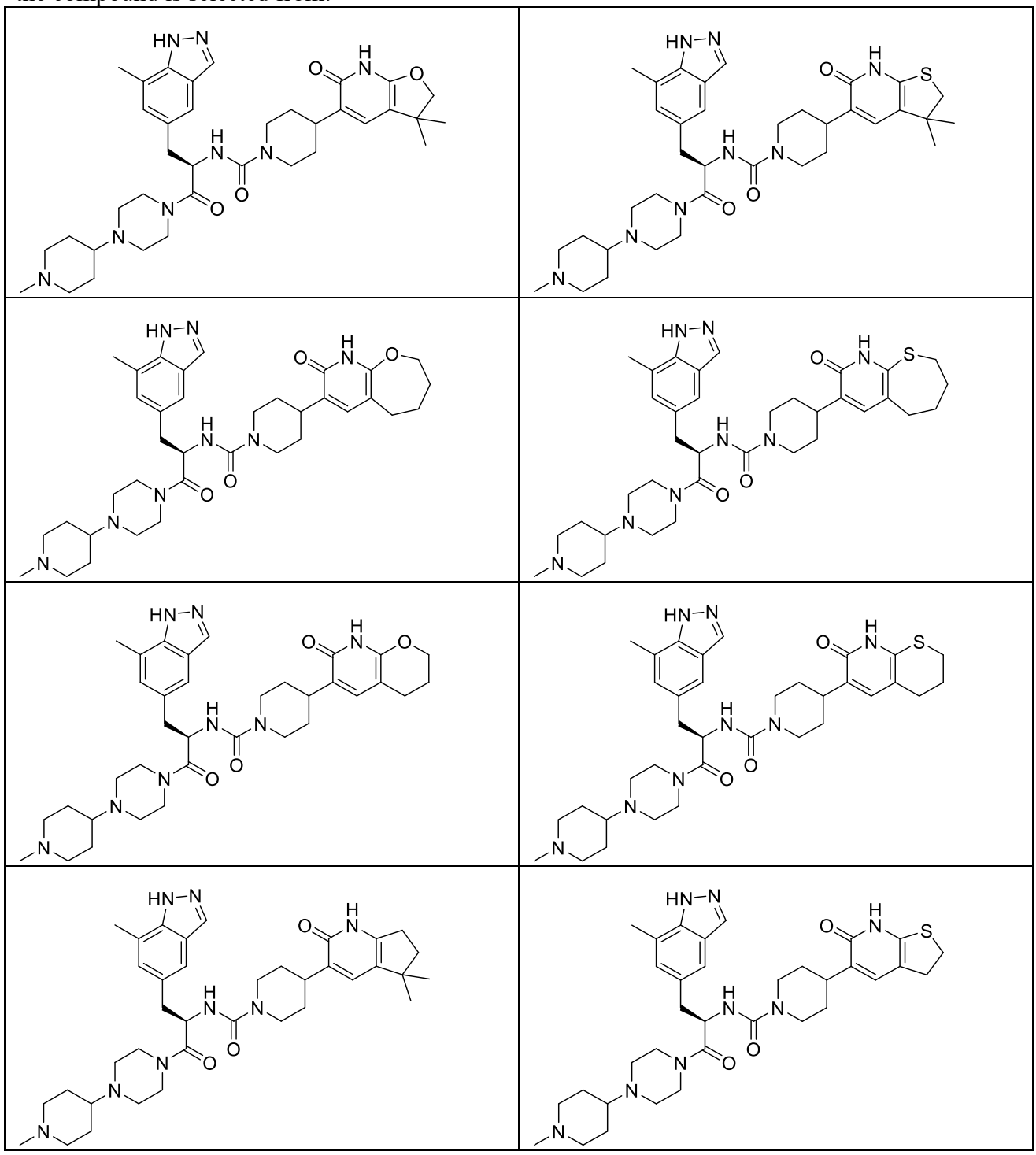
wherein, H on a ring of a pyrazole group in indazolyl in the compound are substituted by D.

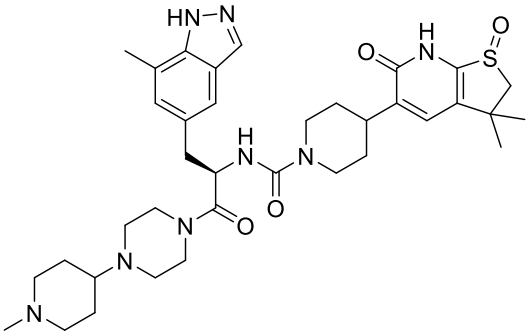
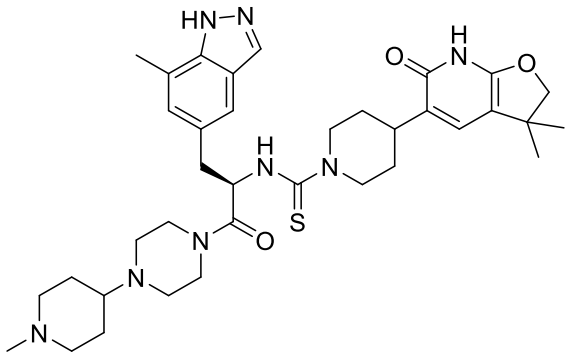
16. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 3:

wherein, more than one H in the G-chain group or R^1 are substituted by D.

17. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 1:

the compound is selected from:

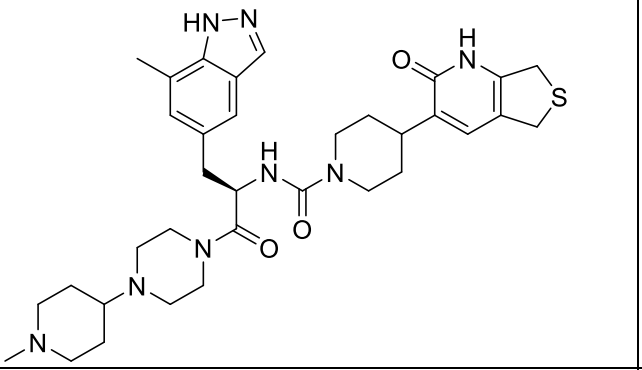
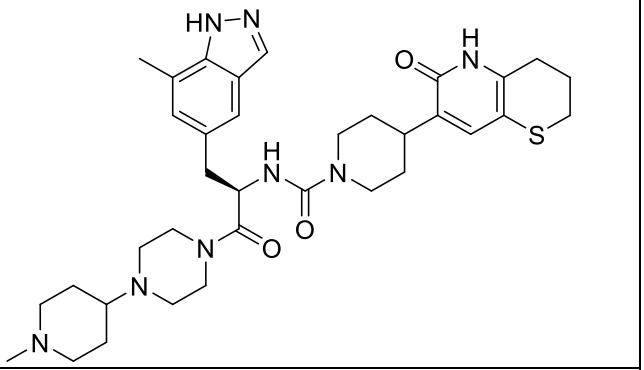
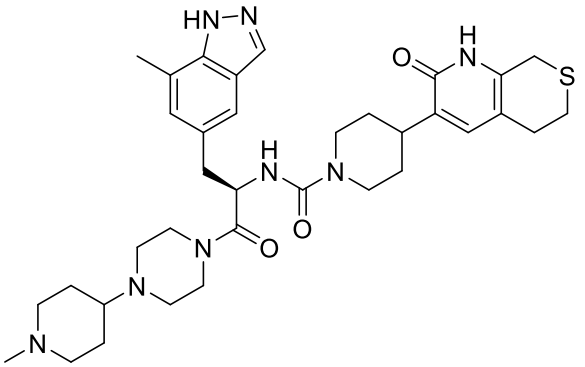
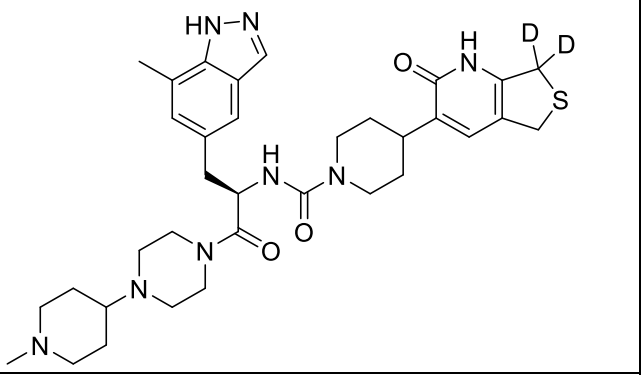
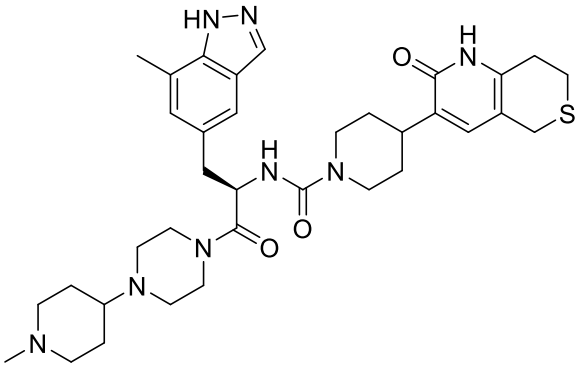
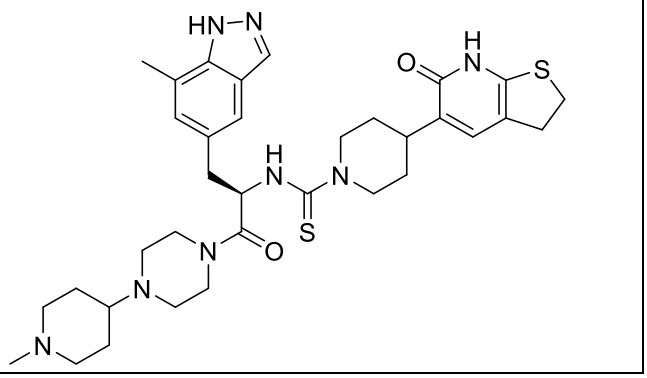


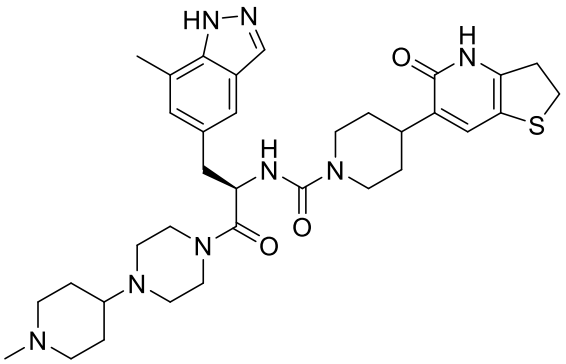
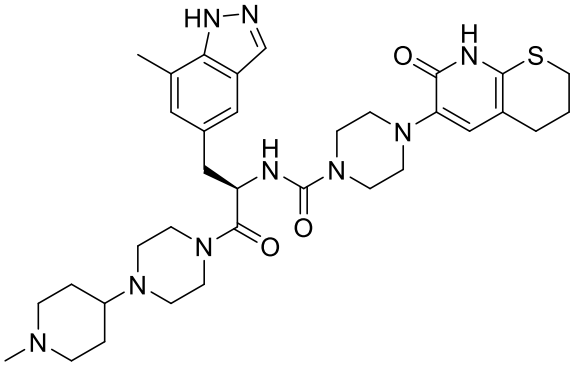
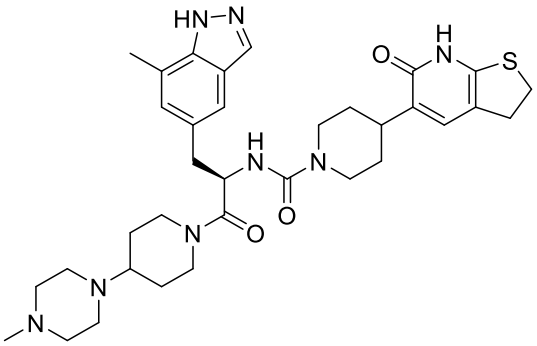
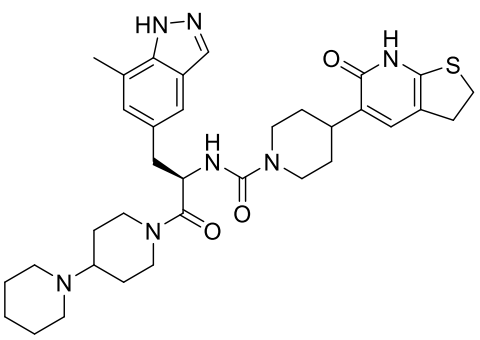
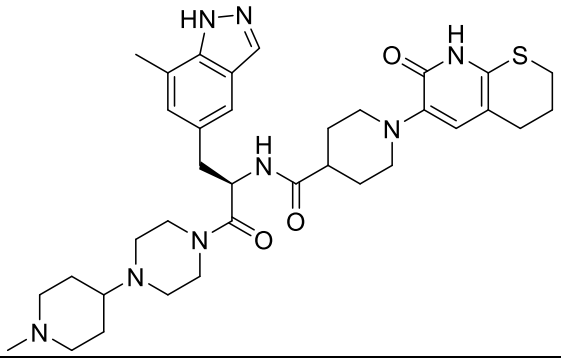
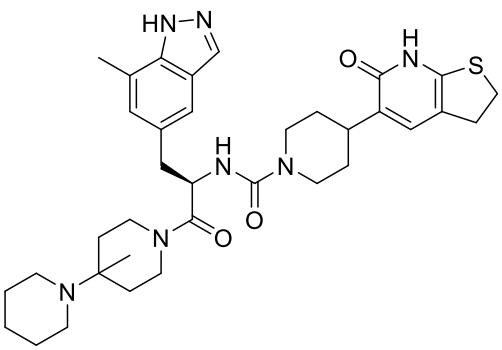
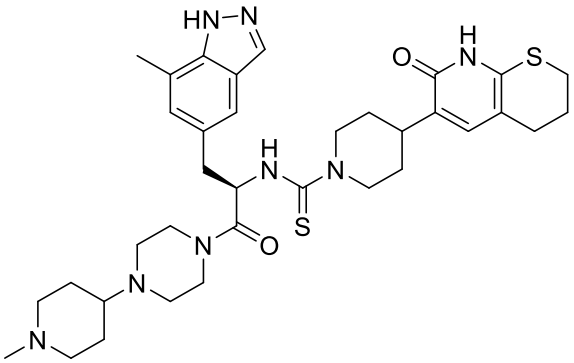
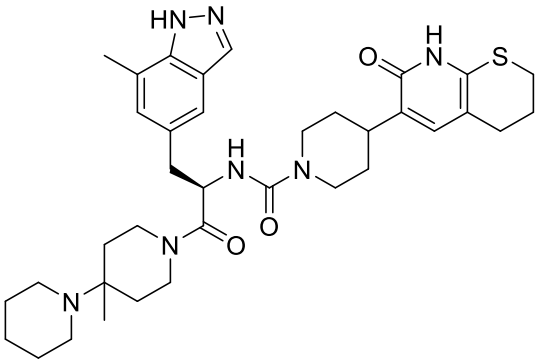
	

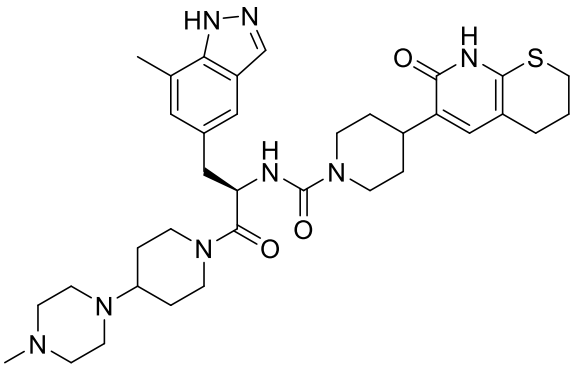
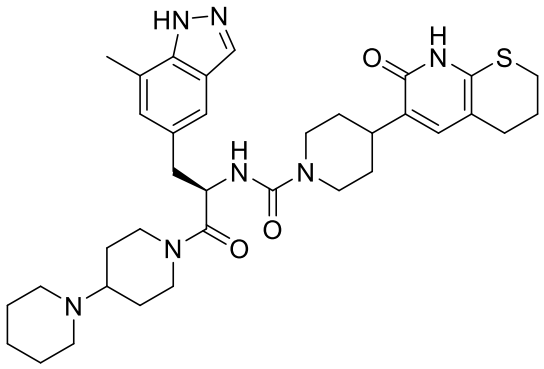
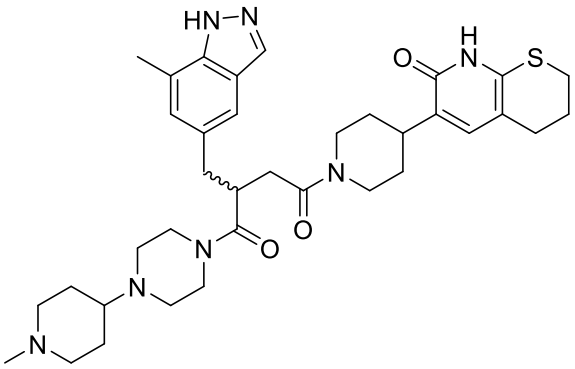
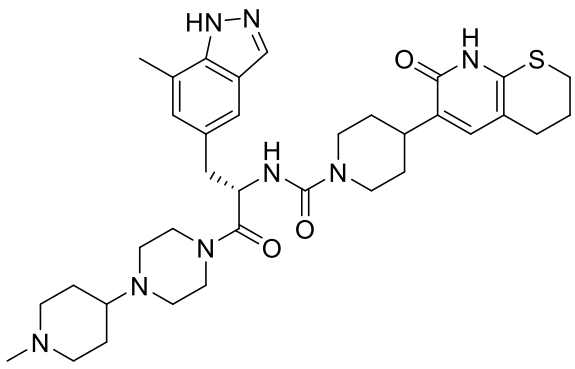
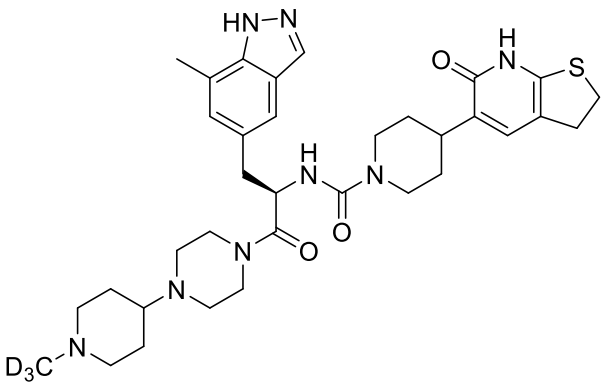
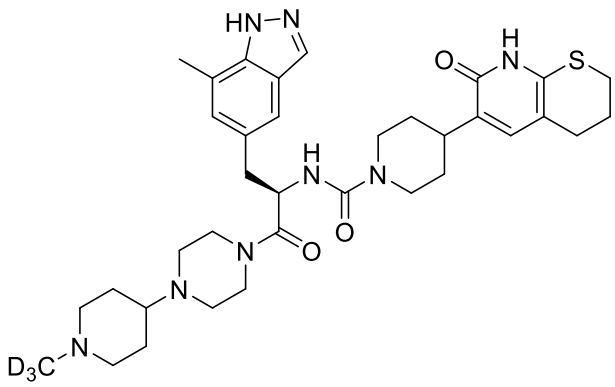
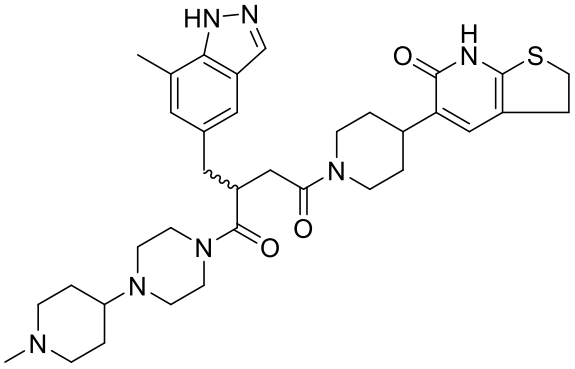
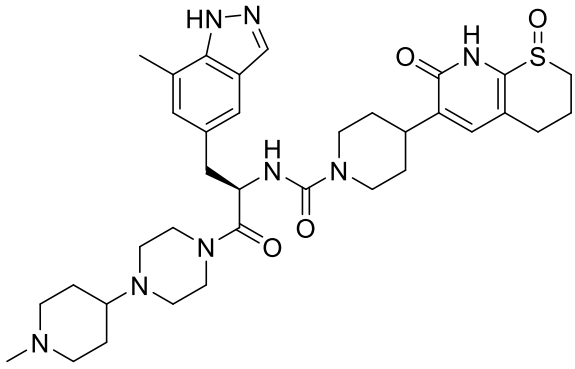
;

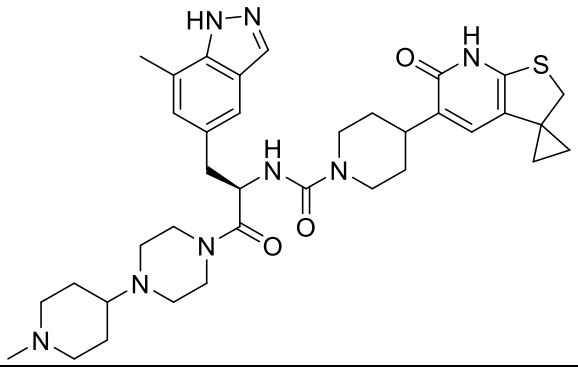
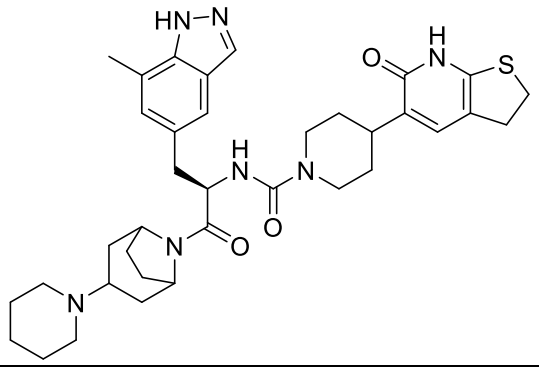
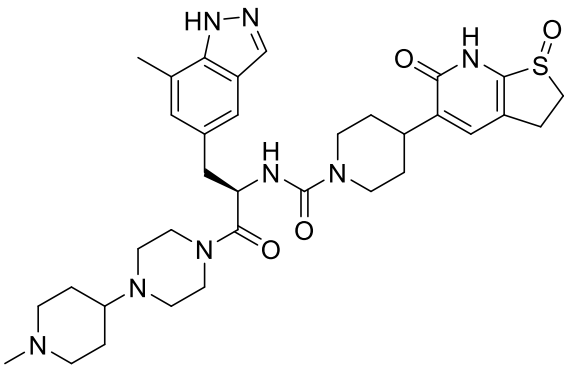
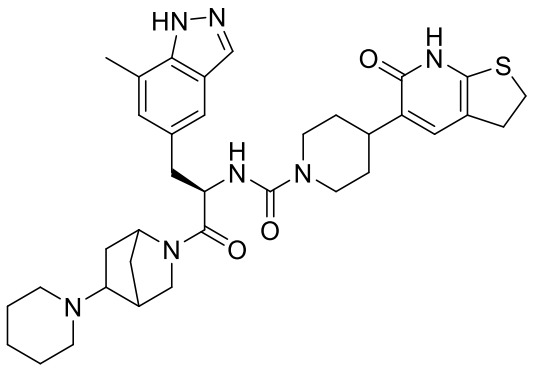
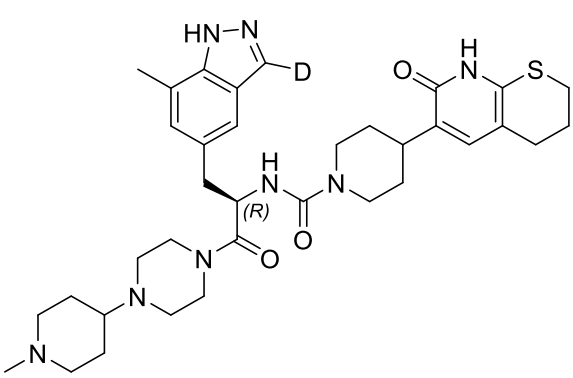
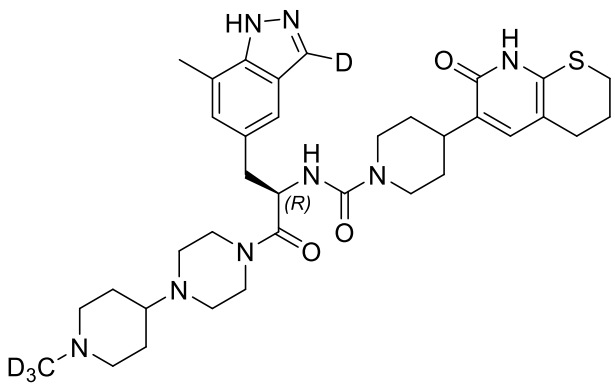
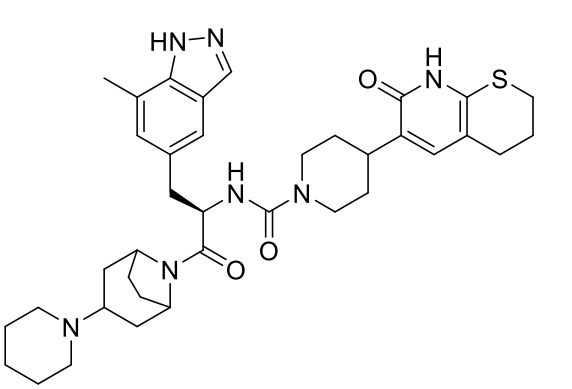
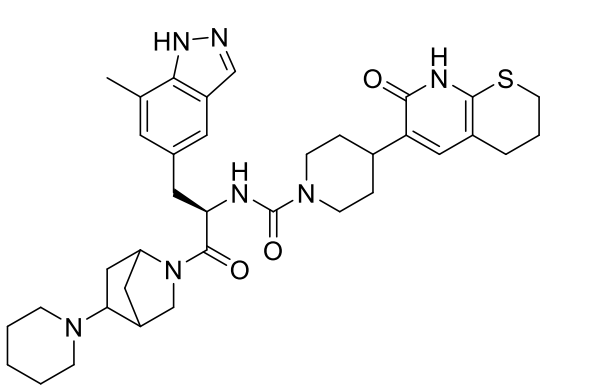
or

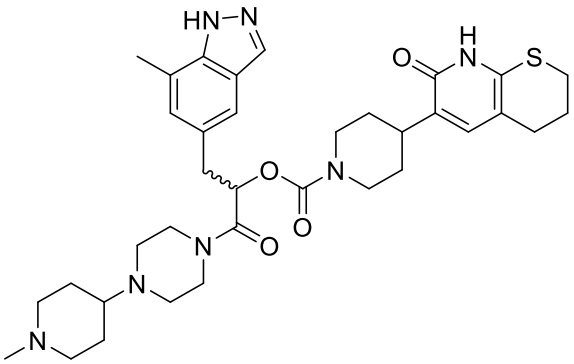
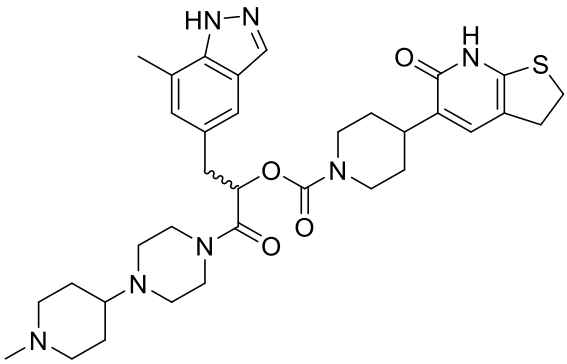
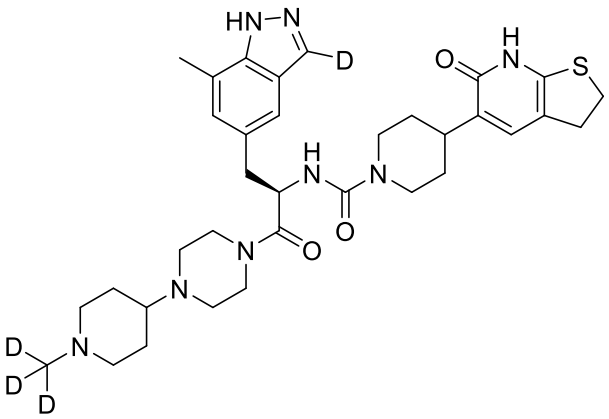
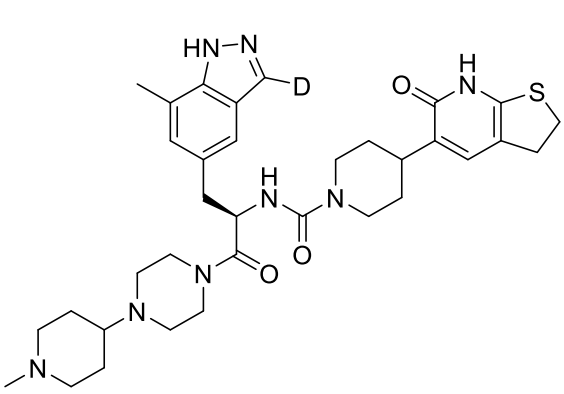
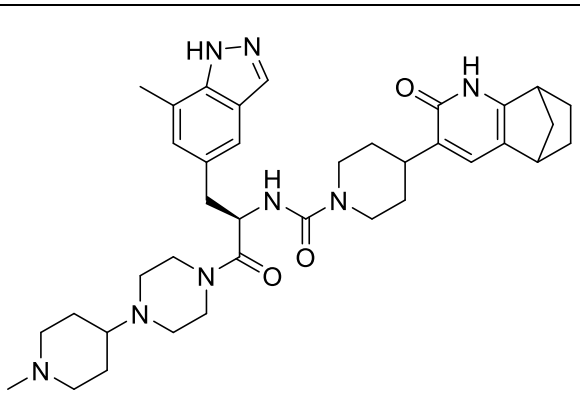
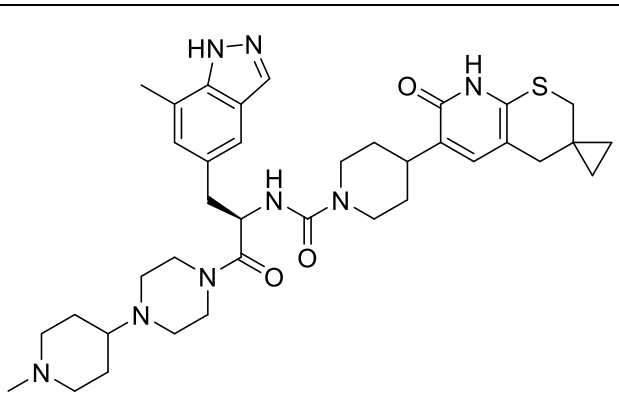
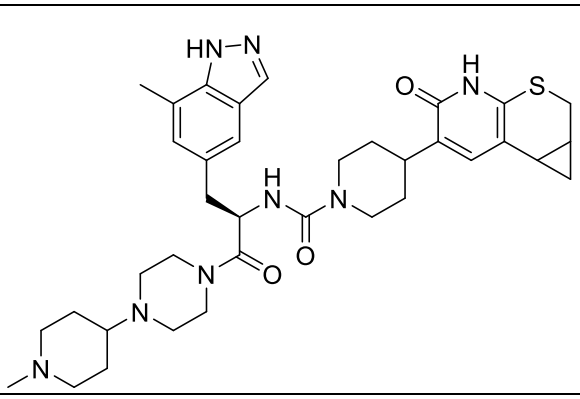
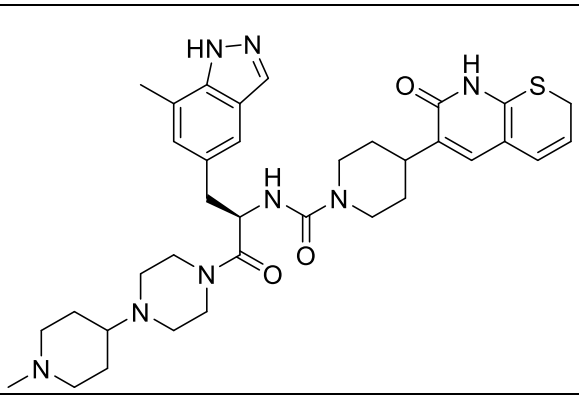
the compound is selected from:

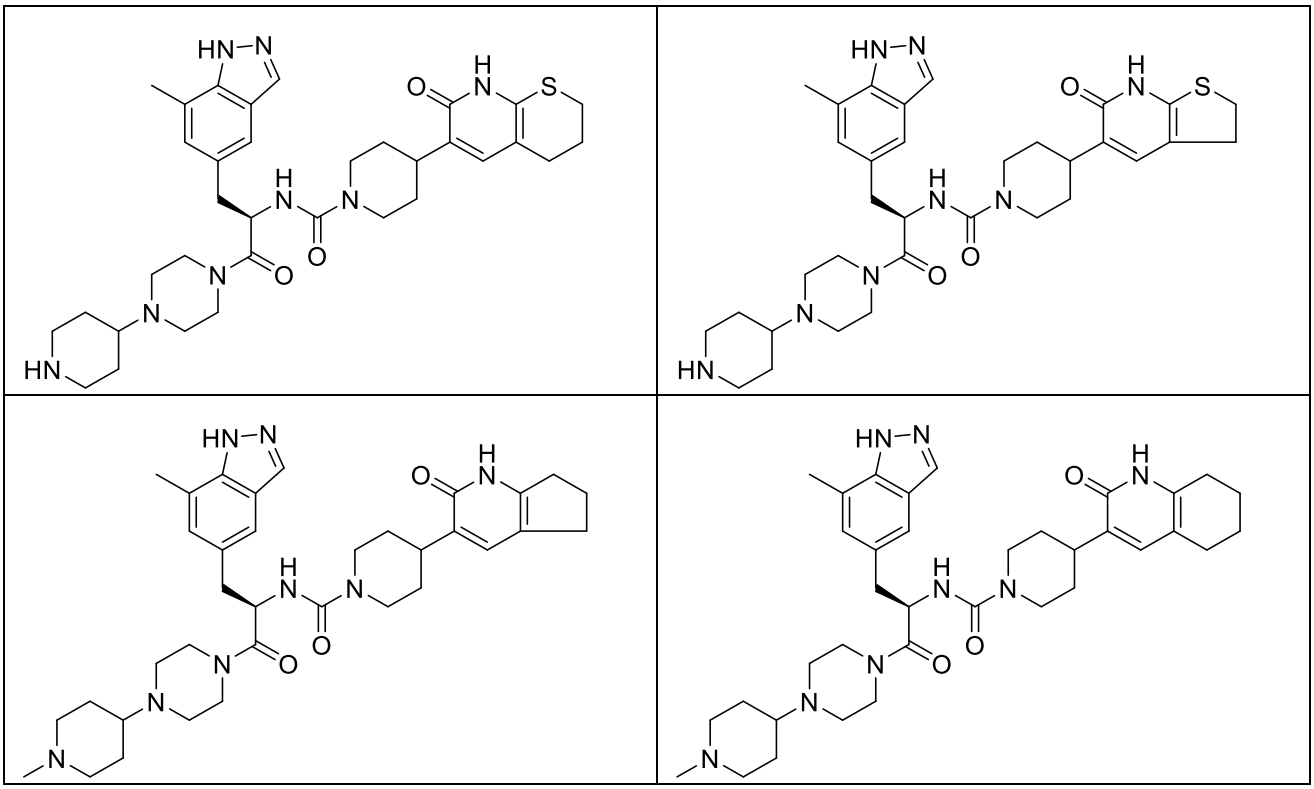
	
	
	

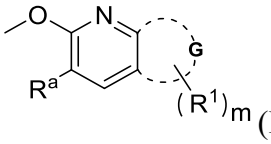


.

18. The compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 17 for use as a medicament.

19. Use of the compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 17 in the manufacture of a medicament for preventing, treating or relieving CGRP-mediated diseases, such as migraine or neuropathic pain.

20. An intermediate compound as represented by the following formula III, IV or V, or an isomer, pharmaceutically acceptable salt or solvate thereof, wherein:

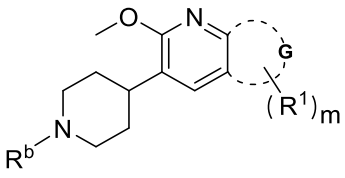
 (III),

in the formula III, R^a is Cl, Br, I, -OTf or $-B(OH)_2$, the G-chain group is as defined in any part of the compound in claim 1, 3 or 8, and R_1 and m are as defined in any part of the compound in claim 1, or 4, under conditions that:

when R^a is Br, the ring formed by the G-chain group together with the two carbon atoms attached to the G-chain group is not cyclopentane, cyclohexane and 1,4-dioxane,

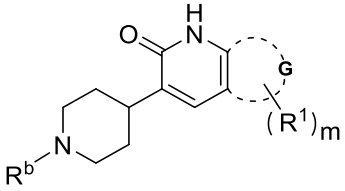
when R^a is Cl, the ring formed by the G-chain group together with the two carbon atoms attached to the G-chain group is not cyclohexane,

when the ring formed by the G-chain group together with the two carbon atoms attached to the G-chain group is tetrahydrofuran, and m is 1, R^1 is not isopropyl;

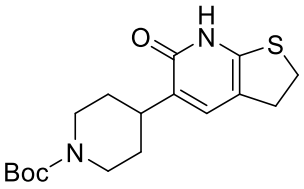
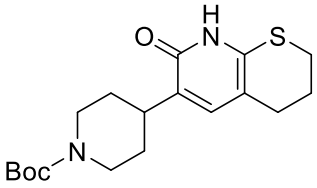

(IV),

in the formula IV, R^b is -H or an amino protecting group, and the amino protecting group is optionally -Cbz, -Boc, -Fmoc, -PMB, -Bn, -Trt, -Tos or -Alloc, and the amino protecting group is preferably -Boc,

the G-chain group is as defined in any part of the compound in claim 1, 3, or 8, and R^1 and m are as defined in any part of the compound in claim 1, or 4;


(V),

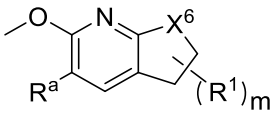
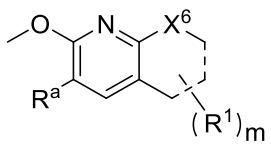
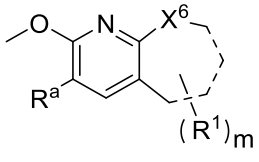
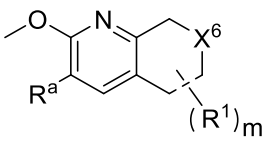
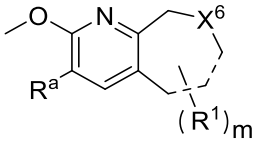
in the formula V, R^b is -H or an amino protecting group, and the amino protecting group is optionally -Cbz, -Boc, -Fmoc, -PMB, -Bn, -Trt, -Tos or -Alloc, and the amino protecting group is preferably -Boc,

when R^b is -Boc, the formula V is optionally not  or , and

the G-chain group is as defined in any part of the compound in Claim 1, 2, 3 or 7, and R^1 and m are as defined in any part of the compound in claim 1, 3 or 4.

21. The intermediate compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 20, wherein:

the intermediate compound as represented by the formula III is selected from formula III-1, III-2, III-3, III-4 or III-5,


(III-1),

(III-2),

(III-3),

(III-4) and

(III-5),

in the formulas III-1, III-2, III-3, III-4 and III-5, X^6 is -O-, -S- or ,

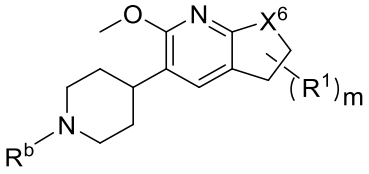
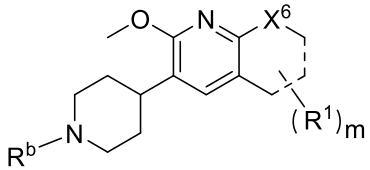
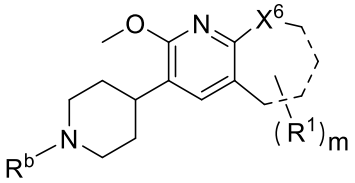
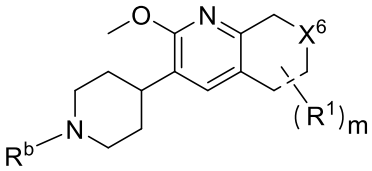
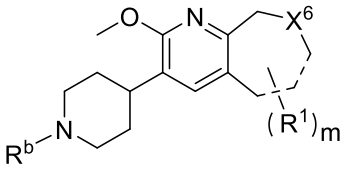
in the formula III-2, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond,

in the formula III-3, three "---" all refer to single bonds, or any one of the three "---" is a double bond and the other two are both single bonds,

in the formula III-4, "---" refers to a single bond or a double bond, and

in the formula III-5, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond;

the intermediate compound as represented by the formula IV is selected from formula IV-1, IV-2, IV-3, IV-4 or IV-5,


(IV-1),

(IV-2),

(IV-3),

(IV-4) and

(IV-5),

in the formulas IV-1, IV-2, IV-3, IV-4 and IV-5, X^6 is -O-, -S- or ,

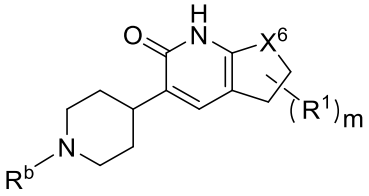
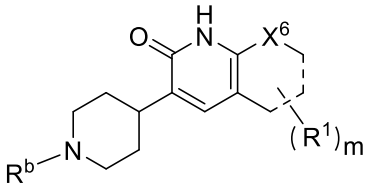
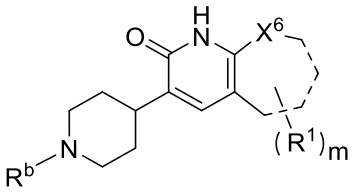
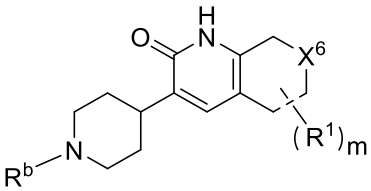
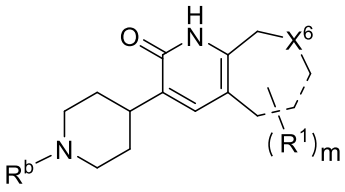
in the formula IV-2, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond,

in the formula IV-3, three "---" all refer to single bonds, or any one of the three "---" is a double bond and the other two are both single bonds,

in the formula IV-4, "---" refers to a single bond or a double bond, and

in the formula IV-5, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond;

the intermediate compound as represented by the formula V is selected from formula V-1, V-2, V-3, V-4 or V-5,


(V-1),

(V-2),

(V-3),

(V-4) and

(V-5),

in the formulas V-1, V-2, V-3, V-4 and V-5, X^6 is -O-, -S- or ,

in the formula V-2, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond,

in the formula V-3, three "---" all refer to single bonds, or any one of the three "---" is a double bond and the other two are both single bonds,

in the formula V-4, "---" refers to a single bond or a double bond, and

in the formula V-5, two "---" both refer to single bonds, or any one of the two "---" is a double bond and the other one is a single bond.

22. The intermediate compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to claim 20 or 21:

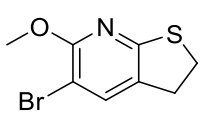
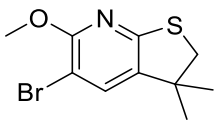
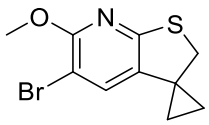
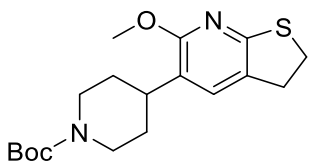
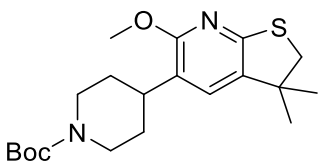
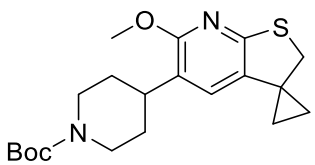
wherein, the salt is hydrochloride or trifluoroacetate;

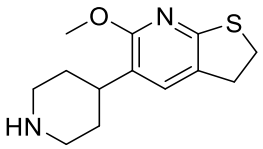
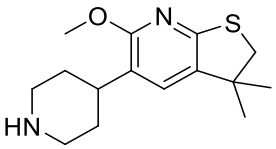
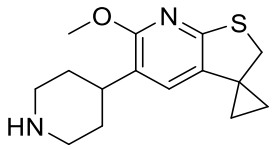
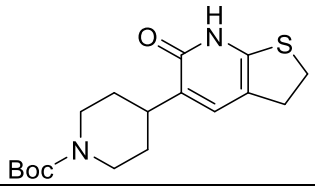
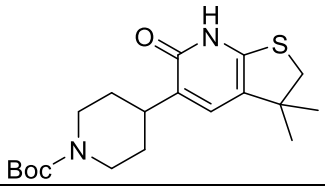
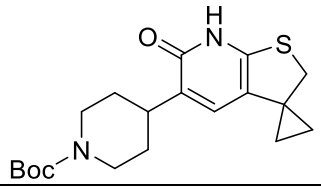
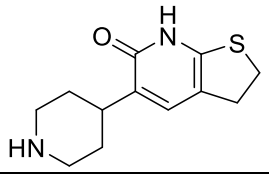
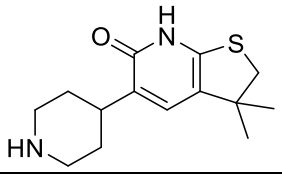
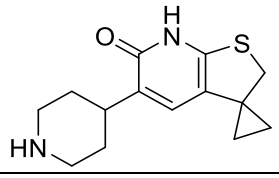
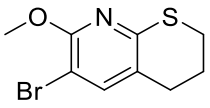
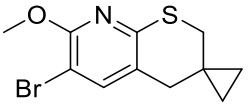
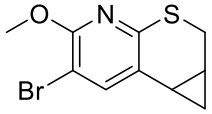
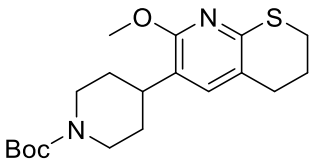
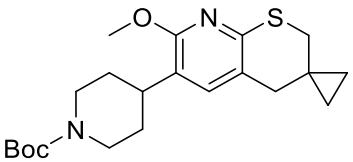
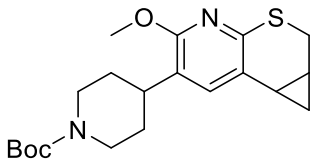
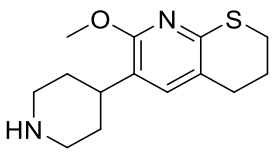
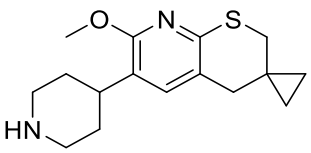
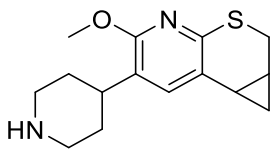
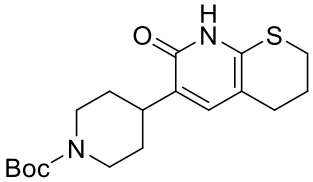
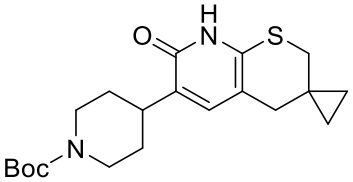
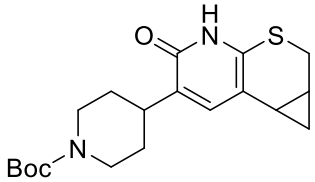
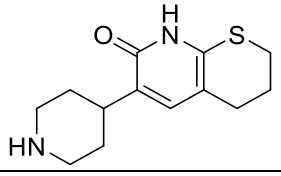
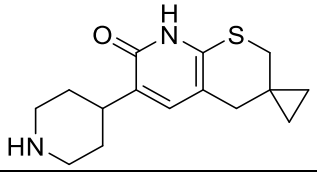
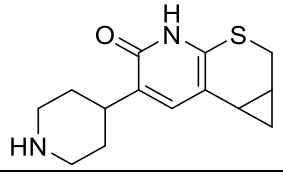
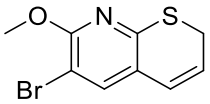
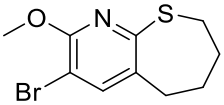
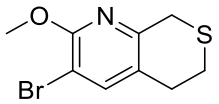
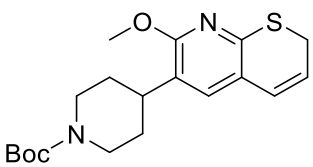
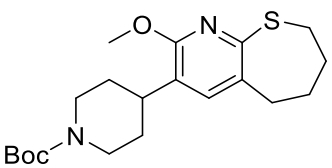
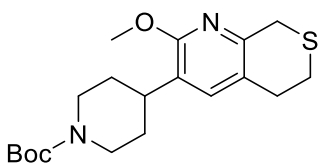
or

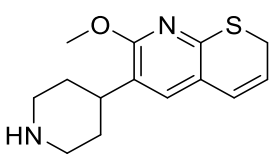
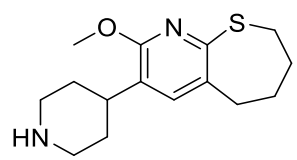
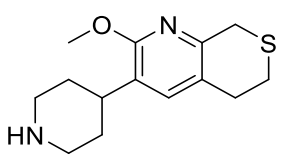
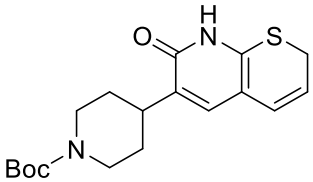
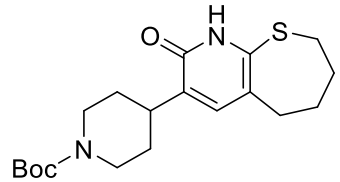
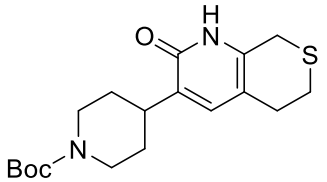
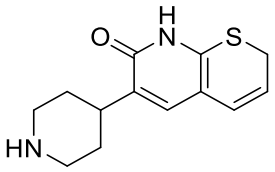
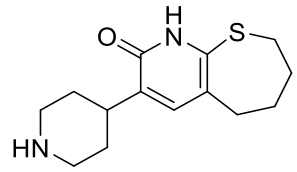
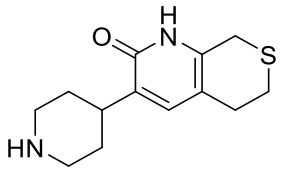
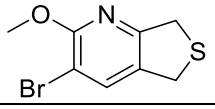
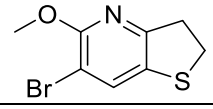
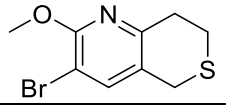
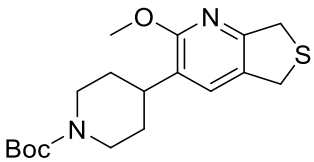
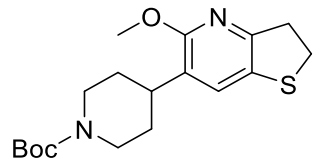
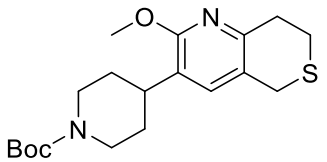
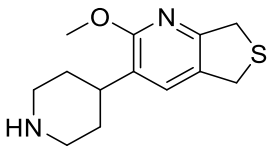
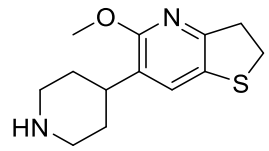
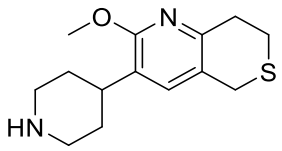
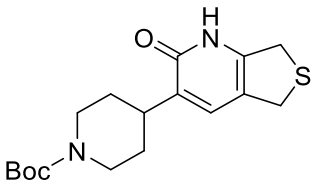
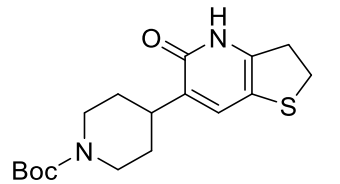
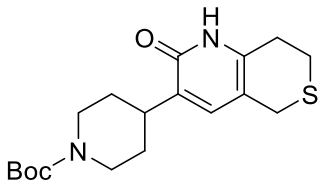
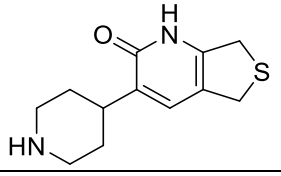
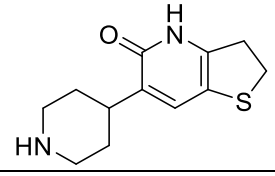
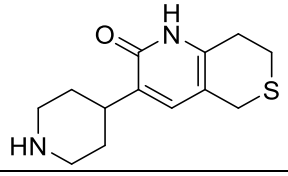
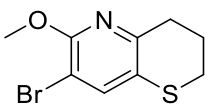
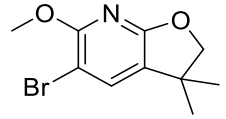
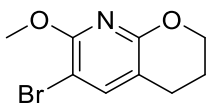
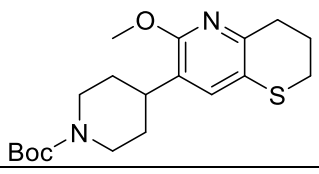
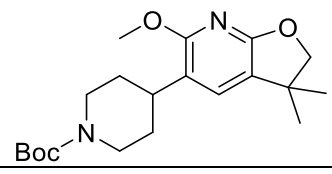
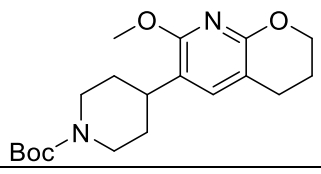
wherein, more than one H in the intermediate compound are substituted by D, and optionally, more than one H in the G-chain group or R^1 are substituted by D.

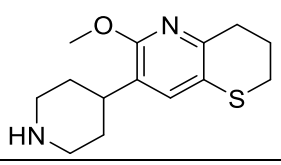
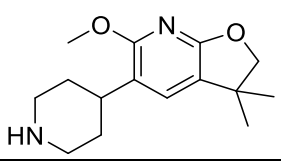
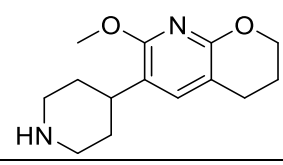
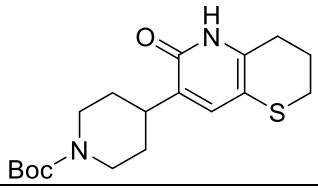
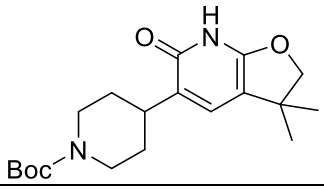
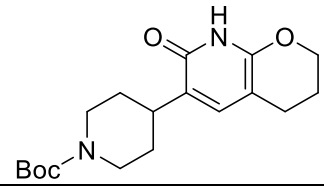
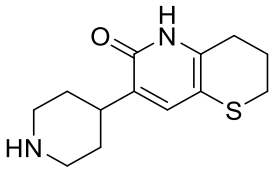
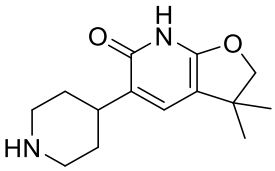
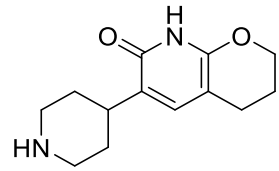
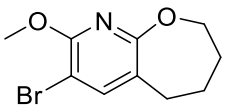
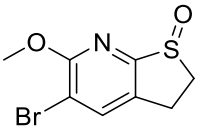
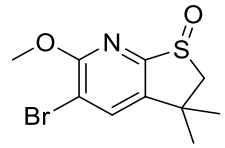
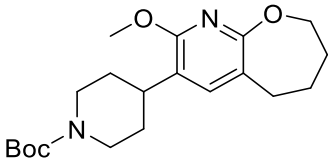
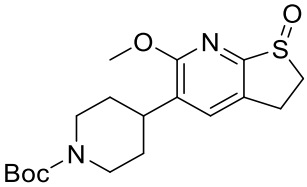
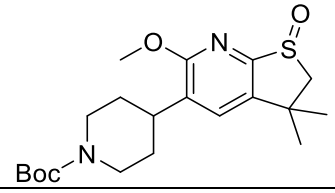
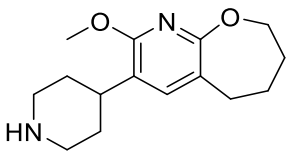
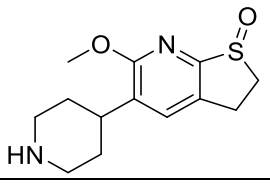
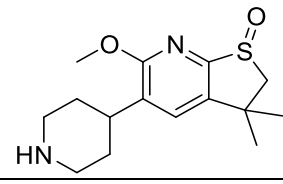
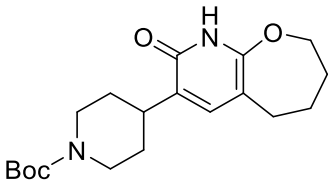
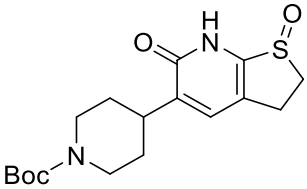
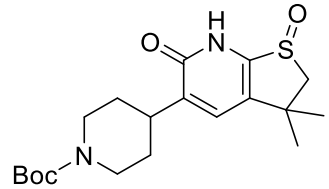
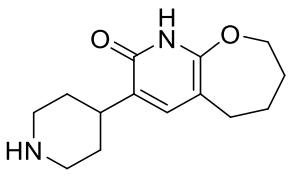
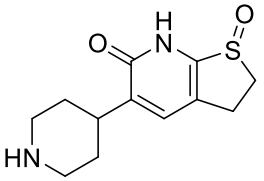
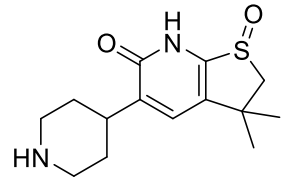
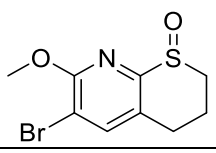
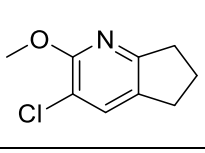
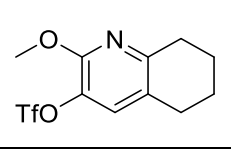
23. The intermediate compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to any one of claims 20 to 22:

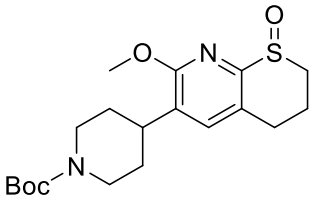
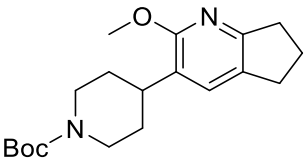
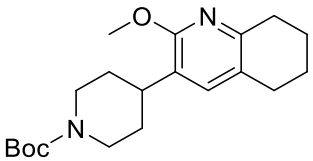
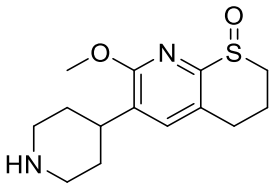
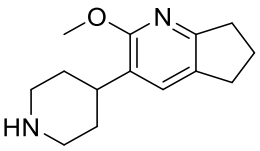
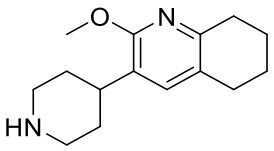
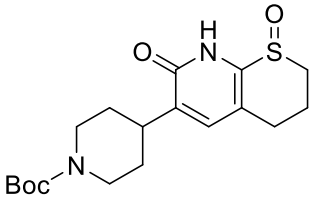
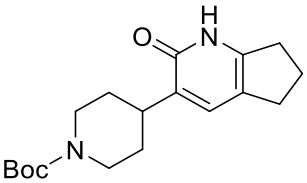
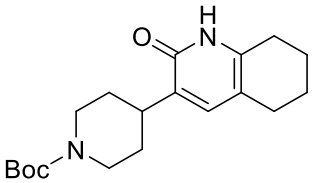
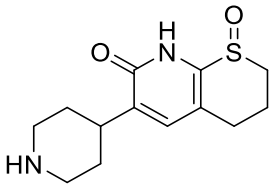
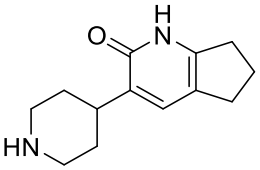
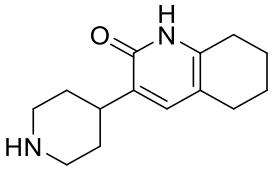
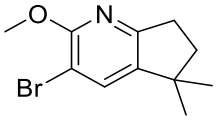
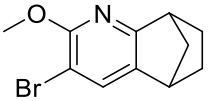
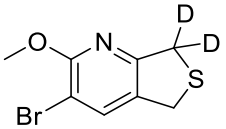
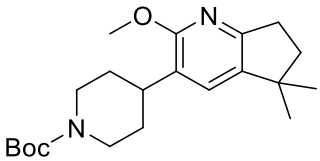
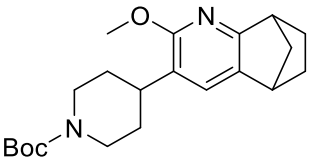
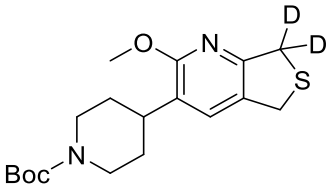
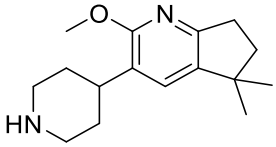
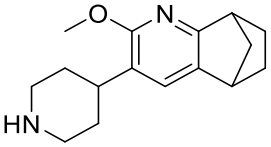
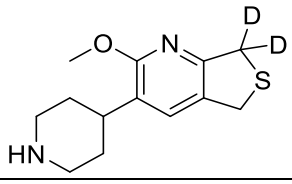
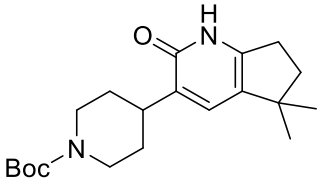
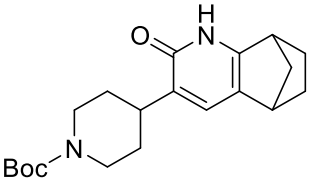
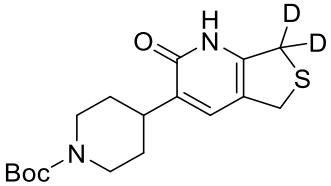
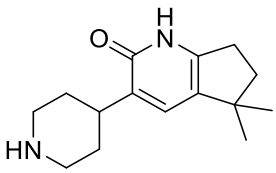
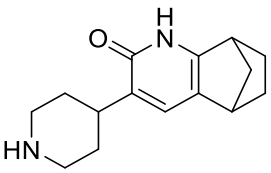
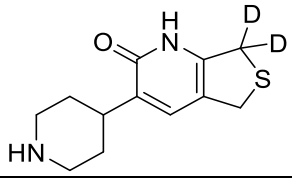
wherein, the intermediate compound is selected from:

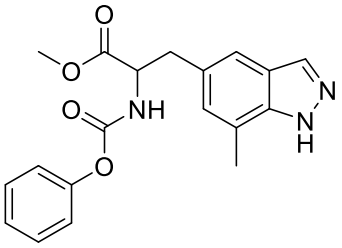
		
		
		
		
		
		
		
		
		
		

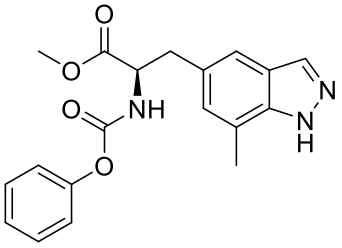
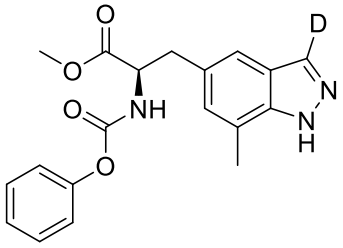
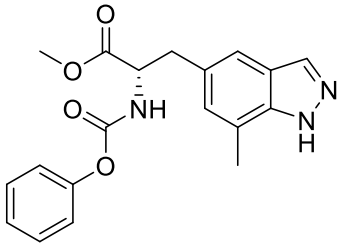
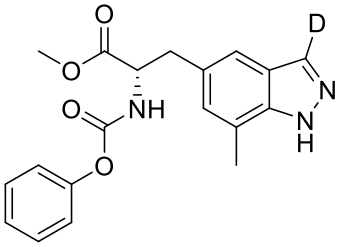
		
		
		
		
		
		
		
		
		

24. An intermediate compound as represented by the following formula VI, or an isomer, pharmaceutically acceptable salt or solvate thereof:

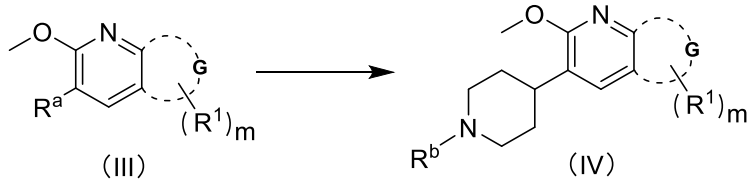


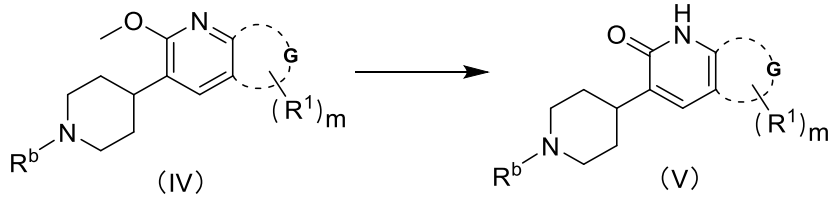
(VI);

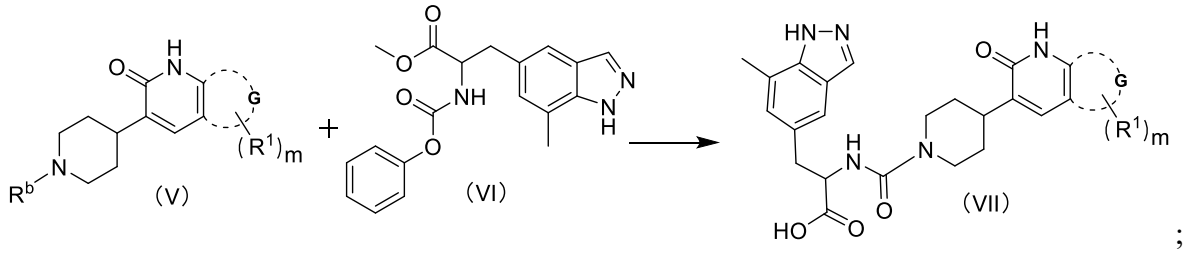
preferably, the intermediate compound as represented by the formula VI is selected from any one of the following structures:


,

,

and

.

25. A preparation method for an intermediate compound as represented by formula I, comprising any one or a combination of the following synthetic routes (1)-(3):

(1)

;

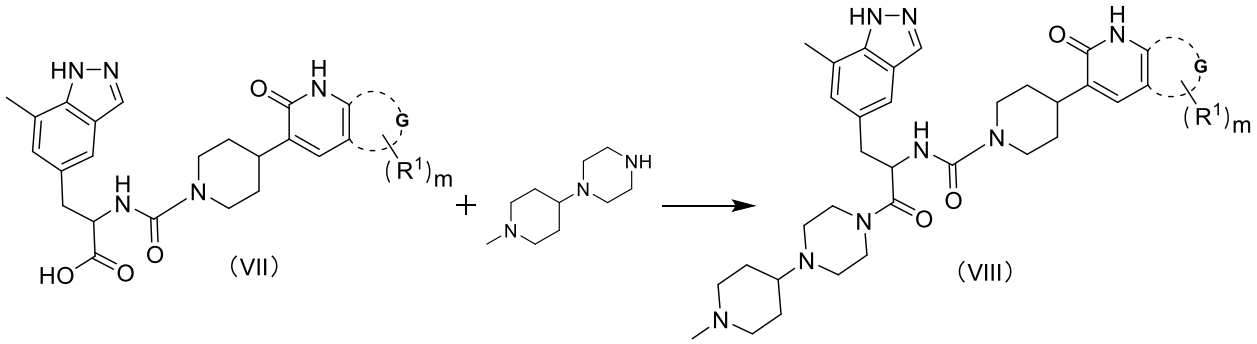
(2)

; and

(3)

;

wherein, formulas III, IV and V are respectively as defined in the formulas III, IV and V of the intermediate compound in claim 20 sequentially, formula VI is as defined in the formula VI of the

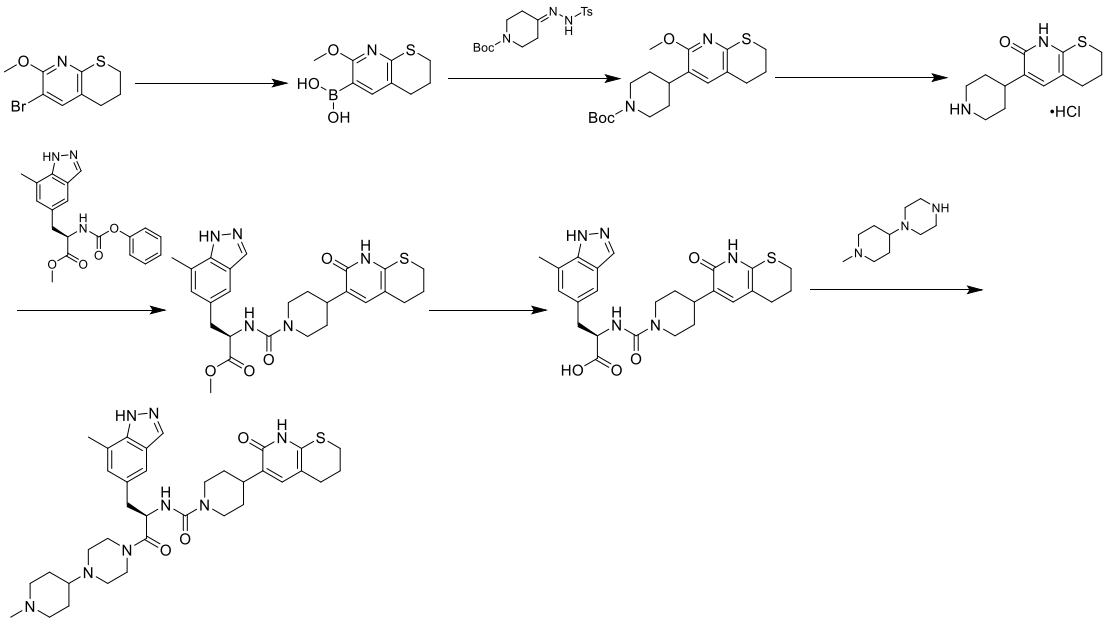
intermediate compound in claim 24, and the G-chain group, R^1 and m in formula VII are as defined in the G-chain group, R^1 and m in any structure of the formula III, IV or V in the intermediate compound in claim 20.

26. A synthetic method for a compound as a CGRP antagonist, comprising the following synthetic route:

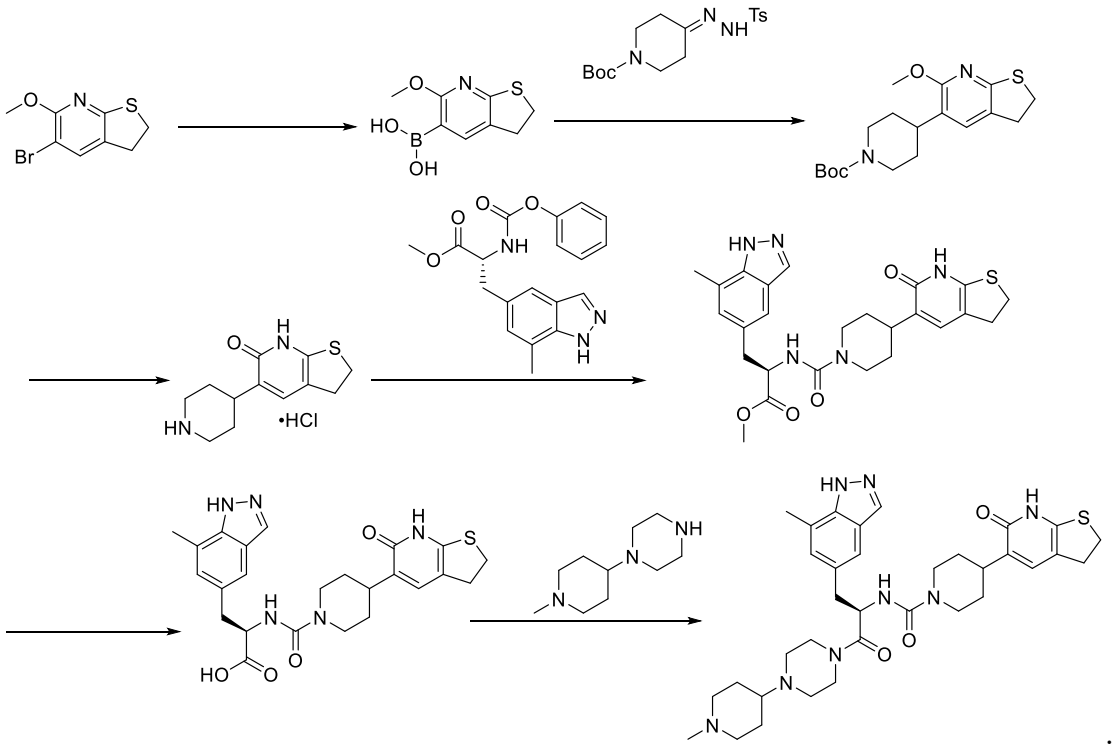


wherein, the G-chain group, R^1 and m in formulas VII and VIII are as defined in claim 1.

27. A synthetic method for a compound as a CGRP antagonist, comprising the following synthetic route:



or,



28. A pharmaceutical composition, comprising the compound, or the isomer, pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 17, and a pharmaceutically acceptable excipient.