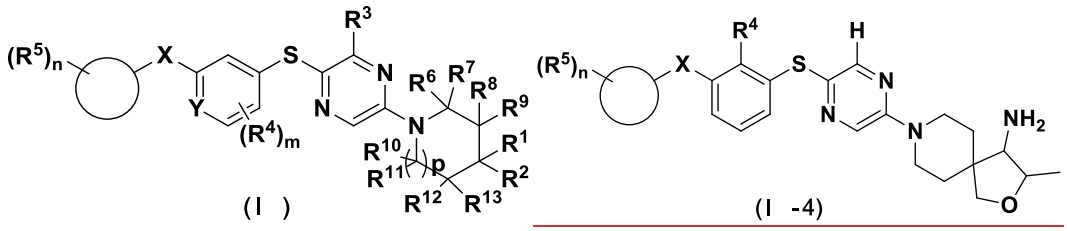
triple-negative breast cancer. SHP2 can also affect vascular smooth muscle cell proliferation, which is closely related to the development and progression of atherosclerosis. Therefore, SHP2 is a potential drug target with broad application prospects.

Summary

In a first aspect, the present disclosure refers to a compound of formula (I-4), or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, characterized in that, said compound of formula (I-4) ~~having~~ has the structure ~~of~~shown below:



~~(I)~~

~~Wherein:~~

~~R1 and R2 are each the same or different, each independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkyloxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl; or 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl formed by R1 and R2, optionally, said 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl is substituted by 1-3 of -OH, -NH2, -CN, NO2, halogen, C1-C10 alkyl, C1-C10 alkoxy, C1-C10 alkylamino, C3-C12 cycloalkyl, C6-C10 aryl or 5-10 membered heteroaryl;~~

~~R3 is selected from H, D, -NH2;~~

X is selected from chemical bonds, -NH-, -CONH-;

~~Y is selected from N or CR0, wherein R0 is selected from H, D, -OH, -CN, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkylamino, C1-C10 alkylamino, C3-C12 cycloalkyl, 3-8 membered heterocyclyl, halogenated C1-C10 alkylamino, C6-C10 aryl or 5-10 membered heteroaryl, said heterocyclyl or heteroaryl optionally contains 1-4 heteroatoms, said heteroatoms are selected from S, O, N or NH;~~

~~Each~~ R^4 is ~~the same or different, and each is independently~~ selected from H, D, halogen, -CN,

-COOH, -CHO, -OH, -NO_2, -$CONHR^{14}$, or -$NHCOR^{15}$, a substituted or unsubstituted group of: -NH_2, C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl; wherein R^{14} and R^{15} are each independently and optionally selected from C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl; said substitution is substituted by one or more substituents selected from of C_1-C_{10} alkyl, halogen, -NH_2, -CN, -COOH, -CHO, -OH, -NO_2, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl or 3-12 membered heterocyclyl, the above substituents are optionally substituted by 1-3 of C_1-C_{10} alkyl, halogen, -NH_2, -CN, -COOH, -CHO, -OH, -NO_2, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl;

 is selected from C_6-C_{10} aryl, 5-10 membered heteroaryl, C_4-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{14} bridged cyclyl or spirocyclyl, C_6-C_{14} bridged heterocyclyl or spiro heterocyclyl; wherein said 5-10 membered heteroaryl, 3-12 membered heterocyclyl, C_6-C_{14} bridged heterocyclyl or spiro heterocyclyl contains 1-3 heteroatoms or groups optionally from N, NH, O, S, C (O), S (O);

Each R^5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO_2, aminoacyl, a substituted or unsubstituted group of: C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, -NH_2, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl, said substitution is substituted with one or more of C_1-C_{10} alkyl, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, halogen, -NH_2, -CN, -COOH, -CHO, -OH, -NO_2, hydroxy-C_1-C_{10}-alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, 5-10 membered heteroaryl, C_6-C_{10} aryl or 3-12 membered heterocyclyl; or a 3-6 membered saturated or unsaturated ring formed by any two adjacent R^5, optionally, said 3-6 membered saturated or unsaturated ring is substituted by 1-3 -OH, -NH_2, -CN, halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkylamino, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, halogenated C_1-C_{10} alkylamino, C_6-C_{10} aryl or 5-10 membered heteroaryl;

~~R6, R7, R8, R9, R10, R11, R12, R13 are independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkyloxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl, said substitution is substituted by one or more of C1-C10 alkyl, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, halogen, -NH2, -CN, -~~

~~COOH, -CHO, -OH, -NO2, hydroxy-C1-C10 alkyl, C1-C10 alkoxy, C1-C10 alkylamino, 5-10 membered heteroaryl, or C6-C10 aryl.~~

~~m is 0, 1, 2, or 3;~~

n is 0, 1, 2, or 3~~;~~

~~p is 0, 1 or 2~~.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of formula (I-4) disclosed herein, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof.

In yet another aspect, the present disclosure refers to a compound of formula (I-4) disclosed herein, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition disclosed herein, or a pharmaceutical preparation disclosed herein for use in the prevention and~~-~~/~~-~~or treatment of non-receptor protein tyrosine phosphatase-mediated or dependent diseases or disorders, wherein the non-receptor protein tyrosine phosphatase-mediated or dependent disease or disorder is cancer.

In a further aspect, the present disclosure refers to a form of pharmaceutical combination comprising a compound of formula (I-4) disclosed herein, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition disclosed herein, and at least one additional therapeutic agent.

In another aspect, the present disclosure refers to a use of a compound of formula (I-4) disclosed herein, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition disclosed herein, or a pharmaceutical preparation disclosed herein, in the manufacture of a medicament for the prevention and / or treatment of non-receptor protein tyrosine phosphatase-mediated or dependent diseases or disorders, wherein the non-receptor protein tyrosine phosphatase-mediated or dependent disease or disorder is cancer.

Content of the invention

Problems to be solved by the invention

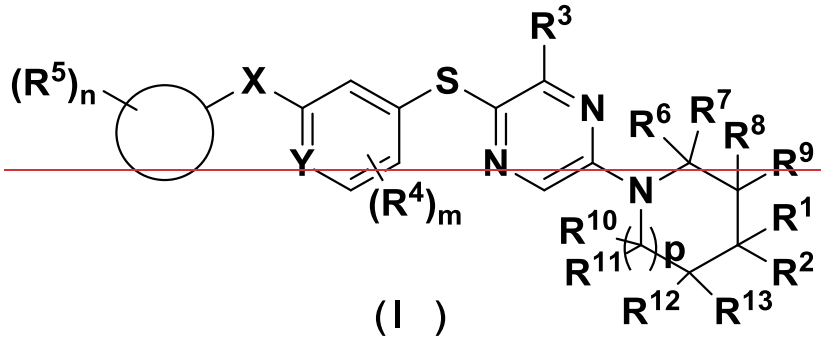
As none of the drugs for protein tyrosine phosphatase have been marketed to date and compounds in the prior art have poor SHP2 inhibitory activity (e.g., WO2016/203406A1); the objective of the current invention is to provide a novel pyrazine derivative that has superior SHP2 inhibitory activity and can be used for the prevention and/or treatment of non-receptor protein tyrosine phosphatase-mediated or dependent diseases or disorders.

Plans used to solve the problem

To solve the above technical problem, the present invention provides a compound of formula

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, said compound of formula (I) having the structure of:



(I)

Wherein:

R1 and R2 are each the same or different, each independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkyloxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl; or 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl formed by R1 and R2, optionally, said 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl is substituted by 1-3 of -OH, -NH2, -CN, NO2, halogen, C1-C10 alkyl, C1-C10 alkoxy, C1-C10 alkylamino, C3-C12 cycloalkyl, C6-C10 aryl or 5-10 membered heteroaryl;

R3 is selected from H, D, -NH2;

X is selected from chemical bonds, -NH-, -CONH-;

Y is selected from N or CR0, wherein R0 is selected from H, D, -OH, -CN, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkylamino, C1-C10 alkylamino, C3-C12 cycloalkyl, 3-8 membered heterocyclyl, halogenated C1-C10 alkylamino, C6-C10 aryl or 5-10 membered heteroaryl, said heterocyclyl or heteroaryl optionally contains 1-4 heteroatoms, said heteroatoms are selected from S, O, N or NH;

Each R4 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, -CONHR14, or -NHCOR15, a substituted or unsubstituted group of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl; wherein R14 and R15 are each

independently optionally selected from C1-C10 alkylamino, C3-C12 cycloalkyl, C6-C10 aryl, or 5-10 membered heteroaryl; said substitution is substituted by one or more of C1-C10 alkyl, halogen, -NH2, -CN, -COOH, -CHO, -OH, -NO2, C1-C10 alkoxy, C1-C10 alkylamino, C3-C12 cycloalkyl, C6-C10 aryl, 5-10 membered heteroaryl or 3-12 membered heterocyclyl, the above substituents are optionally substituted by 1-3 of C1-C10 alkyl, halogen, -NH2, -CN, -COOH, -CHO, -OH, -NO2, C1-C10 alkoxy, C1-C10 alkylamino, C3-C12 cycloalkyl;

 is selected from C6-C10 aryl, 5-10 membered heteroaryl, C4-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C14 bridged cyclyl or spirocyclyl, C6-C14 bridged heterocyclyl or spiro heterocyclyl; wherein said 5-10 membered heteroaryl, 3-12 membered heterocyclyl, C6-C14 bridged heterocyclyl or spiro heterocyclyl contains 1-3 heteroatoms or groups optionally from N, NH, O, S, C (O), S (O);

Each R5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, aminoacyl, a substituted or unsubstituted group of: C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, -NH2, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C10 aryl, or 5-10 membered heteroaryl, said substitution is substituted with one or more of C1-C10 alkyl, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, halogen, -NH2, -CN, -COOH, -CHO, -OH, -NO2, hydroxy-C1-C10-alkyl, C1-C10 alkoxy, C1-C10 alkylamino, 5-10 membered heteroaryl, C6-C10 aryl or 3-12 membered heterocyclyl; or a 3-6 membered saturated or unsaturated ring formed by any two adjacent R5, optionally, said 3-6 membered saturated or unsaturated ring is substituted by 1-3 -OH, -NH2, -CN, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkylamino, C1-C10 alkylamino, C3-C12 cycloalkyl, halogenated C1-C10 alkylamino, C6-C10 aryl or 5-10 membered heteroaryl;

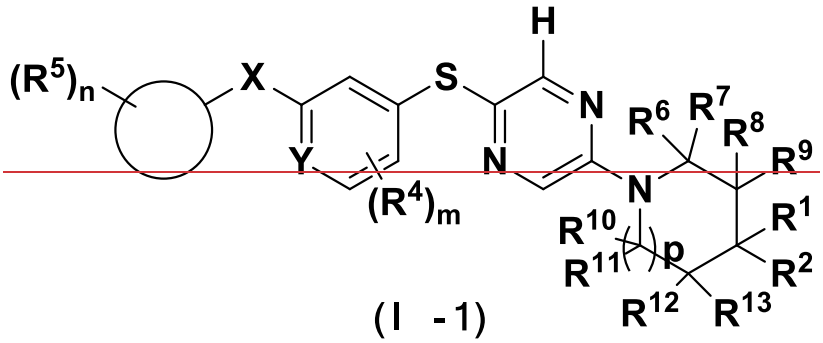
R6, R7, R8, R9, R10, R11, R12, R13 are independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkyloxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl, said substitution is substituted by one or more of C1-C10 alkyl, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, halogen, -NH2, -CN, -COOH, -CHO, -OH, -NO2, hydroxy-C1-C10-alkyl, C1-C10 alkoxy, C1-C10 alkylamino, 5-10 membered heteroaryl, or C6-C10 aryl.

m is 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1 or 2.

2. The compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that said compound of formula (I) has the following structure as shown in formula (I-1):

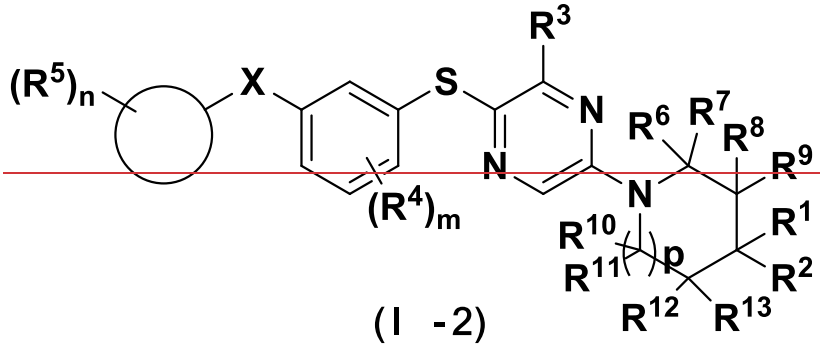


(I -1)

(I-1)

Wherein, R1, R2, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, X, Y, m, n, p and ⊖ are defined as shown in claim 1.

3. The compound of formula (I) according to claim 1 or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that said compound of formula (I) has the following structure as shown in formula (I-2):



(I -2)

(I-2)

Wherein, R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, X, m, n, p and ⊖ are defined as shown in claim 1.

4. The compound of formula (I) according to any one of claims 1-3, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

R1 and R2 are each the same or different, and each of them is independently selected from H,

D, halogen, -CN, -COOH, -CHO, -OH, -NO2, substituted or unsubstituted groups of: -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkoxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl; wherein said substituted -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkoxy, 3-12-membered heterocyclyl, C6-C10 aryl, 5-10-membered heteroaryl are substituted by one or more of C1-C10 alkyl, C1-C10 alkylamino, halogen, -NH2, -CN, -NO2, -OH, hydroxy substituted C1-C10 alkylamino, C1-C10 alkoxy, C3-C8 alkylamino, C3-C12 cycloalkyl, 5-10 membered heteroaryl, C6-C10 aryl, and 5-10 membered heterocyclyl; said heterocyclyl or heteroaryl optionally contains 1-4 heteroatoms or heteroatom-containing groups, said heteroatoms or heteroatom-containing groups are selected from S, O, N, NH or C(O); or 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl formed by R1 and R2, optionally, said 3-8 membered saturated or unsaturated cycloalkyl or heterocyclyl is substituted by 1-3 -OH, -NH2, -CN, NO2, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkyl, C6-C10 aryl or 5-10 membered heteroaryl; wherein said saturated or unsaturated cycloalkyl or heterocyclyl is optionally a carbocyclic ring or a heterocyclyl containing 1-3 heteroatoms or groups selected from N, NH, O, S, C (O), S (O).

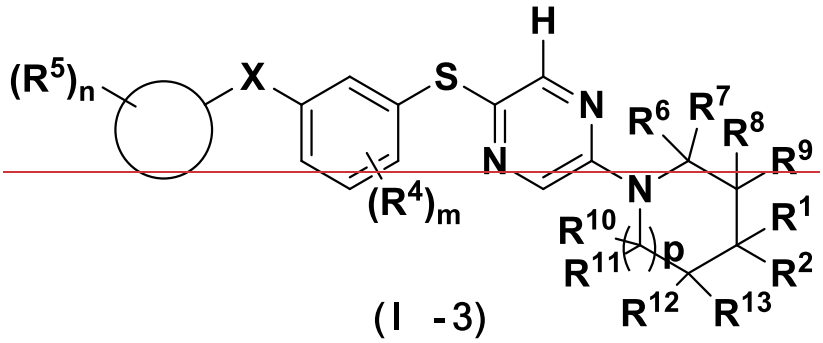
5. The compound of formula (I) according to claim 4, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

R1 and R2 form a 5-6-membered heterocyclic group, said heterocyclic group containing 1-3 heteroatoms selected from N, NH, O, and S, and optionally, said 5-6-membered heterocyclic group is substituted by 1-3 halogen, -OH, -NH2, C1-C10 alkylamino, C1-C10 alkyl, or C1-C10 alkoxy.

6. The compound of formula (I) according to any one of claims 1-3, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

 is selected from C6-C10 aryl, 5-10 membered heteroaryl, or 3-12 membered heterocyclyl; wherein said 5-10 membered heteroaryl or 3-12 membered heterocyclyl contains 1-3 heteroatoms or groups optionally from N, NH, O, S, C (O), S (O).

7. The compound of formula (I) according to any one of claims 1-3, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that, said compound in formula (I) has the following structure as shown in formula (I-3):



(I -3)

~~(I-3)~~

~~Wherein R1 and R2 form a 5-6 membered heterocyclyl, said heterocyclyl contains 1-3 heteroatoms selected from N, NH, O, and S, optionally, said 5-6 membered heterocyclyl is substituted by 1-3 halogen, -OH, -NH2, C1-C10 alkylamino, C1-C10 alkyl, or C1-C10 alkoxy;~~

~~ is selected from C6-C10 aryl or 5-10 membered heteroaryl or 3-12 membered heterocyclyl; wherein said 5-10 membered heteroaryl or 3-12 membered heterocyclyl contains 1-3 heteroatoms or groups optionally selected from N, NH, O, S, C (O), S (O).~~

~~8. The compound of formula (I) according to any one of claims 1-7, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,~~

~~Each R4 is the same or different, and is independently selected from H, D, -NH2, halogen, -CN, -COOH, -CHO, -OH, -NO2, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C10 aryl, or 5-10 membered heteroaryl.~~

~~9. The compound of formula (I) according to any one of claims 1-7, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,~~

~~Each R5 is the same or different, and is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, C1-C10 alkyl, C1-C10 alkylamino, C1- C10 alkoxy, -NH2, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C10 aryl or 5-10 membered heteroaryl; or a 3-6 membered saturated or unsaturated ring formed by any two adjacent R5, optionally, said 3-6 membered saturated or unsaturated ring group is substituted by 1-3 -OH, -NH2, -CN, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkylamino, C1-C10 alkylamino, C3-C12 cycloalkyl, halogenated C1-C10 alkylamino, C6-C10 aryl or 5-10 membered heteroaryl.~~

~~10. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,~~

Each R5 is the same or different, each is independently selected from H, D, halogen, C1-C6 alkyl, C1-C6 alkylamino, C1-C6 alkoxy, -NH2; or two adjacent R5 can form a 5-6 membered saturated ring group, optionally, said 5-6 membered saturated ring group is substituted with 1-2 -OH, -NH2, -CN, halogen, C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkylamino, C1-C6 alkylamino, C3-C6 cycloalkyl, halogenated C1-C6 alkylamino, C6-C10 aryl, or 5-6 membered heteroaryl.

11. The compound of formula (I) according to any one of claims 1-7, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

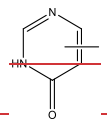
R1 and R2 form a 3-6 membered saturated or unsaturated cycloalkyl or heterocyclyl, optionally, said 3-6 membered saturated or unsaturated cycloalkyl or heterocyclyl is substituted by 1-3 -OH, -NH2, -CN, NO2, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkyl, C6-C10 aryl or 5-10 membered heteroaryl;

R3 is selected from H;

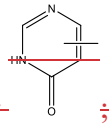
X is selected from chemical bond, -NH-, -CONH-;

Y is selected from CR0, wherein R0 is selected from H, D, -OH, -CN, halogen, C1-C10 alkyl, C1-C10 alkoxy, C3-C12 cycloalkylamino, C1-C10 alkylamino, C3-C12 cycloalkyl, or halogenated C1-C10 alkylamino;

Each R4 is the same or different, and each is independently selected from H, D, -NH2, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, 3-12 membered heterocyclyl, C6-C10 aryl, or 5-10 membered heteroaryl;

 is selected from C6-C10 aryl, 5-10 membered heteroaryl, 3-12 membered heterocyclyl, wherein said 5-10 membered heteroaryl and 3-12 membered heterocyclyl contain 1-3 heteroatoms or groups selected from any of N, NH, O, S, C(O), preferably, said 3-12 membered heterocyclyl is any of aziridinyl, azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, tetrahydropyranyl, 1,1-dioxothiomorpholinyl, butyrolactamyl, valerolactamyl, caprolactamyl, butyrolactone, valerolactone, caprolactone, succinimide or 

; more preferably, said 3-12 membered

heterocyclyl is any of butyrolactamyl, pyrrolidinyl, succinimide or  ;

Each R5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, a substituted or unsubstituted group of: C1-C6 alkyl , C1-C6 alkylamino, C1-C6 alkoxy, -NH2, C3-C6 cycloalkyl, 3-6 membered heterocyclyl, C6-C10 aryl or 5-10 membered heteroaryl, or a 5-6 membered saturated ring formed by any adjacent two of R5, optionally, said 5-6 membered saturated ring is substituted by 1-3 of -OH, -NH2, -CN, halogen, C1-C6 alkyl, C1-C6 alkoxy, C3-C6 cycloalkylamino, C1-C6 alkylamino, C3-C6 cycloalkyl, halogenated C1-C6 alkylamino, C6-C10 aryl or 5-10 membered heteroaryl;

R6, R7, R8, R9, R10, R11, R12, R13 are independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, -NO2, -NH2, C1-C10 alkyl, C1-C10 alkylamino, C1-C10 alkoxy, C3-C12 cycloalkyl, C3-C12 cycloalkoxy, 3-12 membered heterocyclyl, C6-C10 aryl, 5-10 membered heteroaryl, 3-12 membered heterocyclyl;

m is 1 or 2;

n is 1 or 2 or 3;

p is 0 or 1.

12. The compound of formula (I) according to any one of claims 1-11, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

R1 and R2 form a 5-6 membered saturated ring group, preferably cyclohexane, cyclopentane, tetrahydrofuran ring, tetrahydropyrrole ring, tetrahydrothiophene ring, tetrahydropyran ring; optionally, said 5-6 membered saturated ring group is substituted by 1-3 -OH, -NH2, -CN, NO2, halogen, methyl, methoxy;

R3 is selected from H;

X is selected from chemical bonds, -NH-, -CONH-;

Y is selected from CR0, wherein R0 is selected from H, halogen, C1-C6 alkyl, C1-C6 alkoxy;

Each R4 is the same or different, and is independently selected from H, -NH2, halogen, -CN, C1-C6 alkyl, C1-C6 alkylamino, or C1-C6 alkoxy;

 is selected from C6-C10 aryl, 5-10 membered heteroaryl, 5-12 membered heterocyclyl, preferably C6-C10 aryl, 5-9 membered heteroaryl; wherein said 5-10 membered heteroaryl, 5-12 membered heterocyclyl contains 1-3 heteroatoms or groups optionally from N, NH, O, S, C (O);

Each R5 is the same or different, each is independently selected from H, halogen, -CN, -COOH, -CHO, -OH, -NO2, C1-C6 alkyl, C1-C6 alkoxy, -NH2, or a 5-6 membered saturated ring formed by any two adjacent R5, optionally, said 5-6 membered saturated ring is substituted by 1-3 -OH, -NH2, -CN, halogen, C1- C6 alkyl, C1-C6 alkoxy;

R6, R7, R8, R9, R10, R11, R12, R13 are independently selected from H, halogen, -CN, -COOH, -CHO, -OH, -NO2, -NH2, C1-C6 alkyl, or C1- C6 alkoxy;

m is 1 or 2;

n is 1 or 2 or 3;

p is 0 or 1.

13. The compound of formula (I) according to any one of claims 1-12, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that,

R1 and R2 form a cyclopentane, a tetrahydrofuran ring, a tetrahydropyrrole ring, and a tetrahydrothiophene ring; optionally, said cyclopentane, tetrahydrofuran ring, tetrahydropyrrole ring, tetrahydrothiophene ring is substituted by 1-3 -OH, -NH2, halogen, methyl, or methoxy;

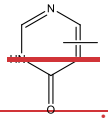
R3 is selected from H;

X is selected from chemical bonds, -NH-, -CONH-;

Y is selected from CR0, wherein R0 is selected from H, halogen, C1-C6 alkyl, or C1-C6 alkoxy;

Each R4 is the same or different and is independently selected from H, halogen, C1-C6 alkyl, or C1-C6 alkoxy;

 is selected from phenyl, naphthyl, 5-10 membered heteroaryl or 5-12 membered heterocyclyl; wherein said 5-10 membered heteroaryl contains 1-3 optionally selected from N, NH, O, S, heteroatoms; Preferably, said 5-10 membered heteroaryl ring is selected from thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, thiazolyl, 1,2,3- triazolyl, 1,2,4-triazolyl, imidazolyl, tetrazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, indolo[1,2-a]pyrazinyl, 4,7-diazaindole, pyrazolopyrimidinyl, imidazopyrimidinyl, oxazolopyrimidinyl, isoxazolopyrimidinyl, imidazopyrazinyl, pyrazolopyrazine, pyrrolopyrazinyl, furanopyrazinyl, thienopyrazinyl, pyridopyrimidinone, benzoxazolyl or benzothiazolyl; said 5-12-membered heterocyclyl is selected from any one of butyrolactamyl, pyrrolidinyl, succinimide

group or  .

Each R5 is the same or different, and each is independently selected from H, halogen, -CONH2, -COOH, -CN, C1-C6 alkyl, hydroxy-substituted C1-C6 alkyl, amino-substituted C1-C6 alkyl, C1-C6 alkoxy, -NH2, or any two adjacent R5 forming a cyclohexane or cyclopentane;

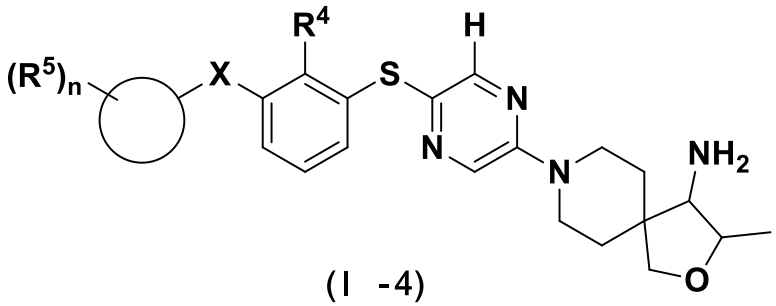
R6, R7, R8, R9, R10, R11, R12, R13 are all H;

m is 1;

n is 1 or 2 or 3;

p is 1.

141. The A compound of formula (I-4) according to any one of claims 1-7, or a pharmaceutically acceptable salt, ester, isomer, solvate, prodrug or isotope label thereof, characterized in that, said compound of formula (I-4) has the structure shown in formula (I-4). below:



(I -4)

(I-4)

X is selected from chemical bonds, -NH-, -CONH-;

R^4 is selected from H, D, halogen, -CN, -COOH, -CHO, -OH, $-NO_2$, $-CONHR^{14}$ or $-NHCOR^{15}$, a substituted or unsubstituted group of: $-NH_2$, C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl; wherein R^{14} and R^{15} are each independently and optionally selected from C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl; said substitution is one or more substituents selected from C_1-C_{10} alkyl, halogen, $-NH_2$, -CN, -COOH, -CHO, -OH, $-NO_2$, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, or 3-12 membered heterocyclyl, the above substituents are optionally substituted with 1-3 C_1-C_{10} alkyl, halogen, $-NH_2$, -CN, -COOH, -CHO, -OH, $-NO_2$, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl;.

 is selected from C_6-C_{10} aryl, 5-10 membered heteroaryl, C_4-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{14} bridged cyclyl or spirocyclyl, C_6-C_{14} bridged heterocyclyl or spiro heterocyclyl; wherein said 5-10 membered heteroaryl, 3-12 membered heterocyclyl, C_6-C_{14} bridged heterocyclyl or spiro heterocyclyl contains 1-3 heteroatoms or groups optionally from N, NH, O, S, C (O), S (O);

Each R^5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, $-NO_2$, aminoacyl, a substituted or unsubstituted group of: C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, $-NH_2$, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl, said substitution is substituted with one or more of C_1-C_{10} alkyl, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclyl, halogen, $-NH_2$, -CN, -COOH, -CHO, -OH, $-NO_2$, hydroxy-C_1-C_{10}-alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, 5-10 membered heteroaryl, C_6-C_{10} aryl or 3-12 membered heterocyclyl; or a 3-6 membered saturated or unsaturated ring formed by any two adjacent R^5, optionally, said 3-6 membered saturated or unsaturated ring is substituted by 1-3 -OH, $-NH_2$, -CN, halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkylamino, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, halogenated C_1-C_{10} alkylamino, C_6-C_{10} aryl or 5-10 membered heteroaryl;

n is 0, 1, 2, or 3;

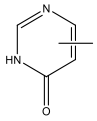
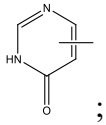
~~15~~2. The compound of formula (I-4) according to claim ~~14~~1, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, characterized in that

R4 is selected from H, D, halogen, -CN, unsubstituted or halogen substituted C_1-C_{10} alkyl;

 is selected from phenyl, naphthyl, 5-10-membered heteroaryl or 3-12-membered heterocyclyl;

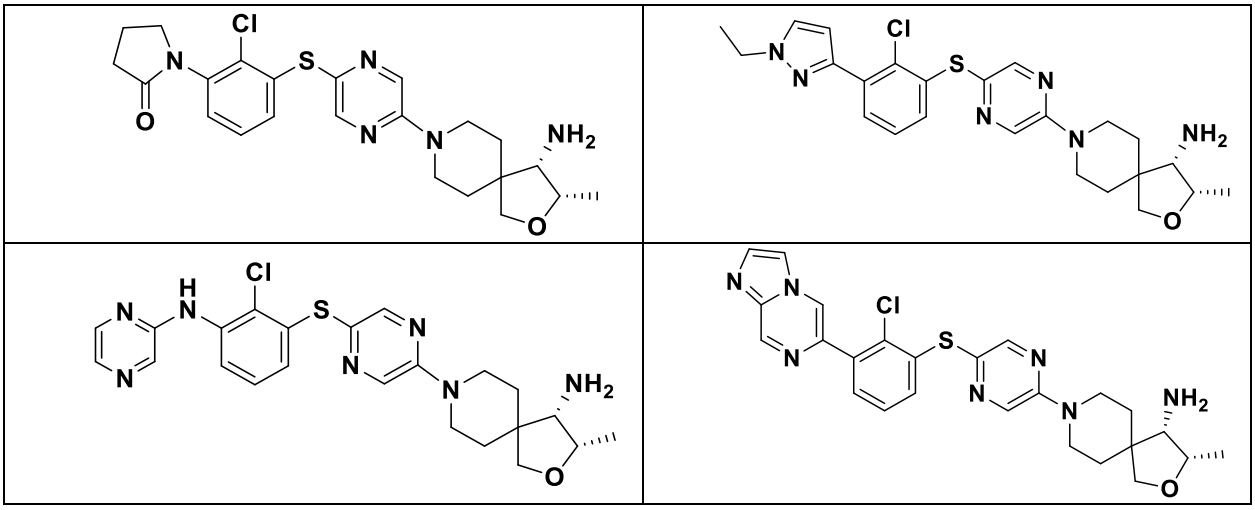
wherein said 5-10-membered heteroaryl, 3-12-membered heterocyclyl contains 1-3 heteroatoms or groups optionally selected from any of N, NH, O, S, C(O),

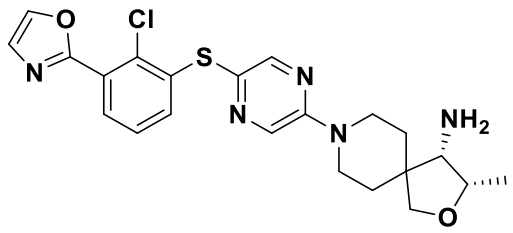
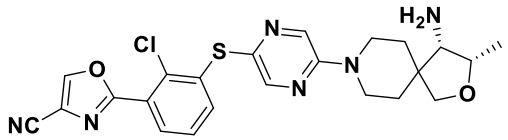
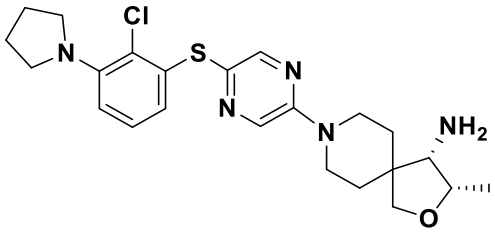
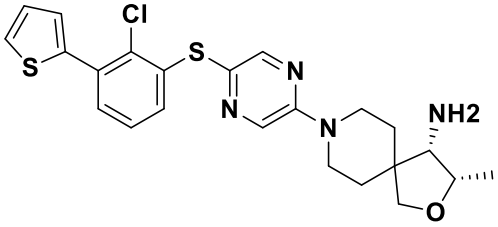
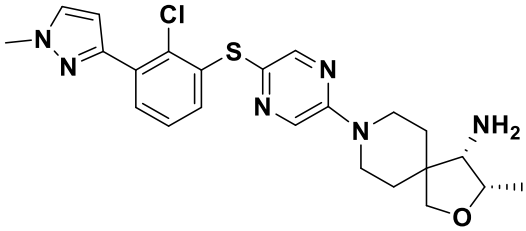
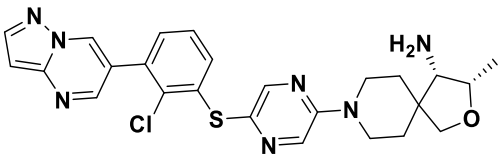
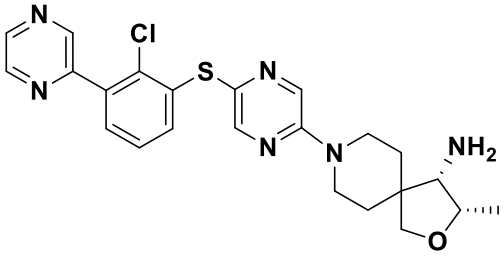
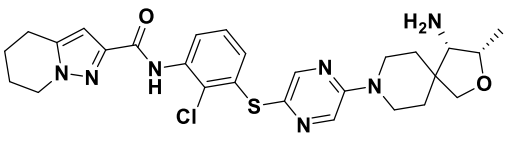
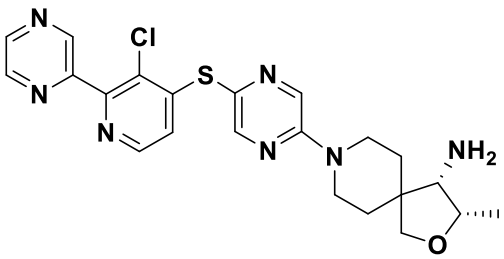
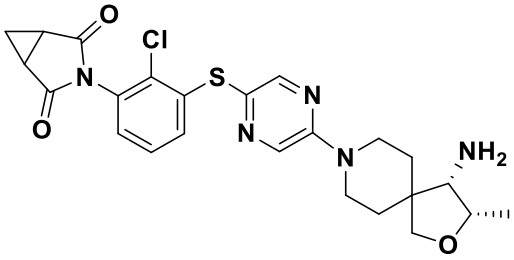
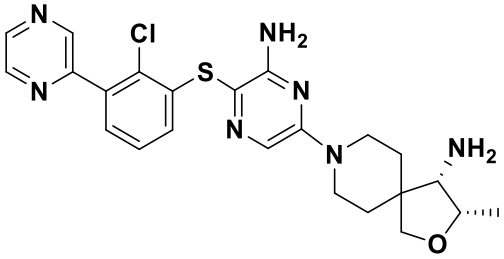
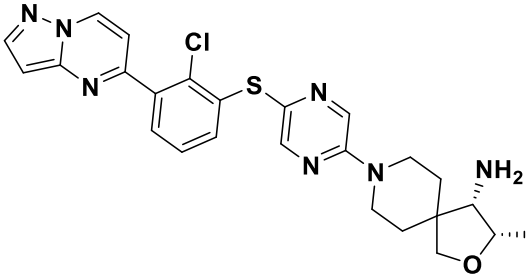
~~Preferably~~preferably, said 5-10 membered heteroaryl ring is selected from thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, thiazolyl, 1,2,3- triazolyl, 1,2,4-triazolyl, imidazolyl, tetrazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, benzothienyl, indolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, indolo[1,2-a]pyrazinyl, 4,7-diazaindole, pyrazolopyrimidinyl, imidazopyrimidinyl,

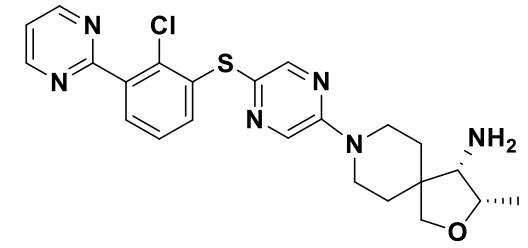
oxazolopyrimidinyl, isoxazolopyrimidinyl, imidazopyrazinyl, pyrazolopyrazine, pyrrolopyrazinyl, furanopyrazinyl, thienopyrazinyl, pyridopyrimidinone, benzoxazolyl or benzothiazolyl; said 3-12 membered heterocyclyl is any of aziridinyl, azetidinyl, oxetanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, tetrahydropyranyl, 1,1-dioxothiomorpholinyl, butyrolactamyl, valerolactamyl, caprolactamyl, butyrolactone, valerolactone, caprolactone, succinimide or  ; more preferably, said 3-12 membered heterocyclyl is selected from any of butyrolactamyl, pyrrolidinyl, succinimide or  ;

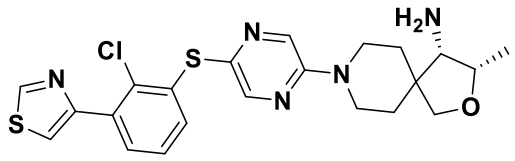
Each R^5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, $-NO_2$, aminoacyl, a substituted or unsubstituted group of: C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, $-NH_2$, said substitution is substituted with one or more of C_1-C_{10} alkyl, halogen, $-NH_2$, -CN, -OH, $-NO_2$; or a 3-6 membered saturated or unsaturated ring formed by any two adjacent R^5, optionally, said 3-6 membered saturated or unsaturated ring is substituted by 1-3 -OH, $-NH_2$, -CN, halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy.

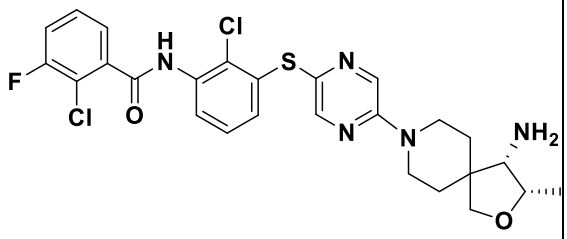
~~16~~3. The compound of formula (I-4) according to any one of claims 1-~~7~~2, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, characterized in that, said compound of formula (I-4) is selected from:

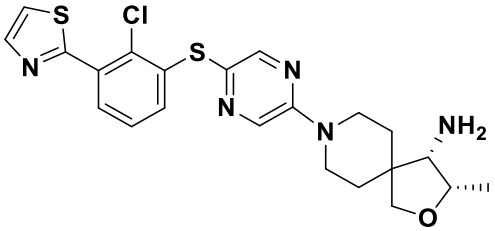


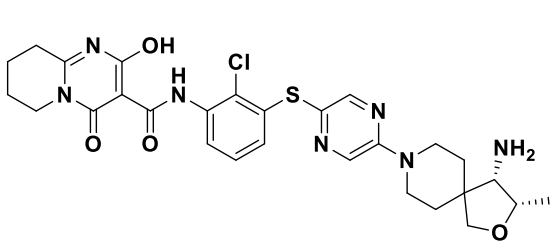
	
	
	
	
	
	

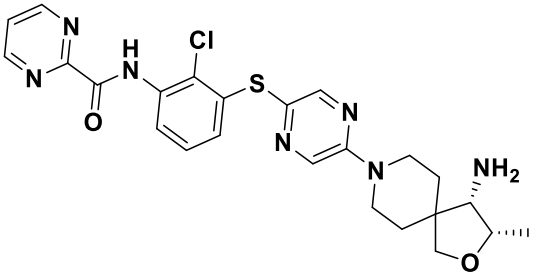


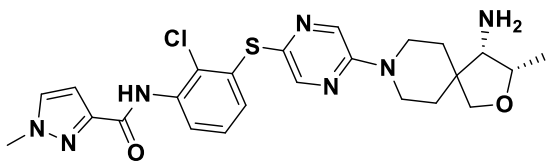


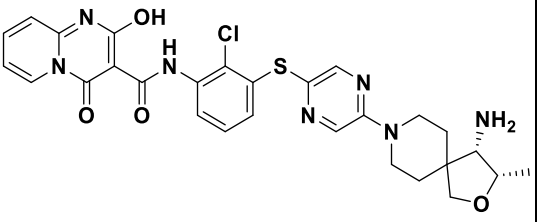


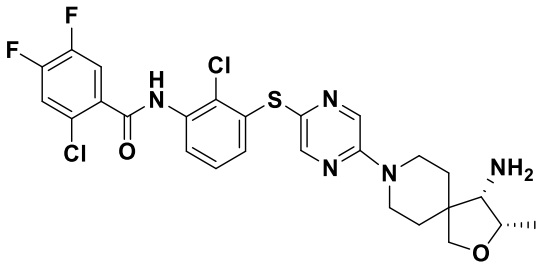


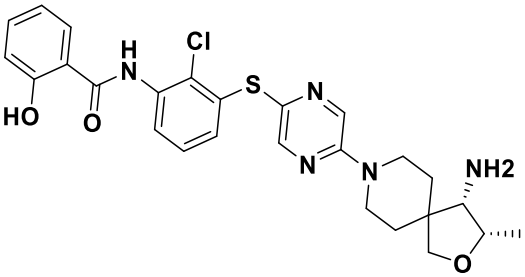


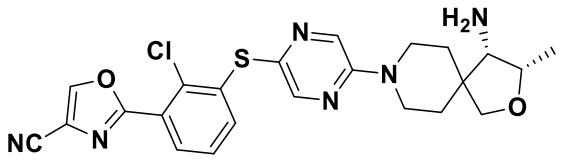
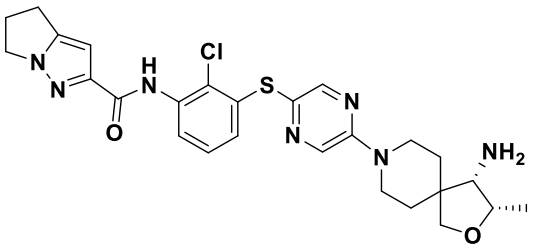
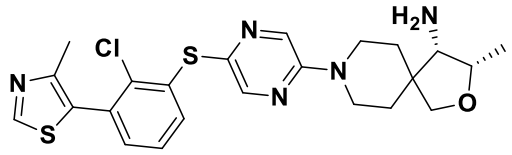
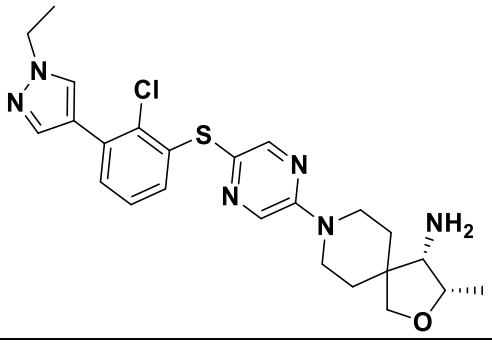
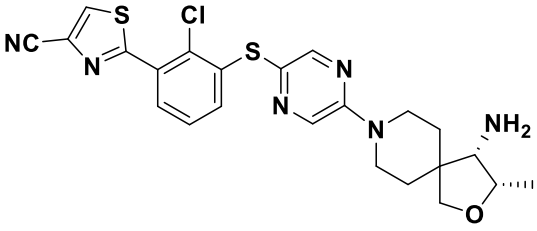
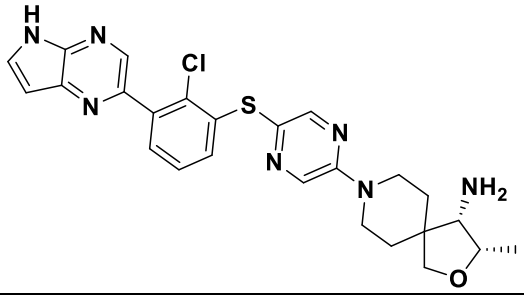
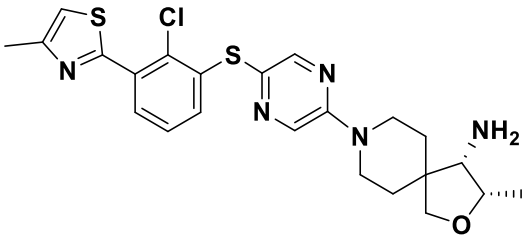
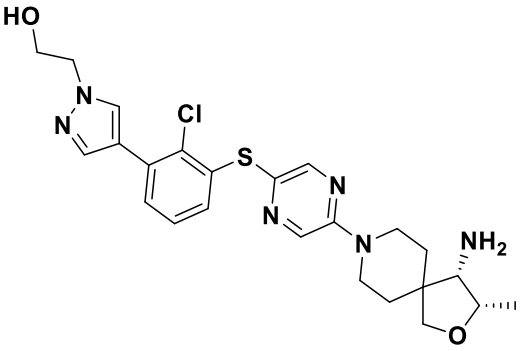
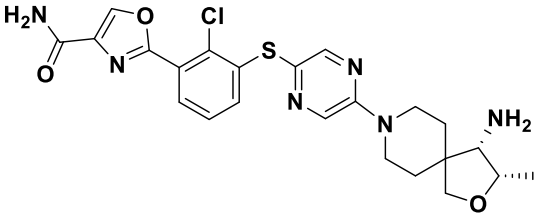
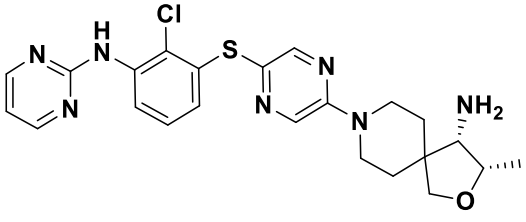


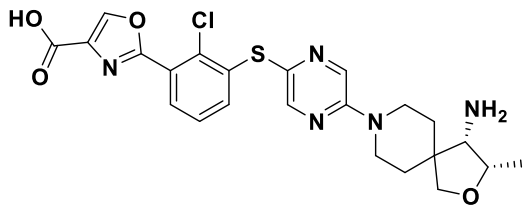
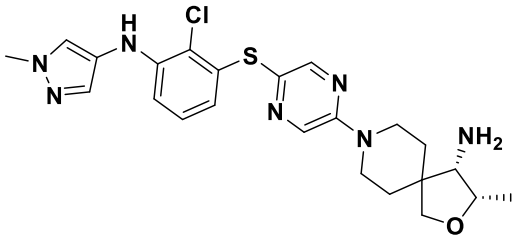
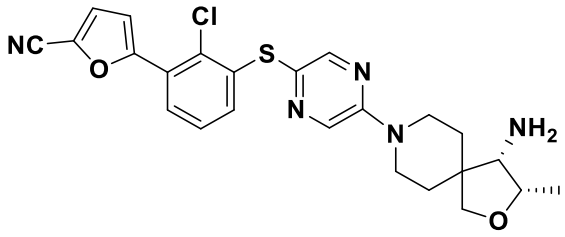
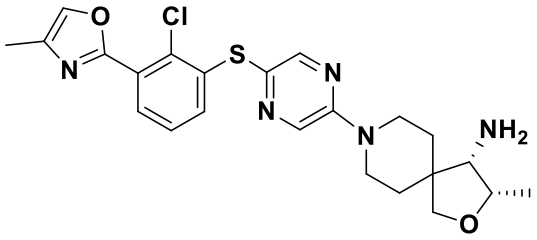
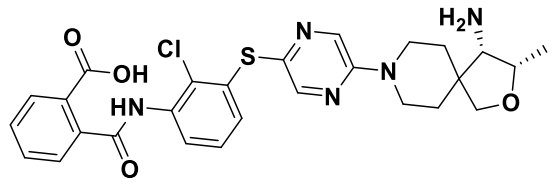
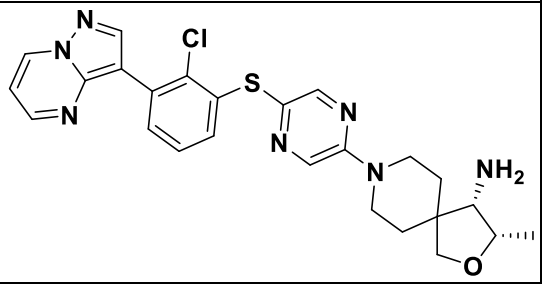








~~174~~. A pharmaceutical composition comprising a compound of formula (I-4) according to any one of claims 1-~~163~~, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof.

~~185~~. The pharmaceutical composition as set forth in claim ~~174~~, said preparation is any of, tablet, capsule, injection, granule, powder, suppository, pill, cream, paste, gel, dispersion, oral solution, inhaler, suspension, dry suspension, patch, or lotion.

~~196~~. A compound of formula (I-4) as set forth in any one of claims 1-~~163~~, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition as set forth in claim ~~174~~, or a pharmaceutical preparation of claim ~~18~~ 5 for use in the prevention and~~/~~or treatment of non-receptor protein tyrosine phosphatase-mediated or dependent diseases or disorders, wherein the non-receptor protein tyrosine phosphatase-mediated or dependent disease or disorder is cancer.

~~20~~7. A form of pharmaceutical combination comprising a compound of formula (I-4) according to any one of claims 1-~~16~~3, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition of claim ~~17~~4, and at least one additional therapeutic agent.

~~21~~8. Use of a compound of formula (I-4) as set forth in any one of claims 1-~~16~~3, or a pharmaceutically acceptable salt~~, ester, isomer, solvate, prodrug or isotope label~~ thereof, or a pharmaceutical composition as set forth in claim ~~17~~4, or a pharmaceutical preparation of claim ~~18~~5, in the manufacture of a medicament for the prevention and / or treatment of non-receptor protein tyrosine phosphatase-mediated or dependent diseases or disorders, wherein the non-receptor protein tyrosine phosphatase-mediated or dependent disease or disorder is cancer.