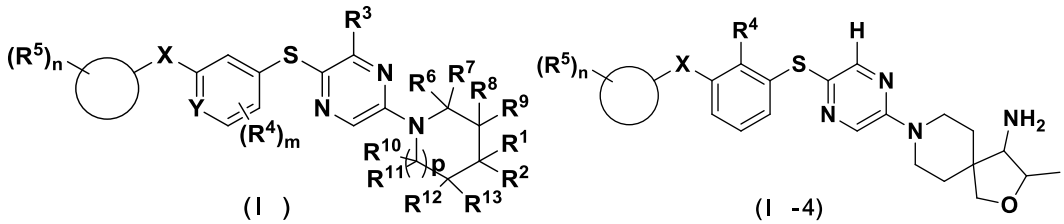
triple-negative breast cancer. SHP2 can also affect vascular smooth muscle cell proliferation, which is closely related to the development and progression of atherosclerosis. Therefore, SHP2 is a potential drug target with broad application prospects.

Summary

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



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 by 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.

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 thereof.

In yet another aspect, the present disclosure refers to a compound of formula (I-4) disclosed herein, or a pharmaceutically acceptable salt 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 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 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

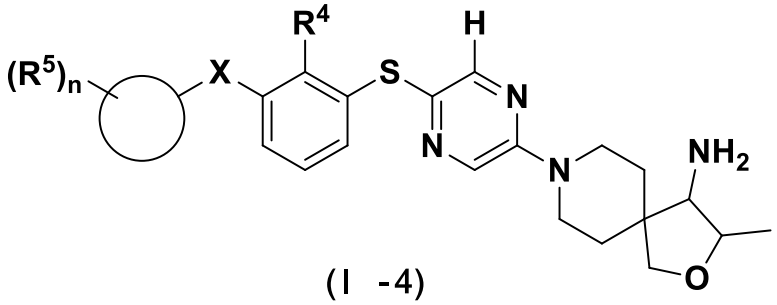
As none of the drugs for protein tyrosine phosphatase have been marketed to date and compounds in the prior art have poor SHP2 inhibitory activity (e.g., WO2016/203406A1); the objective of the current invention is to provide a novel pyrazine derivative that has superior SHP2 inhibitory activity and can 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-4), or a pharmaceutically acceptable salt thereof, characterized in that, said compound of formula (I-4) has the structure shown below:



(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;

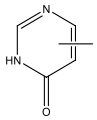
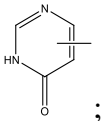
n is 0, 1, 2, or 3;

2. The compound of formula (I-4) according to claim 1, or a pharmaceutically acceptable salt 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;

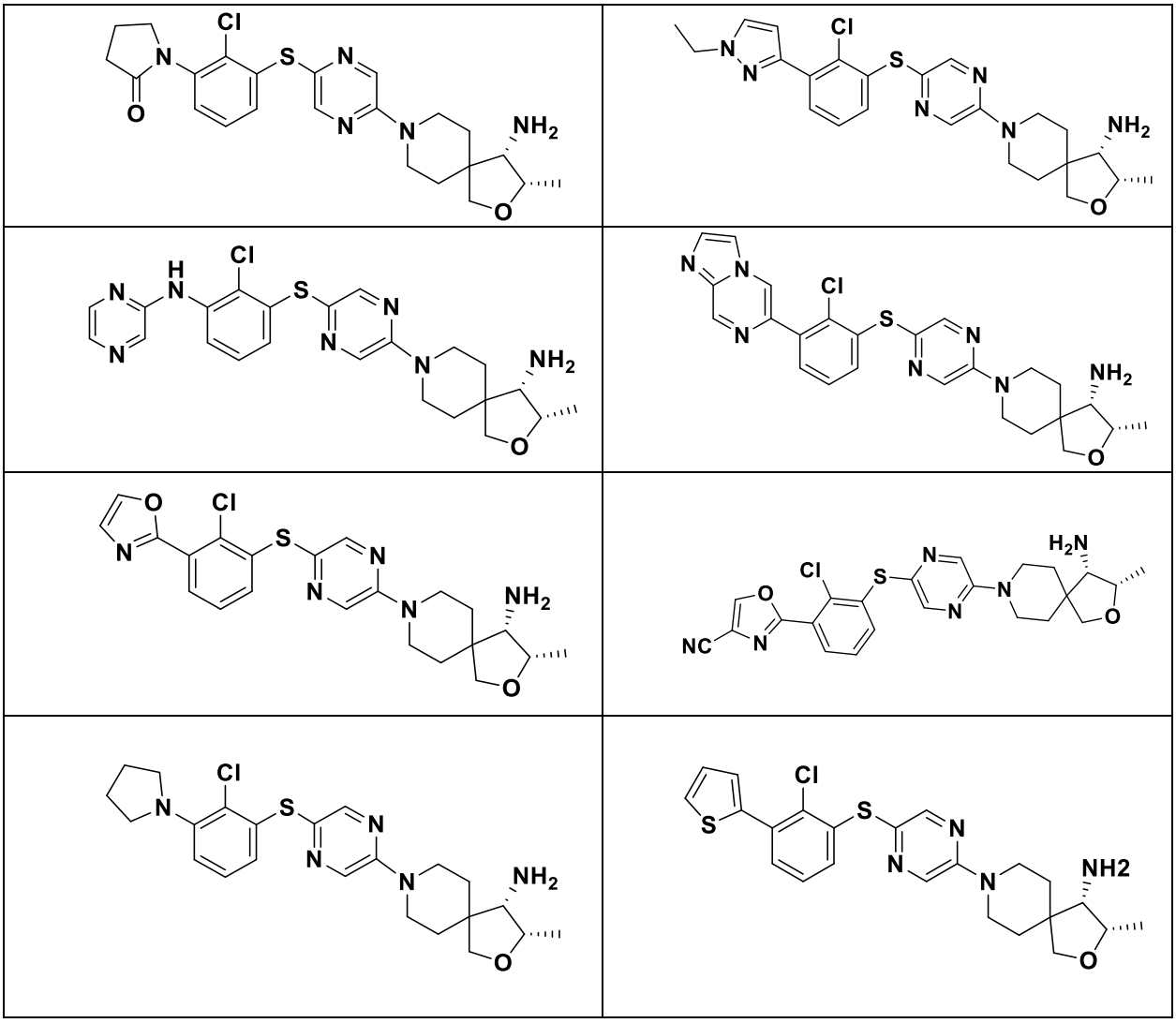
wherein said 5-10-membered heteroaryl, 3-12-membered heterocyclyl contains 1-3 heteroatoms or groups optionally selected from any of N, NH, O, S, C(O),

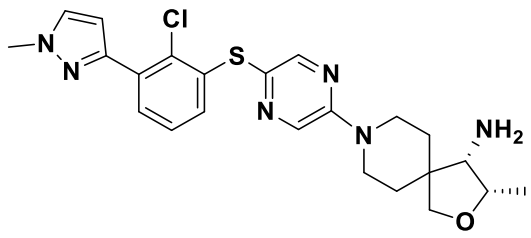
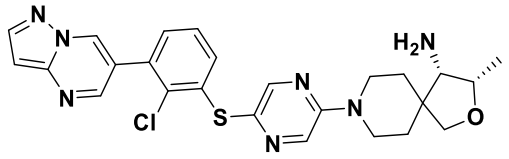
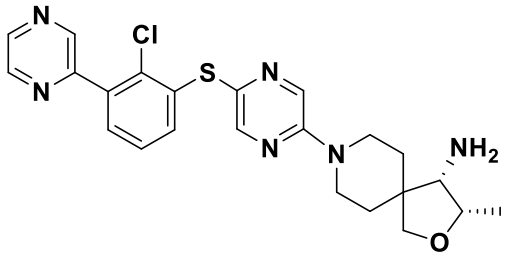
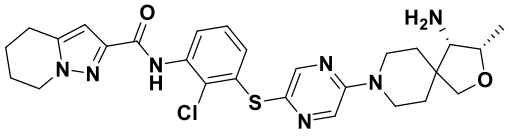
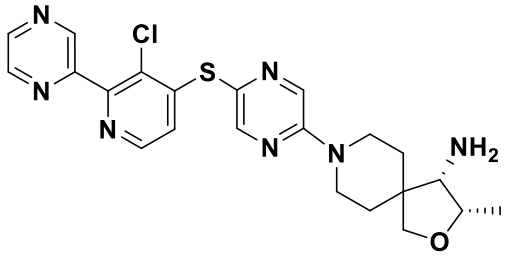
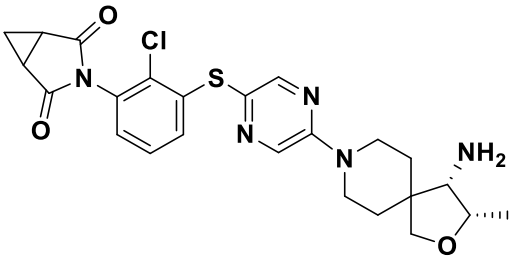
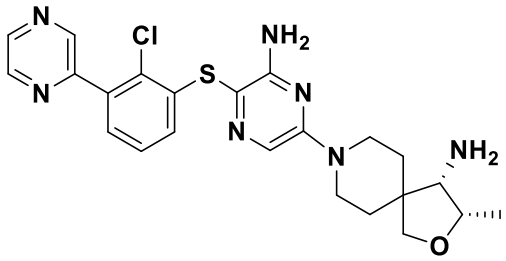
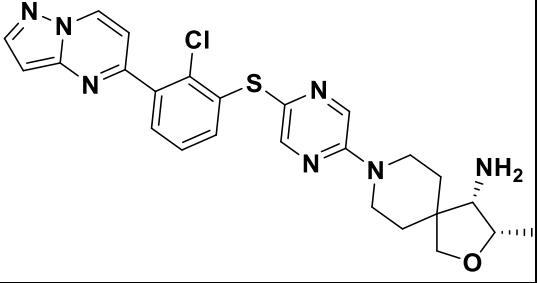
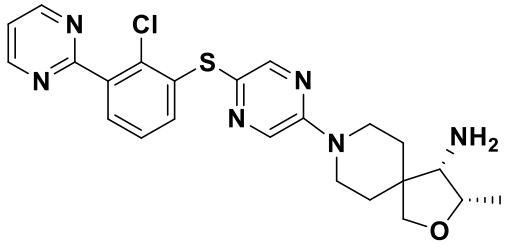
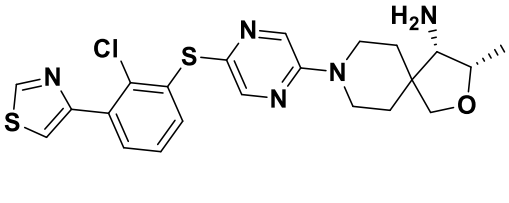
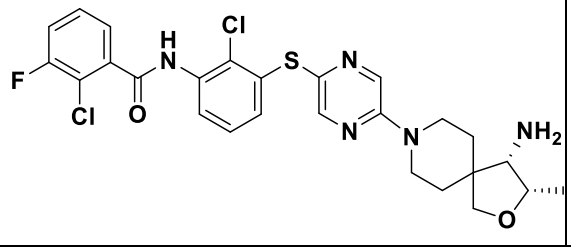
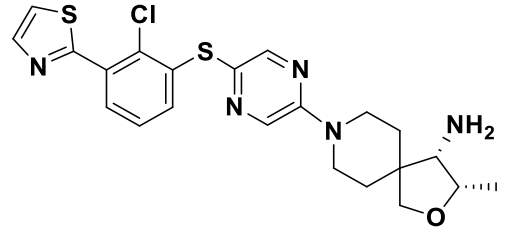
preferably, said 5-10 membered heteroaryl ring is selected from thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, thiazolyl, 1,2,3- triazolyl, 1,2,4-triazolyl, imidazolyl, tetrazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, benzothienyl, indolyl, benzimidazolyl, 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 ;

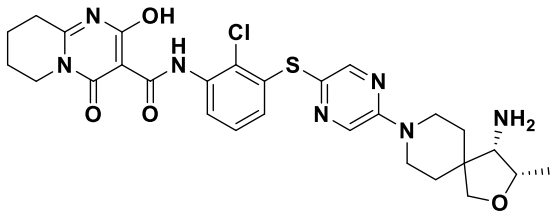
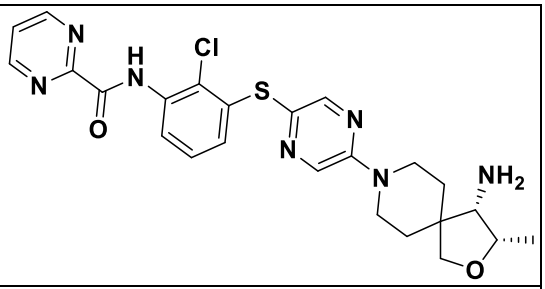
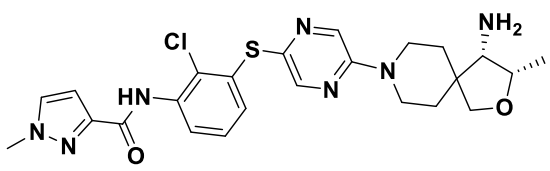
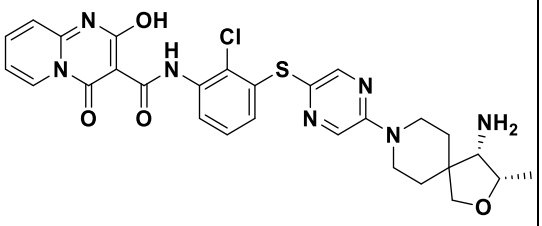
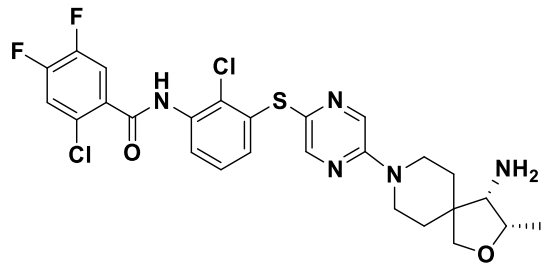
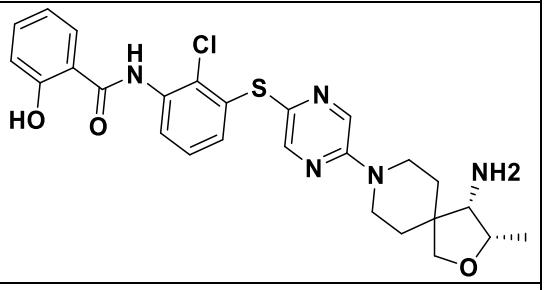
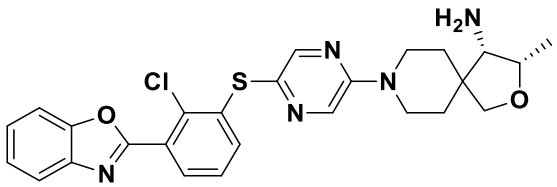
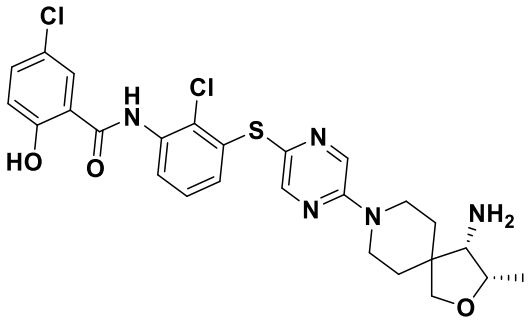
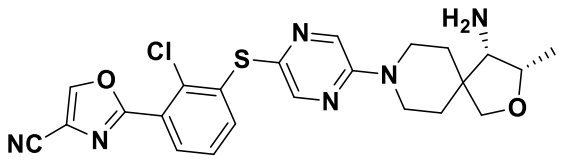
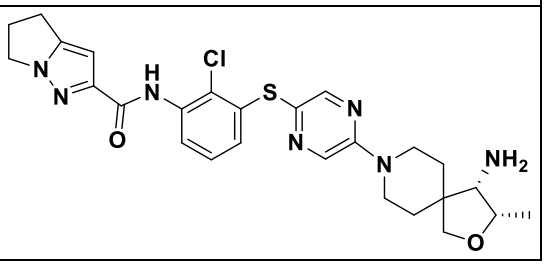
Each R^5 is the same or different, and each is independently selected from H, D, halogen, -CN, -COOH, -CHO, -OH, $-NO_2$, aminoacyl, a substituted or unsubstituted group of: C_1-C_{10} alkyl, C_1-

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.

3. The compound of formula (I-4) according to any one of claims 1-2, or a pharmaceutically acceptable salt thereof, characterized in that, said compound of formula (I-4) is selected from:



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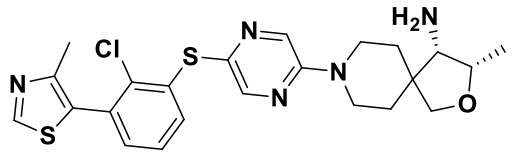	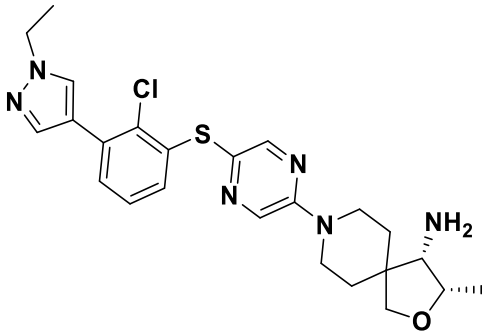
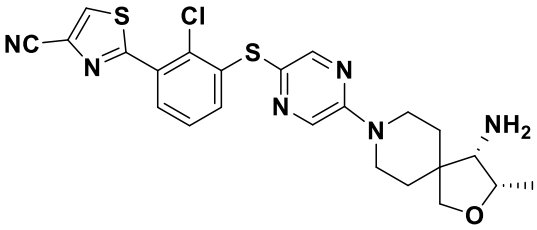	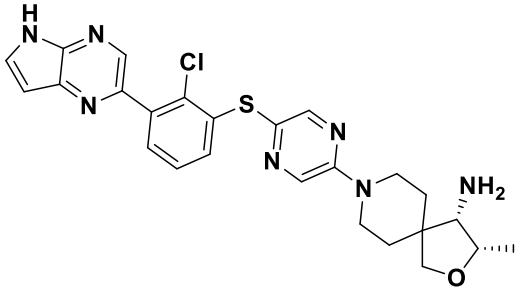
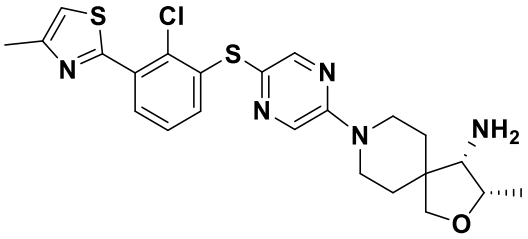	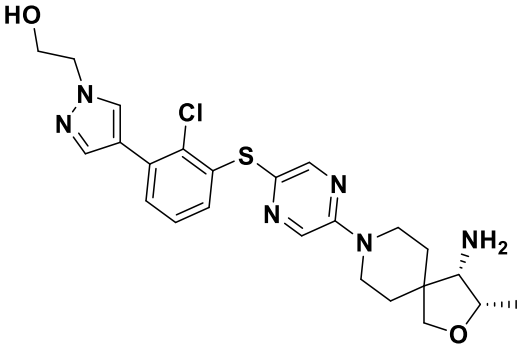
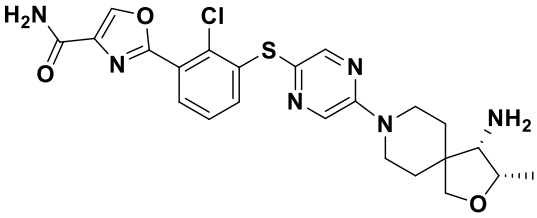	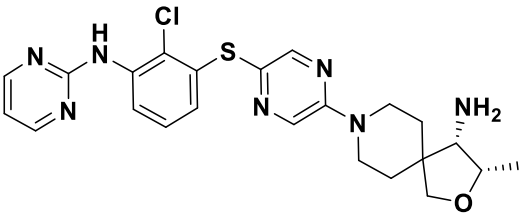
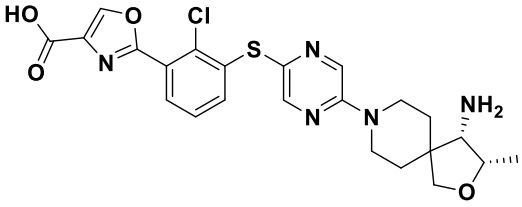	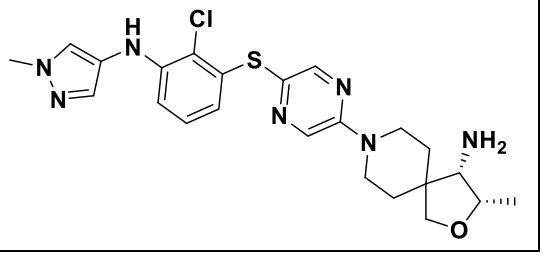

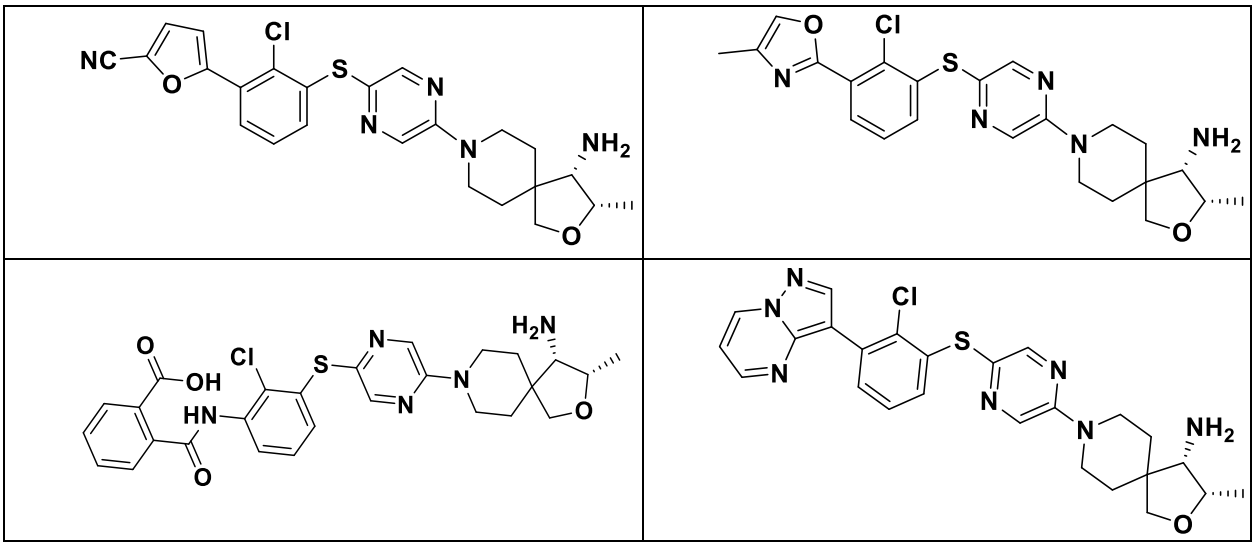

4. A pharmaceutical composition comprising a compound of formula (I-4) according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition as set forth in claim 4, 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.

6. A compound of formula (I-4) as set forth in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as set forth in claim 4, or a pharmaceutical preparation of claim 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.

7. A form of pharmaceutical combination comprising a compound of formula (I-4) according to any one of claims 1-3, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 4, and at least one additional therapeutic agent.

8. Use of a compound of formula (I-4) as set forth in any one of claims 1-3, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as set forth in claim 4,

or a pharmaceutical preparation of claim 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.