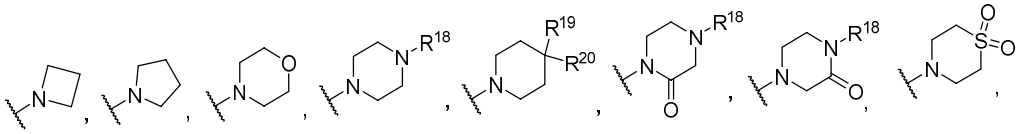
attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following groups:



[00125] R^{18} is selected from -H, methyl, ethyl, formyl, acetyl, hydroxyethyl, hydroxypropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, or ethylsulfonyl,

[00126] R^{19} and R^{20} are each independently selected from -H, methyl, ethyl, hydroxyl, cyano, or fluoro.

[00127] According to some embodiments of the present disclosure, the pharmaceutically acceptable salt of the compound is selected from the group consisting of one or more of the following salts: hydrochloride, hydrobromide, hydroiodide, perchlorate, sulfate, nitrate, phosphate, formate, acetate, propionate, glycolate, lactate, succinate, maleate, tartrate, malate, citrate, fumarate, gluconate, benzoate, mandelate, methanesulfonate, isethionate, benzenesulfonate, oxalate, palmitate, 2-naphthalenesulfonate, p-toluenesulfonate, cyclohexylsulfamate, salicylate, hexonate, trifluoroacetate, aluminum salt, calcium salt, chloroprocaine salt, choline salt, diethanolamine salt, ethylenediamine salt, lithium salt, magnesium salt, potassium salt, sodium salt and zinc salt.

[00128] Another aspect of the present disclosure relates to use of the compound of formula (I), or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, in the manufacture of a medicament for treating diseases related to tyrosine kinase FGFR4 or autoimmune diseases, wherein the diseases related to tyrosine kinase FGFR4 or the autoimmune diseases include fundus oculi disease, xerophthalmia, psoriasis, vitiligo, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn’s disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, bone marrow fibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic granulocytic leukemia, acute myelocytic leukemia, non-Hodgkin’s lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor,

characterized by positive FGFR4 expression.

[00162] The compounds of the present disclosure can also be used to treat solid malignancies characterized by positive KLB (beta-klotho) expression.

[00163] The compounds of the present disclosure can also be used to treat solid malignancies characterized by positive FGF19 expression.

[00164] The compounds of the present disclosure can also be used to treat solid malignancies characterized by positive FGFR4 and positive KLB expression.

[00165] The compounds of the present disclosure can also be used to treat solid malignancies characterized by positive FGFR4 and positive FGF19 expression.

[00166] The compounds of the disclosure can also be used to treat solid malignancies characterized by positive FGFR4, positive KLB and positive FGF19 expression.

[00167] Any positive expression in FGFR4, KLB and/or FGF19 as described above can be assessed by methods known to those skilled in the art, e.g., RT-qPCR, Western blotting, ELISA, and immunohistochemistry.

[00168] Thus, as a further embodiment, the present disclosure provides use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in treatment of a disease. In a further embodiment, the disease is selected from diseases that can be treated by inhibiting FGFR4. In a further embodiment, the disease is selected from the list mentioned above, suitably liver cancer.

[00169] In another embodiment, the present disclosure provides a method of treating a disease that can be treated by inhibition of FGFR4, comprising administering a therapeutically acceptable amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In a further embodiment, the disease is selected from the list mentioned above, suitably liver cancer.

[00170] Thus, as a further embodiment, the present disclosure provides use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament. In a further embodiment, the medicament is used for the treatment of a disease that can be treated by inhibiting FGFR4. In a further embodiment, the disease is selected from the list mentioned above, suitably liver cancer.

[00171] The present disclosure also provides methods for preparing the corresponding compounds. Various synthetic methods can be used to prepare the compounds described herein,

[00198] $Pd_2(dba)_3$: Tris(dibenzylideneacetone)dipalladium

[00199] Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

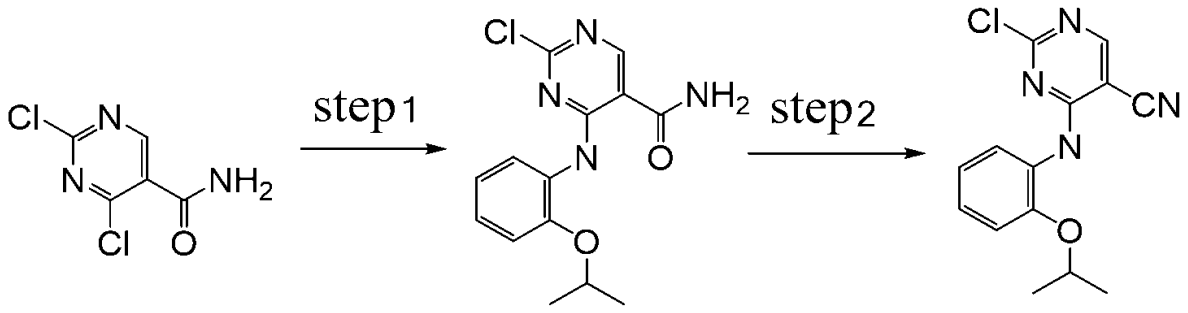
[00200] Binap: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene

[00201] $(Boc)_2O$: Di-tert-butyl dicarbonate

[00202] III. Preparation of intermediates

[00203] Intermediates of series A

[00204] Intermediate A1. 2-chloro-4-((2-isopropoxyphenyl)amino)pyrimidine-5-carbonitrile



[00205] Step 1). Synthesis of 2-chloro-4-((2-isopropoxyphenyl)amino)pyrimidine-5-carboxamide

[00206] 2,4-Dichloropyrimidine-5-carboxamide (1.9 g, 10 mmol), 2-isopropoxyaniline (1.65 g, 11 mmol) and triethylamine (2 g, 20 mmol) were added to DMF (10mL), respectively. The reaction solution was stirred at room temperature for 2 hours, and then water was added for slurrying. The resultant slurry was filtered, and the filter cake was dried to give 2.5 g of product as a white solid with a yield of 82%, MS:307 $[M+H]^+$;

[00207] Step 2). Synthesis of 2-chloro-4-((2-isopropoxyphenyl)amino)pyrimidine-5-carbonitrile

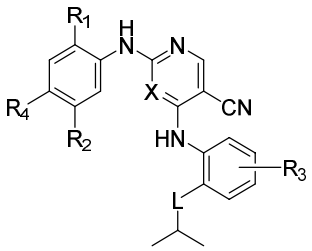
[00208] 2-Chloro-4-((2-isopropoxyphenyl)amino)pyrimidine-5-carboxamide (307 mg, 1 mmol) was added to phosphorus oxychloride (2 mL). The mixture was heated to 120 °C, and reacted with stirring for 5 hours. The reaction solution was concentrated, and washed with saturated sodium bicarbonate solution to give 220 mg of product as a yellowish solid with a yield of 76%, MS: 289 $[M+H]^+$.

[00209] The following intermediates A2-A23 were obtained through the same reaction steps as those of intermediate A1 by replacing the 2-isopropoxyaniline in the above Step 1 with

CLAIMS

What is claimed is:

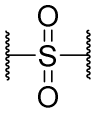
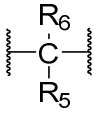
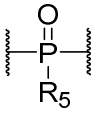
1. A compound represented by formula (I), or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof,

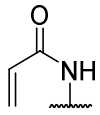


Formula (I)

in formula (I),

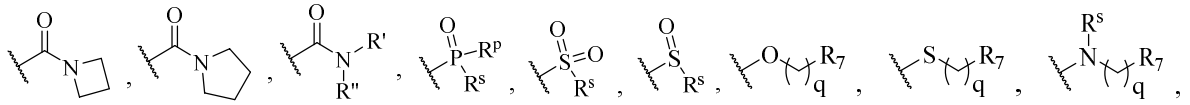
X is N or CH;

L is -O-, -S-, , , , , or -NR_5-, wherein R_5 and R_6 are each independently hydrogen, methyl, ethyl, propyl or isopropyl;

R_1 is ;

R_2 is hydrogen, halogen, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R_3 is selected from hydrogen, halogen, hydroxyl, amino, cyano, carboxyl, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_3 haloalkoxy, C_3-C_6 cycloalkyl, C_2-C_3 alkynyl, C_2-C_3 alkenyl, C_1-C_3 alkoxy, C_1-C_3 alkylthio, mono- or di-C_1-C_3 alkylamino, C_3-C_4 cycloalkyloxy, C_3-C_4 cycloalkyl-substituted C_1-C_3 alkyl, cyano-substituted C_1-C_3 alkyl, carbamoyl-substituted C_1-C_3 alkyl, or the following groups:



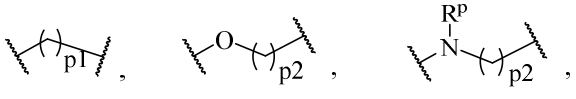
q is an integer of 1-3,

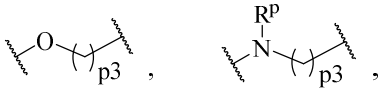
R^s is selected from -H, or C_1-C_3 alkyl, and R^p is selected from -H, or C_1-C_3 alkyl,

R' and R'' are each independently -H, C_1-C_3 alkyl, or C_3-C_4 cycloalkyl,

R_7 is selected from -H, halogen, hydroxyl, cyano, amino, carboxyl, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_1-C_3 alkoxy, or mono- or di-C_1-C_3 alkyl-substituted amino;

R_4 is -T_1-R_8 or -T_2-R_9,

T_1 is: 

T_2 is: 

p1 is an integer of 0-4, p2 is an integer of 2-4, and p3 is an integer of 0-1,

R^p is -H or C_1-C_3 alkyl,

R_8 is selected from -H, halogen, hydroxyl, amino, cyano, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_3 haloalkoxy, C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, C_1-C_3 alkylthio, mono- or di-C_1-C_3 alkylamino, or a 4- to 6-membered heteroalicyclic group, wherein the 4- to 6-membered heteroalicyclic group is unsubstituted or substituted with 1-2 identical or different substituents selected from hydroxyl, C_1-C_6 alkyl, C_1-C_3 alkoxy, formyl, acetyl, propionyl, isopropionyl, hydroxyl-substituted C_1-C_3 alkyl, carboxy-substituted C_1-C_3 alkyl, oxo, C_1-C_3 alkyl-substituted or unsubstituted 4- to 6-membered heteroalicyclic group, or -$NR^{10}R^{11}$,

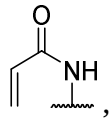
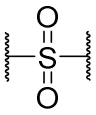
R^{10} and R^{11} are each independently selected from -H, C_1-C_6 alkyl, C_3-C_4 cycloalkyl, hydroxyl-substituted C_2-C_6 alkyl, cyano-substituted C_1-C_2 alkyl, C_1-C_3 alkoxy-substituted C_1-C_3 alkyl, C_1-C_3 alkylthio-substituted C_1-C_3 alkyl, C_1-C_3 haloalkyl, methylsulfonyl-substituted C_1-C_3 alkyl, mono- or di-C_1-C_3 alkylamino-substituted C_1-C_3 alkyl, or C_1-C_3 alkyl-substituted or unsubstituted 4- to 6-membered heteroalicyclic group, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered heteroalicyclic group, wherein the 4- to 6-membered heteroalicyclic group is unsubstituted or substituted with 1-2 identical or different substituents selected from -H, hydroxyl, oxo, halogen, C_1-C_3 alkoxy-substituted C_1-C_3 alkyl, C_1-C_3 alkylsulfonyl, cyano, amino, C_1-C_3 acyl, C_1-C_3 alkyl, mono- or di-C_1-C_3 alkylamino, hydroxyl-substituted C_2-C_3 alkyl, or C_1-C_3 alkoxy,

the 4- to 6-membered heteroalicyclic group contains 1-2 heteroatoms selected from N, O or S;

R^9 is selected from -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or a 4- to 6-membered heteroalicyclic group, wherein the 4- to 6-membered heteroalicyclic group is unsubstituted or substituted with 1-2 identical or different substituents selected from hydroxyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, formyl, acetyl, propionyl, or isopropionyl,

the 4- to 6-membered heteroalicyclic group in R^9 contains 1-2 heteroatoms selected from N, O

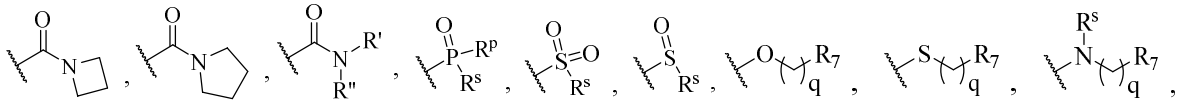
or S;

and, when R^1 is , R_4 is 4-ethyl-piperazin-1-yl, and L is -O- or , R_2 and R_3 are not both hydrogen.

2. The compound of formula (I) according to claim 1, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein R_2 is -H, -F, -Cl, methyl or methoxy.

3. The compound of formula (I) according to any one of claims 1-2, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein

R_3 is selected from -H, -F, -Cl, -Br, hydroxyl, carboxyl, cyano, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclobutyloxy, methylthio, ethylthio, propylthio, isopropylthio, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, ethynyl, ethenyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, or the following groups:



q is an integer of 2-3,

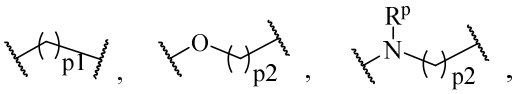
R^s is selected from -H, methyl, or ethyl, and R^p is selected from -H, methyl, or ethyl,

R’ and R’’ are each independently selected from -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, or cyclobutyl,

R_7 is selected from -H, -F, hydroxyl, cyano, carboxyl, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylamino, ethylamino, or dimethylamino.

4. The compound of formula (I) according to any one of claims 1-3, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein

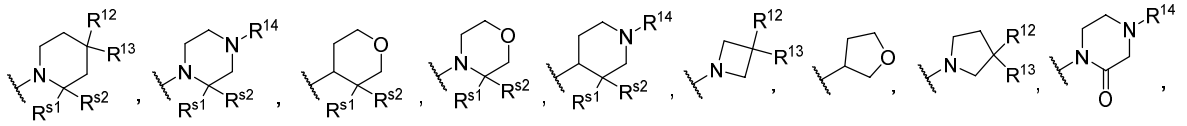
R^4 is $-T_1-R_8$,

T_1 is selected from: 

p1 is an integer of 0-3, and p2 is an integer of 2-3;

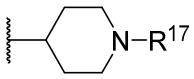
R^p is selected from -H, methyl, or ethyl;

R^8 is selected from -H, -F, -Cl, hydroxyl, amino, cyano, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methyl, ethyl, propyl, butyl, hexyl, isopropyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, methylthio, ethylthio, propylthio, isopropylthio, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino or the following groups:



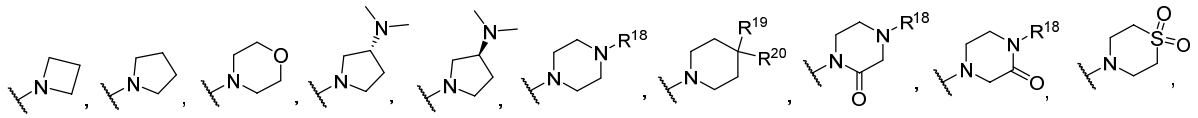
R^{12} is -H, -F, methyl, or ethyl,

R^{13} is -H, -F, hydroxyl, hydroxymethyl, cyano, methyl, ethyl, methoxy, or $-NR^{15}R^{16}$,

R^{14} is -H, -F, methyl, ethyl, propyl, isopropyl, or , wherein R^{17} is -H, -F, methyl, ethyl, propyl, or isopropyl,

R^{s1} and R^{s2} are each independently selected from H or methyl;

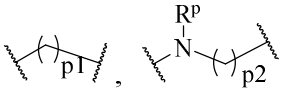
R^{15} and R^{16} are each independently -H, methyl, ethyl, propyl, isopropyl, hydroxyethyl, hydroxypropyl, cyanomethyl, cyanoethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, isopropoxyethyl, isopropoxypropyl, cyclopropyl, cyclobutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, methylethylaminoethyl, methylethylaminopropyl, fluoroethyl, fluoropropyl, methylthioethyl, methylthiopropyl, ethylthioethyl, ethylthiopropyl, isopropylthioethyl, isopropylthiopropyl, methylsulfonylethyl, methylsulfonylpropyl, ethylsulfonylethyl, ethylsulfonylpropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following groups:



R^{18} is selected from -H, methyl, ethyl, formyl, acetyl, hydroxyethyl, hydroxypropyl, fluoroethyl, fluoropropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, or ethylsulfonyl,

R^{19} and R^{20} are each independently selected from -H, methyl, ethyl, hydroxyl, cyano, fluoro, formyl, acetyl, hydroxyethyl, hydroxypropyl, fluoroethyl, fluoropropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, ethylsulfonyl, amino, methylamino, dimethylamino, methoxy, or ethoxy.

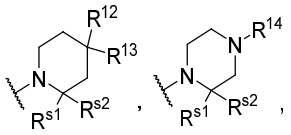
5. The compound of formula (I) according to claim 4, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein R^4 is $-T_1-R_8$,

T_1 is selected from: ,

p1 is 0, and p2 is an integer of 2-3;

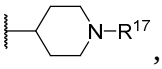
R^p is selected from -H, methyl, or ethyl;

R^8 is selected from methylamino, ethylamino, propylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino or the following groups:



R^{12} is -H, -F, methyl, or ethyl,

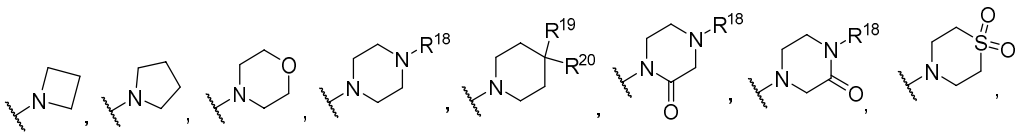
R^{13} is -H, or $-NR^{15}R^{16}$,

R^{14} is -H, methyl, ethyl, propyl, isopropyl, or , wherein R^{17} is methyl, ethyl, propyl, or isopropyl,

R^{s1} and R^{s2} are each independently selected from H or methyl;

R^{15} and R^{16} are each independently -H, methyl, ethyl, propyl, isopropyl, hydroxyethyl, hydroxypropyl, cyanomethyl, cyanoethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, isopropoxyethyl, isopropoxypropyl, cyclopropyl, cyclobutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl,

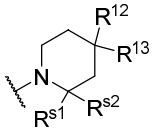
methylethylaminoethyl, methylethylaminopropyl, fluoroethyl, fluoropropyl, methylthioethyl, methylthiopropyl, ethylthioethyl, ethylthiopropyl, isopropylthioethyl, isopropylthiopropyl, methylsulfonylethyl, methylsulfonylpropyl, ethylsulfonylethyl, ethylsulfonylpropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, oxetan-3-yl, tetrahydrofuran-3-yl, or tetrahydro-2H-pyran-4-yl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following groups:



R^{18} is selected from -H, methyl, ethyl, formyl, acetyl, hydroxyethyl, hydroxypropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, or ethylsulfonyl,

R^{19} and R^{20} are each independently selected from -H, methyl, ethyl, hydroxyl, cyano, fluoro, hydroxyethyl, hydroxypropyl, fluoroethyl, fluoropropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, ethylsulfonyl, amino, methylamino, dimethylamino, methoxy, or ethoxy.

6. The compound of formula (I) according to claim 4, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein

R^4 is 

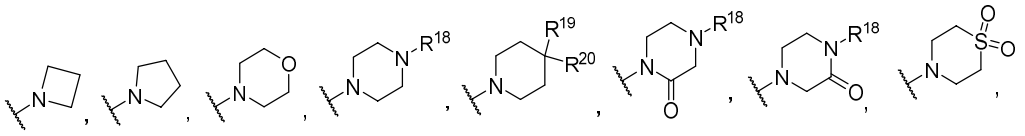
R^{12} is -H, -F, methyl, or ethyl,

R^{13} is -H or -$NR^{15}R^{16}$,

R^{s1} and R^{s2} are H,

R^{15} and R^{16} are each independently -H, methyl, ethyl, propyl, isopropyl, hydroxyethyl, hydroxypropyl, cyanomethyl, cyanoethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, isopropoxyethyl, isopropoxypropyl, cyclopropyl, cyclobutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, methylethylaminoethyl, methylethylaminopropyl, fluoroethyl, fluoropropyl, methylthioethyl,

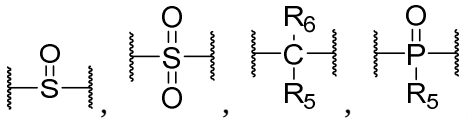
methylthiopropyl, ethylthioethyl, ethylthiopropyl, isopropylthioethyl, isopropylthiopropyl, methylsulfonylethyl, methylsulfonylpropyl, ethylsulfonylethyl, ethylsulfonylpropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, oxetan-3-yl, tetrahydrofuran-3-yl, or tetrahydro-2H-pyran-4-yl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following groups:

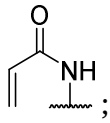


R^{18} is selected from -H, methyl, ethyl, formyl, acetyl, hydroxyethyl, hydroxypropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, or ethylsulfonyl,

R^{19} and R^{20} are each independently selected from -H, methyl, ethyl, hydroxyl, cyano, or fluoro.

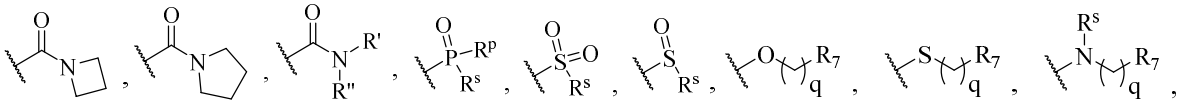
7. The compound of formula (I) according to claim 1, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein X is N or CH;

L is -O-, -S-, , or -NR_5-, wherein R_5 and R_6 are each independently hydrogen, methyl, ethyl, propyl or isopropyl;

R_1 is ;

R_2 is -H, -F, -Cl, methyl, or methoxy;

R_3 is selected from -H, -F, -Cl, -Br, hydroxyl, carboxyl, cyano, methyl, ethyl, propyl, isopropyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclobutyloxy, methylthio, ethylthio, propylthio, isopropylthio, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, ethynyl, ethenyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, or the following groups:



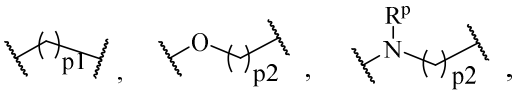
q is an integer of 2-3,

R^s is selected from -H, methyl, or ethyl, and R^p is selected from -H, methyl, or ethyl,

R' and R'' are each independently selected from -H, methyl, ethyl, propyl, isopropyl, cyclopropyl, or cyclobutyl,

R_7 is selected from -H, -F, hydroxyl, cyano, carboxyl, amino, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, methylamino, ethylamino, or dimethylamino;

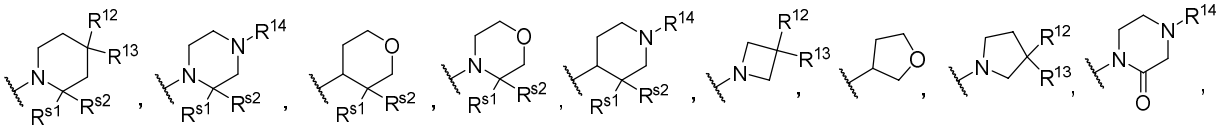
R^4 is $-T_1-R_8$,

T_1 is selected from: 

p1 is an integer of 0-3, and p2 is an integer of 2-3;

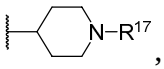
R^p is selected from -H, methyl, or ethyl;

R^8 is selected from -H, -F, -Cl, hydroxyl, amino, cyano, fluoromethoxy, difluoromethoxy, trifluoromethoxy, methyl, ethyl, propyl, butyl, hexyl, isopropyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, butoxy, isopropoxy, methylthio, ethylthio, propylthio, isopropylthio, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino or the following groups:



R^{12} is -H, -F, methyl, or ethyl,

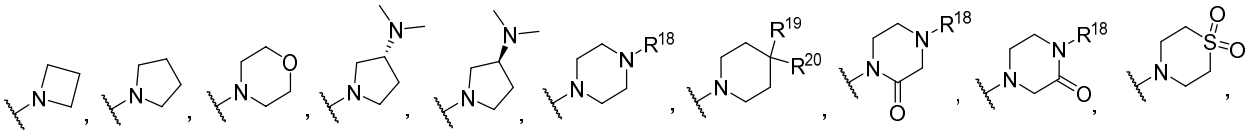
R^{13} is -H, -F, hydroxyl, hydroxymethyl, cyano, methyl, ethyl, methoxy, or $-NR^{15}R^{16}$,

R^{14} is -H, -F, methyl, ethyl, propyl, isopropyl, or , wherein R^{17} is -H, -F, methyl, ethyl, propyl, or isopropyl,

R^{s1} and R^{s2} are each independently selected from -H or methyl;

R^{15} and R^{16} are each independently -H, methyl, ethyl, propyl, isopropyl, hydroxyethyl, hydroxypropyl, cyanomethyl, cyanoethyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, isopropoxyethyl, isopropoxypropyl, cyclopropyl, cyclobutyl, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, diethylaminopropyl, methylethylaminoethyl, methylethylaminopropyl, fluoroethyl, fluoropropyl, methylthioethyl, methylthiopropyl, ethylthioethyl, ethylthiopropyl, isopropylthioethyl, isopropylthiopropyl, methylsulfonylethyl, methylsulfonylpropyl, ethylsulfonylethyl, ethylsulfonylpropyl, 2-

hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following groups:



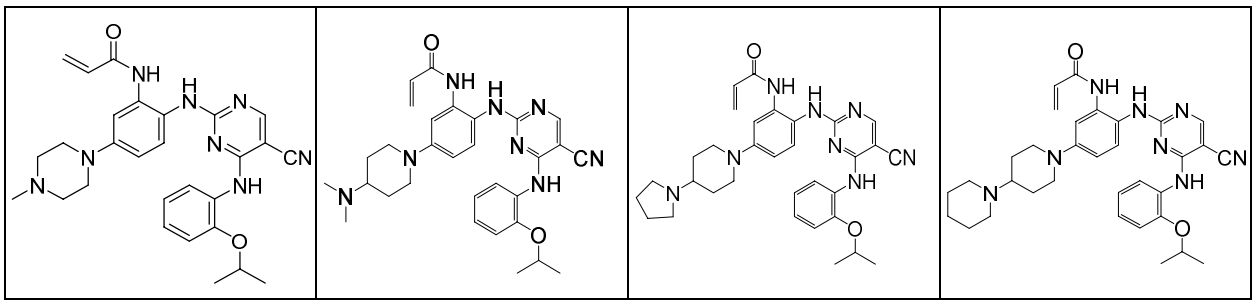
R^{18} is selected from -H, methyl, ethyl, formyl, acetyl, hydroxyethyl, hydroxypropyl, fluoroethyl, fluoropropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, or ethylsulfonyl,

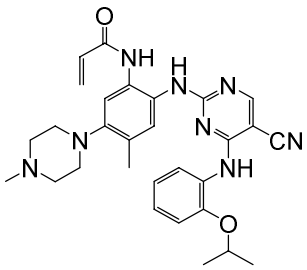
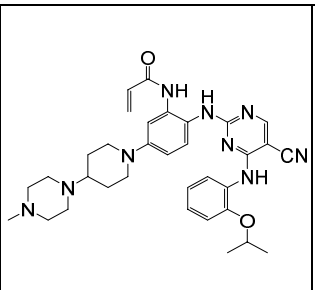
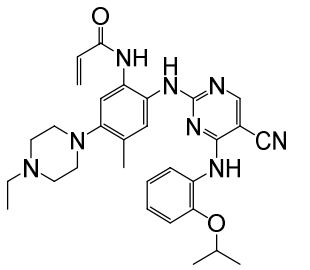
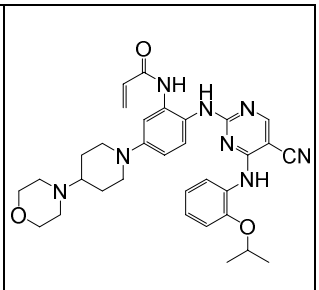
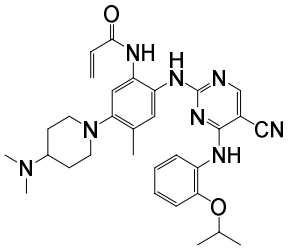
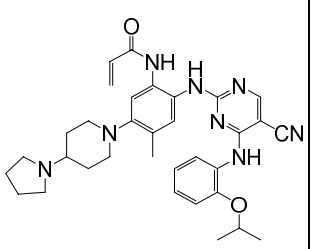
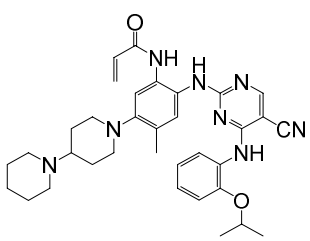
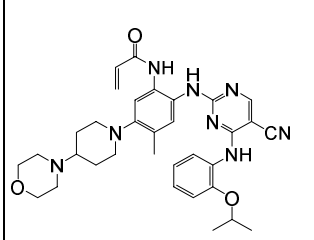
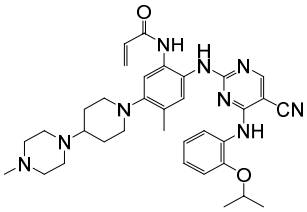
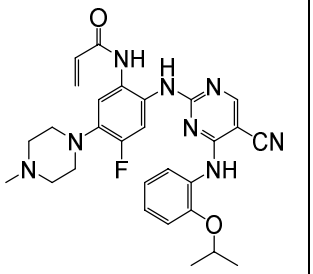
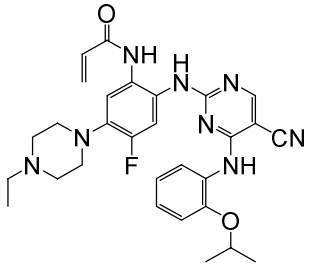
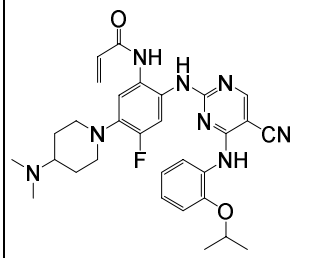
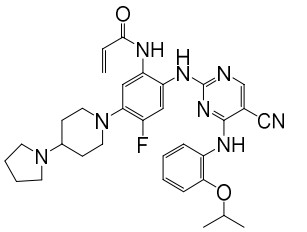
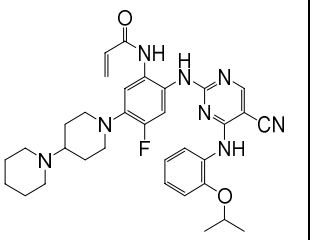
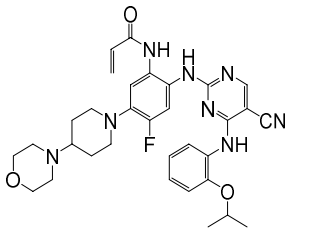
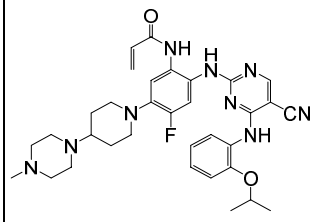
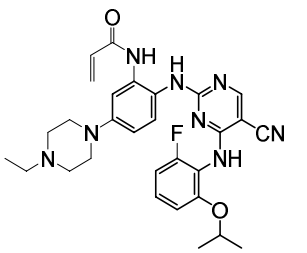
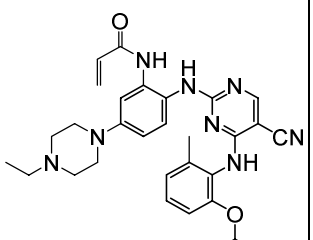
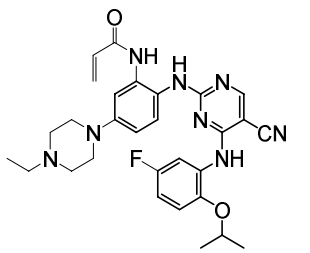
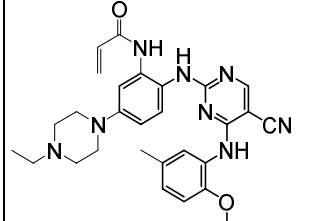
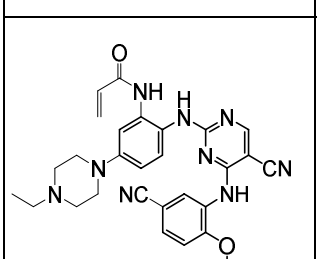
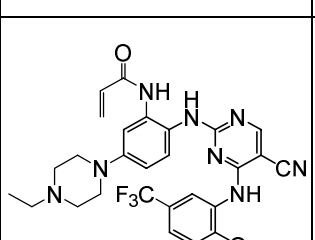
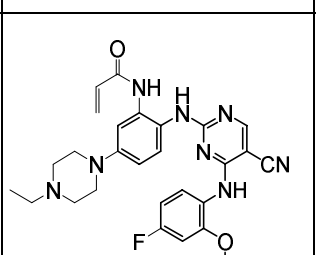
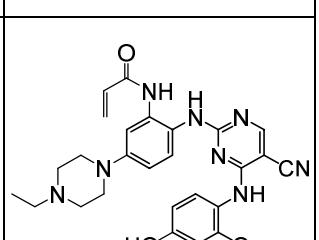
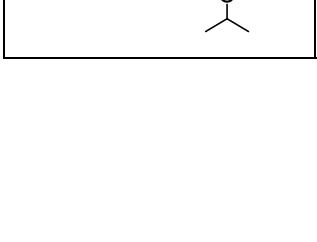
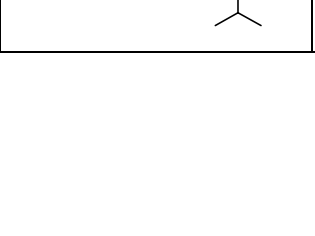
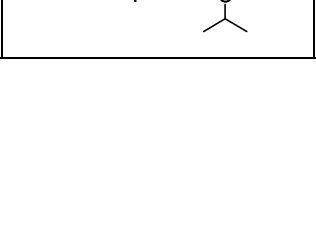
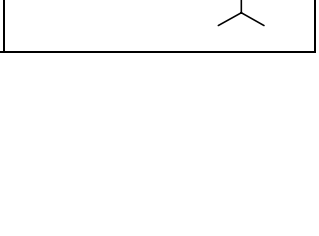
R^{19} and R^{20} are each independently selected from -H, methyl, ethyl, hydroxyl, cyano, fluoro, formyl, acetyl, hydroxyethyl, hydroxypropyl, fluoroethyl, fluoropropyl, methoxyethyl, methoxypropyl, ethoxyethyl, ethoxypropyl, methylsulfonyl, ethylsulfonyl, amino, methylamino, dimethylamino, methoxy, or ethoxy,

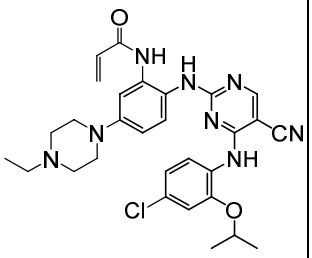
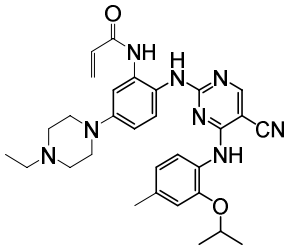
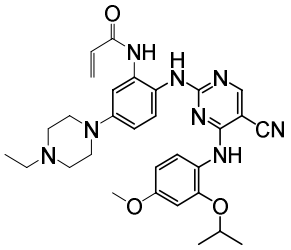
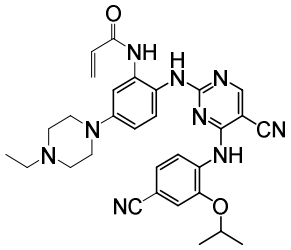
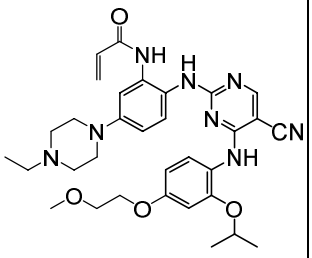
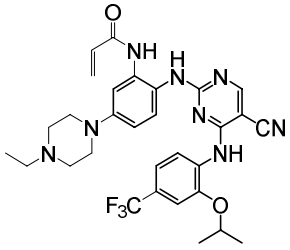
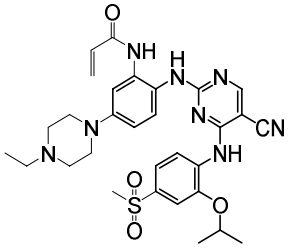
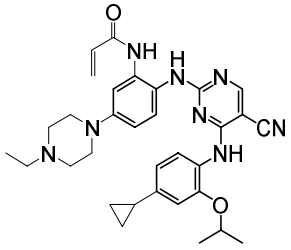
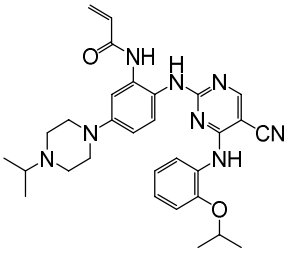
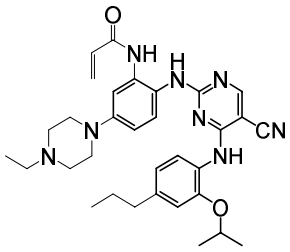
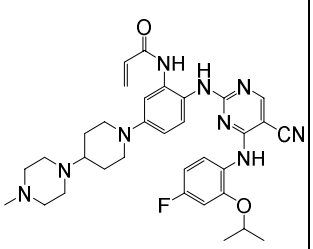
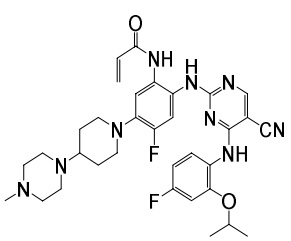
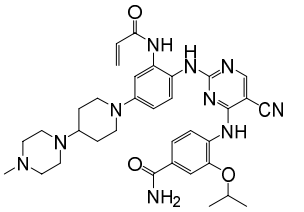
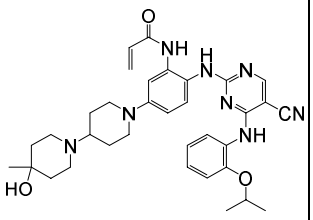
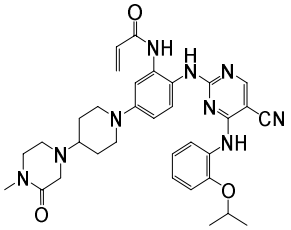
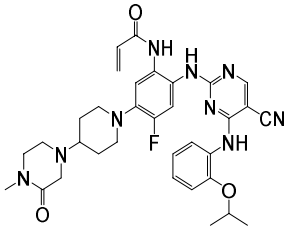
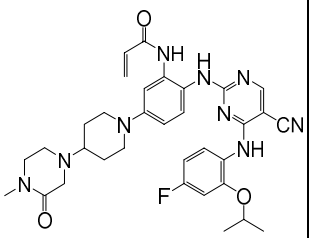
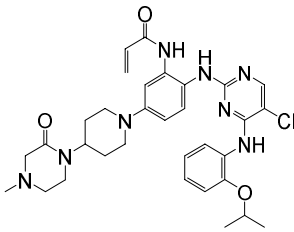
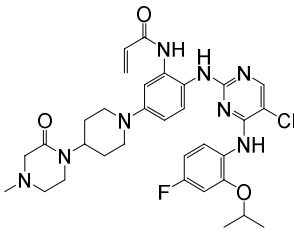
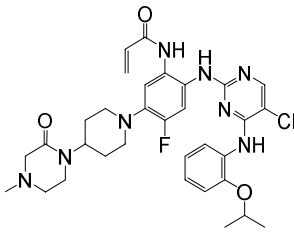
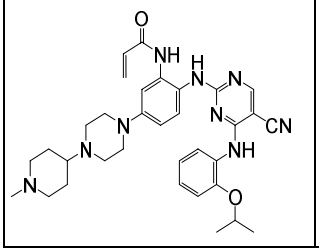
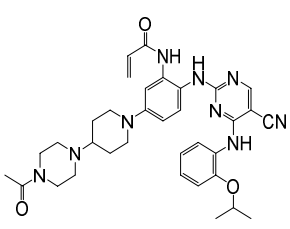
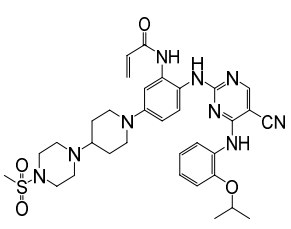
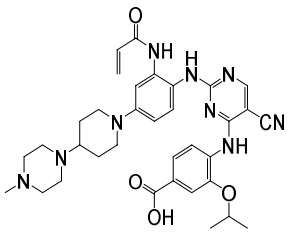
and, when R_4 is 4-ethyl-piperazin-1-yl, and L is -O- or , R_2 and R_3 are not both hydrogen.

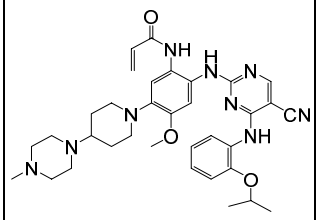
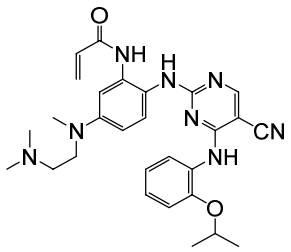
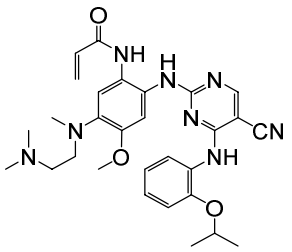
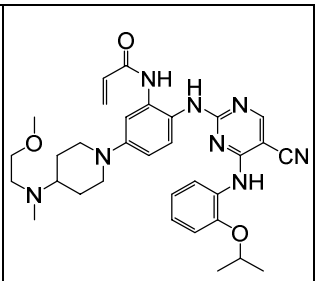
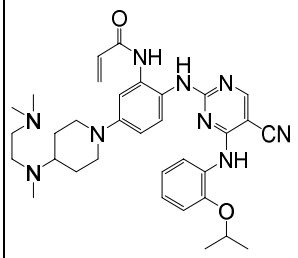
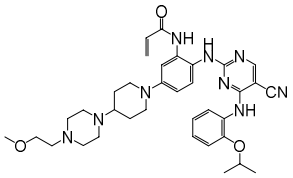
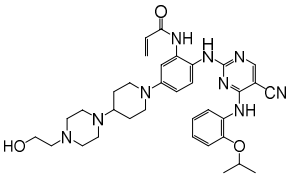
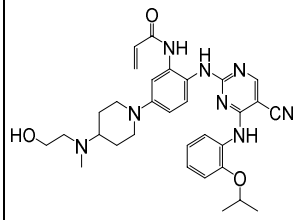
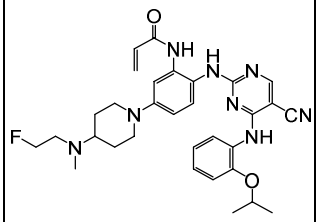
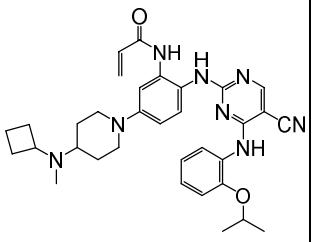
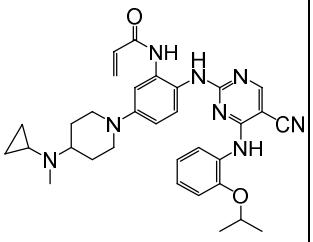
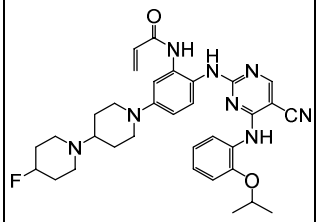
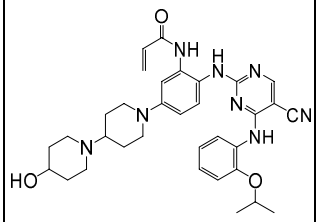
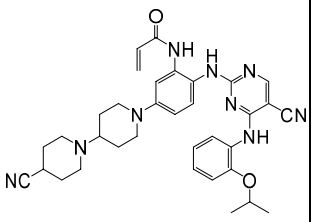
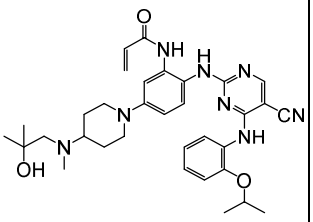
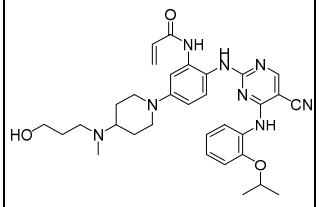
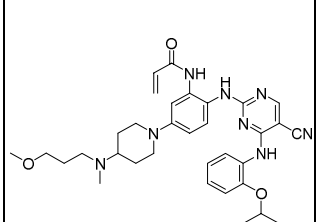
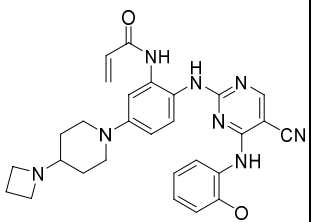
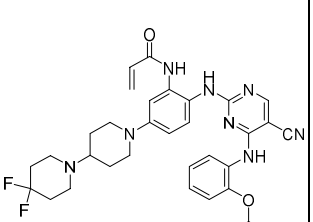
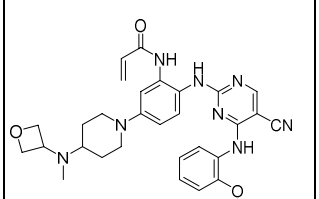
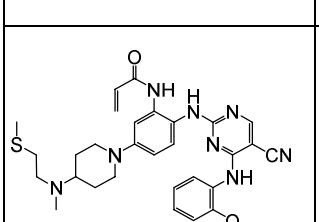
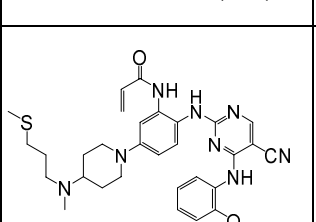
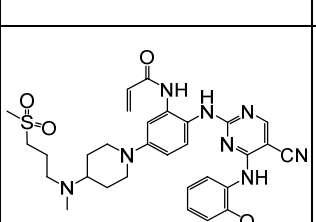
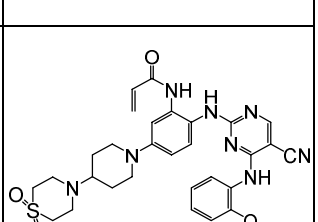
8. The compound of formula (I) according to claim 7, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein L is -O-, and, when R_4 is 4-ethyl-piperazin-1-yl, R_2 and R_3 are not both hydrogen.

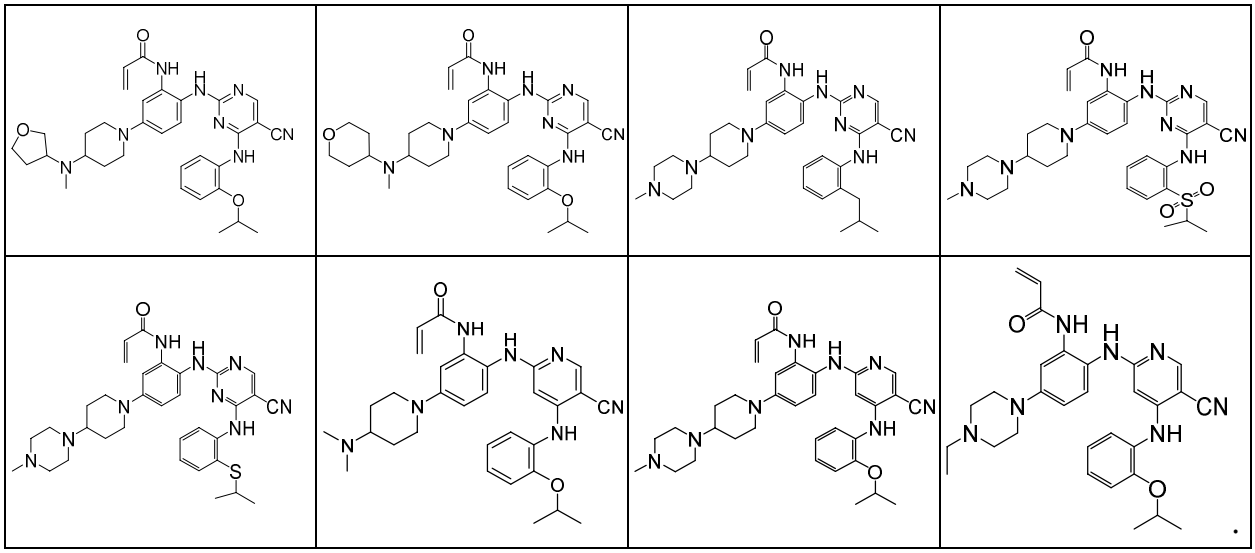
9. The compound of formula (I) according to claim 1, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein the compound is selected from:





10. A pharmaceutical composition, comprising the compound according to any one of claims 1-9, or a pharmaceutically acceptable salt, a hydrate, a solvate, or a prodrug thereof, and a pharmaceutically acceptable carrier or excipient.

11. The pharmaceutical composition according to claim 10, wherein the pharmaceutical composition further comprises one or more other therapeutic agents.

12. Use of the compound according to any one of claims 1-9, or a pharmaceutically acceptable salt, a hydrate, a solvate or a prodrug thereof, or the pharmaceutical composition according to claim 10 or 11 in the manufacture of a medicament for treating diseases related to tyrosine kinase FGFR4 or autoimmune diseases.

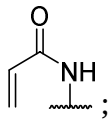
13. The use according to claim 12, wherein the diseases related to tyrosine kinase FGFR4 or the autoimmune diseases include fundus oculi disease, xerophthalmia, psoriasis, vitiligo, dermatitis, alopecia areata, rheumatoid arthritis, colitis, multiple sclerosis, systemic lupus erythematosus, Crohn’s disease, atherosclerosis, pulmonary fibrosis, liver fibrosis, bone marrow fibrosis, non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, ovarian cancer, cervical cancer, colorectal cancer, melanoma, endometrial cancer, prostate cancer, bladder cancer, leukemia, gastric cancer, liver cancer, gastrointestinal stromal tumor, thyroid cancer, chronic granulocytic leukemia, acute myelocytic

leukemia, non-Hodgkin's lymphoma, nasopharyngeal cancer, esophageal cancer, brain tumor, B-cell and T-cell lymphoma, lymphoma, multiple myeloma, biliary tract cancerous sarcoma, and cholangiocarcinoma.

14. The compound of formula (I) according to claim 1, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein

X is N;

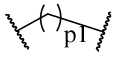
L is -O-;

R_1 is ;

R_2 is hydrogen, or C_1-C_3 alkoxy;

R_3 is selected from hydrogen, or halogen;

R_4 is -T_1-R_8;

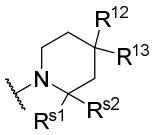
T_1 is: ;

p1 is 0;

R_8 is a 4- to 6-membered heteroalicyclic group, wherein the 4- to 6-membered heteroalicyclic group is unsubstituted or substituted with -$NR^{10}R^{11}$;

R^{10} and R^{11} are each independently selected from -H, C_1-C_6 alkyl, or hydroxyl-substituted C_2-C_6 alkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered heteroalicyclic group, wherein the 4- to 6-membered heteroalicyclic group is unsubstituted or substituted with C_1-C_3 alkyl.

15. The compound of formula (I) according to claim 14, or an isomer, a hydrate, a solvate, a pharmaceutically acceptable salt, or a prodrug thereof, wherein

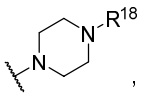
R^4 is 

R^{12} is -H,

R^{13} is -$NR^{15}R^{16}$,

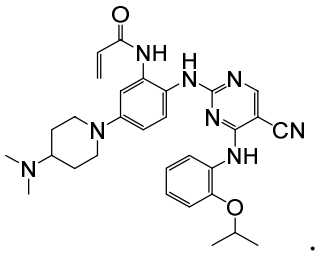
R^{s1} and R^{s2} are H,

R^{15} and R^{16} are each independently -H, methyl, ethyl, propyl, isopropyl, hydroxyethyl, hydroxypropyl, 2-hydroxy-2-methylpropyl, or 3-hydroxy-3-methylbutyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a substituted or unsubstituted 4- to 6-membered heteroalicyclic group selected from the following group:

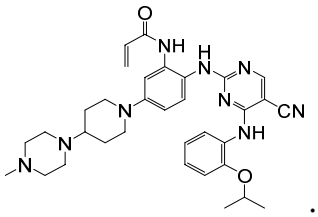


R^{18} is selected from -H, methyl, or ethyl.

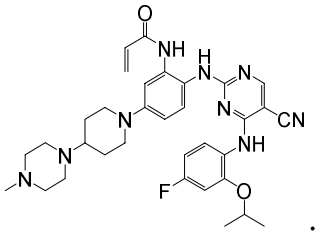
16. A compound of the following structure, or a pharmaceutically acceptable salt thereof:



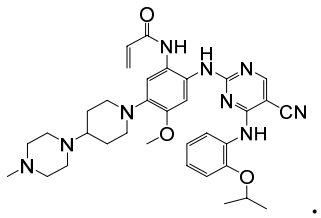
17. A compound of the following structure, or a pharmaceutically acceptable salt thereof:



18. A compound of the following structure, or a pharmaceutically acceptable salt thereof:



19. A compound of the following structure, or a pharmaceutically acceptable salt thereof:



20. A compound of the following structure, or a pharmaceutically acceptable salt thereof:

