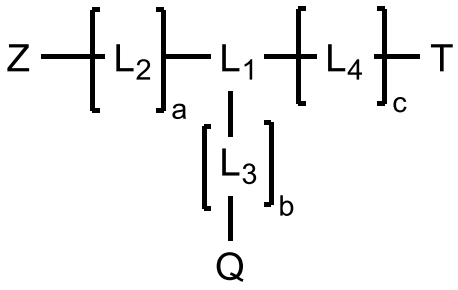
Claims

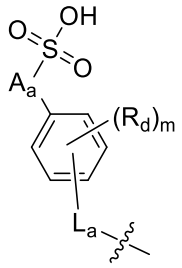
1. A compound represented by Formula (A), or a stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof,



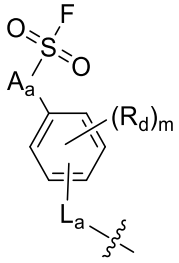
Formula (A)

wherein Z is a payload, T is a targeting moiety,

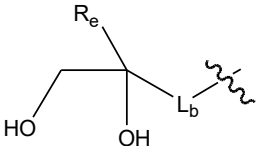
Q is a covalent group selected from the structures represented by the following Formulas (Q-1) to (Q-21):



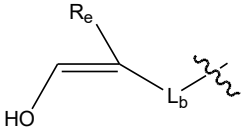
Formula (Q-1),



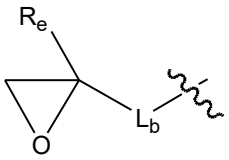
Formula (Q-2),



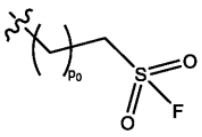
Formula (Q-3),



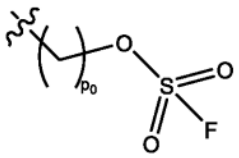
Formula (Q-4),



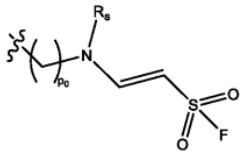
Formula (Q-5),



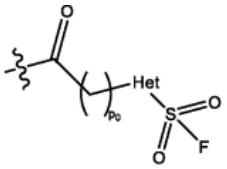
Formula (Q-6),



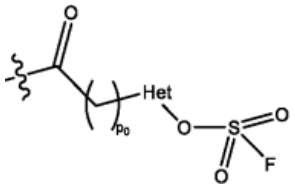
Formula (Q-7),



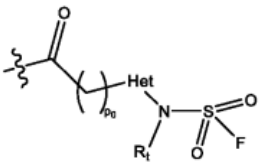
Formula (Q-8),



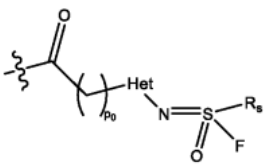
Formula (Q-9),



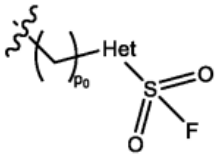
Formula (Q-10),



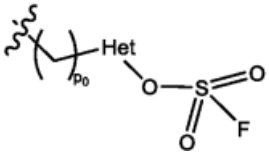
Formula (Q-11),



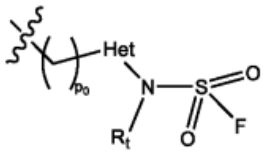
Formula (Q-12),



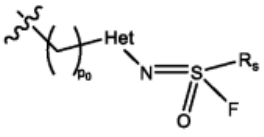
Formula (Q-13),



Formula (Q-14),

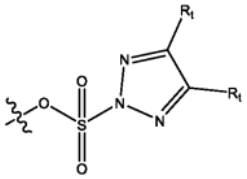


Formula (Q-15),

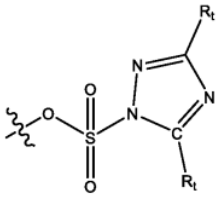


Formula (Q-16),

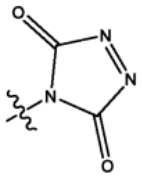
Claims



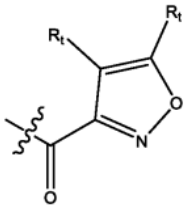
Formula (Q-17),



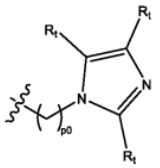
Formula (Q-18),



Formula (Q-19),



Formula (Q-20),



Formula (Q-21);

L_1, L_2, L_3, L_4, A_a, L_a, and L_b are the same or different, and are each independently selected from a bond or a linking group,

a, b, c, m, and p_0 are the same or different, and are each independently selected from an integer of 0 to 6 (e.g., 0, 1, 2, 3, 4, 5, 6),

R_d and R_e are the same or different, and are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-20} alkyl, C_{1-20} alkoxy, and halogenated C_{1-20} alkyl;

Het is an optionally substituted saturated heterocyclylene or heteroarylene;

R_s is selected from hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R_t is independently selected from hydrogen, halogen, nitro, cyano, optionally substituted mercapto, optionally substituted amino, optionally substituted selenyl, optionally substituted C_{1-20} alkyl, optionally substituted C_{3-20} cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, and optionally substituted heteroaryl;

~~~ denotes the linking site of the group.

2. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that, in Formula (A),

L_1 is selected from N, C_{1-20} alkanetriyl optionally substituted with one or more R_0, and any combination thereof;
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Claims

L_2, L_3, L_4, A_a, L_a, and L_b are the same or different, and are each independently selected from a bond, -O-, -S-, -P-, -O-(HO-P=O)-O-, -N(R_0)-, -CO-, C_{1-20} alkylene optionally substituted with one or more R_0, 3- to 20-membered heterocyclylene optionally substituted with one or more R_0, and any combination thereof; further preferably, L_2, L_3, L_4, A_a, L_a, and L_b are each independently selected from a bond, -O-, -S-, -P-, -O-(HO-P=O)-O-, -N(R_0)-, -CO-, C_{1-10} alkylene (C_{1-6} alkylene, C_{1-4} alkylene) optionally substituted with one or more R_0, 3- to 20-membered heterocyclylene (3- to 10-membered heterocyclylene, 3- to 6-membered heterocyclylene) optionally substituted with one or more R_0 , and any combination thereof;

each R_0 is the same or different, and is independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-10} alkyl, C_{1-10} alkoxy, halogenated C_{1-10} alkyl, and halogenated C_{1-10} alkoxy;

preferably, a and c are not 0 at the same time;

when m is not 0, R_d is selected from halogen, hydroxy, cyano, nitro, amino, C_{1-10} alkyl, C_{1-10} alkoxy, halogenated C_{1-10} alkyl, and halogenated C_{1-10} alkoxy; preferably, R_d is selected from halogen, hydroxyl, cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, and halogenated C_{1-6} alkoxy; further preferably, R_d is selected from halogen, hydroxyl, cyano, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, halogenated C_{1-4} alkyl, and halogenated C_{1-4} alkoxy.

3. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that:

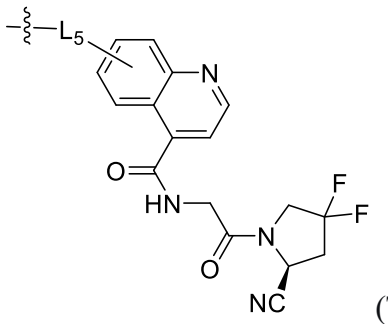
Z is selected from a nuclide-chelating group;

preferably, Z is selected from a group formed by a bifunctional chelating agent; preferably, the bifunctional chelating agent is selected from DOTA, NOTA, NODA, NODAGA, DOTP, TETA, ATSM, PTSM, EDTA, EC, HBEDCC, DTPA, SBAD, BAPEN, Df, DFO, TACN, NO2A/NOTAM, CB-DO2A, Cyclen, NOTA-AA, DO3A, DO3AP, HYNIC, MAS3, MAG3, and isonitrile.

4. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that:

T is selected from a structure targeting fibroblast activation protein-α represented by the following Formula (T-1),

Claims



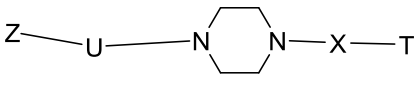
(T-1)

wherein L_5 is a divalent linking group, preferably S, O, or a bond, and preferably L_5 is a bond;

denotes the attachment site of the group.

5. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that:

the compound represented by Formula (A) has the structure represented by the following



Formula (A-1)

wherein,

U is selected from $-U_1-$, $-U_2-U_3(R_a)-U_4-$;

X is selected from X_1-, $-X_2-X_3(R_b)-X_4-$;

when U is selected from $-U_1-$, X is not $-X_1-$;

R_a and R_b are the same or different, and are each independently selected from the structures represented by Formulas (Q-1), (Q-2), (Q-3), (Q-4), and (Q-5);

U_3 and X_3 are the same or different, and are each independently selected from N, C_{1-20} alkanetriyl (C_{1-10} alkanetriyl, C_{1-6} alkanetriyl, C_{1-4} alkanetriyl) optionally substituted with one or more R_0, and any combination thereof; and/or

U_1、U_2、U_4、X_1、X_2、X_4、L_a、L_b、and A_a are the same or different, and are each independently selected from a bond, -O-, -S-, -P-, -O-(HO-P=O)-O-, $-N(R_0)-$, -CO-, C_{1-20} alkylene (C_{1-10} alkylene, C_{1-6} alkylene, C_{1-4} alkylene) optionally substituted with one or more R_0, and any combination thereof; preferably, A_a is selected from a bond;

wherein each R_0 is the same or different, and is independently selected from hydrogen, halogen, hydroxy, cyano, nitro, amino, C_{1-10} alkyl, C_{1-10} alkoxy, halogenated C_{1-10} alkyl, and halogenated C_{1-10} alkoxy; preferably, each R_0 is the same or different, and is independently selected

from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, and halogenated C_{1-6} alkoxy.

6. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 5, characterized in that, in the compound represented by Formula (A-1), U is selected from $-U_1-$, X is selected from $-X_2-X_3(R_b)-X_4-$, and

U_1 is selected from a bond;

X_4 is selected from a bond;

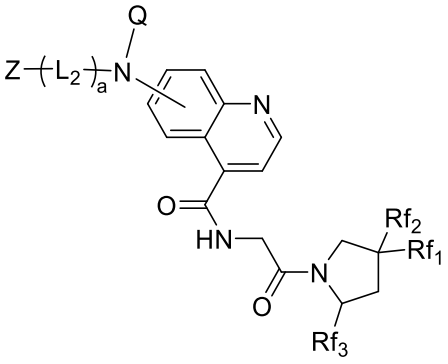
X_3 is selected from N;

X_2 is selected from C_{1-10} alkylene (preferably C_{1-6} alkylene, C_{1-4} alkylene, C_3 alkylene);

Q is selected from the structures represented by Formula (Q-1) or (Q-2), and A_a is selected from a bond, L_a is selected from -CO-, -CO-C_{1-3} alkylene-, -CO-C_{1-3} alkylene-NH-CO-, -CO-C_{1-3} alkylene-NH-CO-C_{1-3} alkylene-, -C_{1-3} alkylene-, C_{1-3} alkylene-NH-CO-C_{1-3} alkylene-, -CO-C_{1-6} alkylene-N(R_0)-CO-, -CO-C_{1-4} alkylene-N(CH_3)-CO-, -CO-C_{1-6} alkylene-CO-NH-C_{1-3} alkylene-; preferably Q is selected from -CO-C_{1-4} alkylene-N(R_0)-CO-, such as -CO-methylene-N(R_0)-CO-; preferably, R_0 is selected from C_{1-4} alkyl.

7. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that,

the compound represented by Formula (A) has the structure represented by the following Formula (A-4):

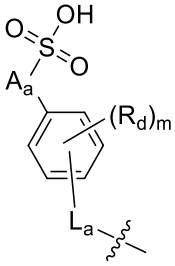


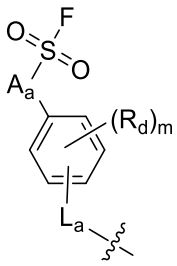
Formula (A-4)

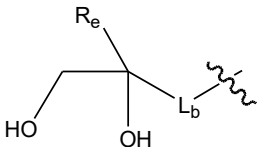
wherein Z is a payload,

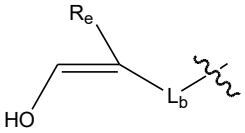
Q is selected from the structures represented by the following Formulas (Q-1), (Q-2), (Q-3), (Q-4), and (Q-5):

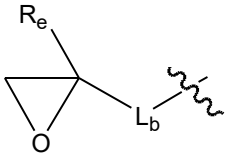
Claims


Formula (Q-1)


Formula (Q-2)


Formula (Q-3)


Formula (Q-4)


Formula (Q-5),

L_2, A_a, L_a, and L_b are the same or different, and are each independently selected from a linking group;

a and m are the same or different, and are each independently selected from an integer of 0 to 6;

R_d and R_e are the same or different, and are each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-20} alkyl, C_{1-20} alkoxy, and halogenated C_{1-20} alkyl;

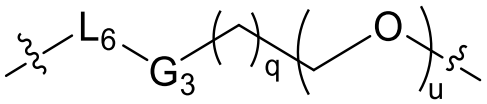
Rf_1 and Rf_2 are independently selected from hydrogen and halogen, such as fluorine, chlorine, iodine, bromine, preferably fluorine;

Rf_3 is selected from hydrogen and cyano;

~ denotes the attachment site of the group.

8. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 7, characterized in that,

L_2 comprises the structure represented by the following Formula (L-1):


Formula (L-1)

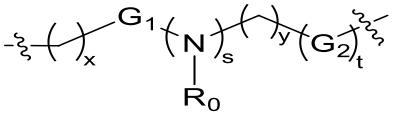
wherein q is an integer of 1 to 20, and u is an integer of 0 to 10;

G_3 is C_{3-10} cycloalkyl, 3- to 10-membered heterocycloalkyl, 5- to 10-membered heteroaryl, or C_{6-10} aryl;

L_6 is a bond or -CO-C_{1-3} alkylene-NH-; and/or,

L_a and L_b are independently selected from the structure represented by the following Formula (L-2):

Claims



Formula (L-2),

x is selected from 0, 1, and 2; s is 0 or 1; y is selected from 0, 1, 2, 3, and 4; t is 0 or 1;

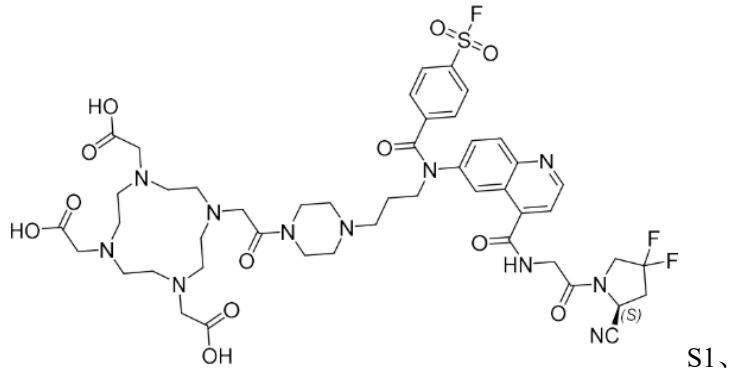
G_1 or G_2 is independently -CH_2- or carbonyl, and they are not -CH_2- at the same time;

R_0 is each independently selected from hydrogen, halogen, hydroxy, cyano, nitro, amino, C_{1-10} alkyl, C_{1-10} alkoxy, halogenated C_{1-10} alkyl, and halogenated C_{1-10} alkoxy,

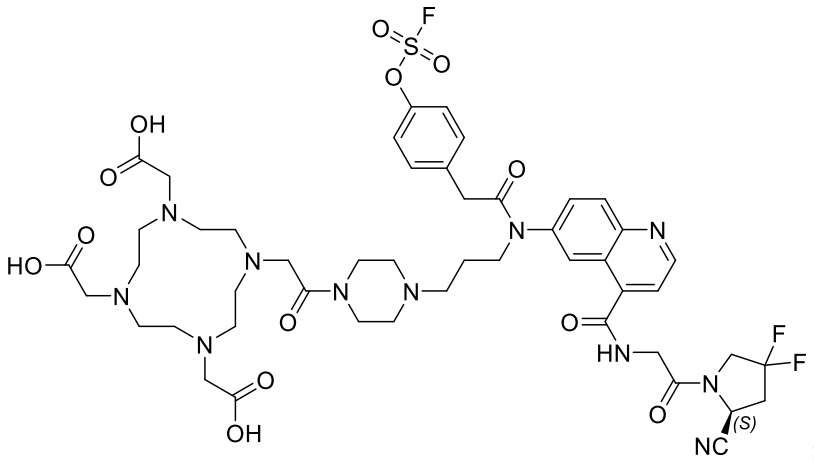
denotes the attachment site of the group.

9. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 1, characterized in that:

the compound represented by Formula (A) is selected from:

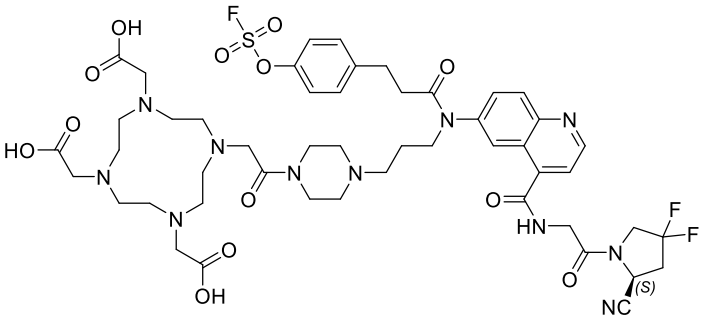


S1、

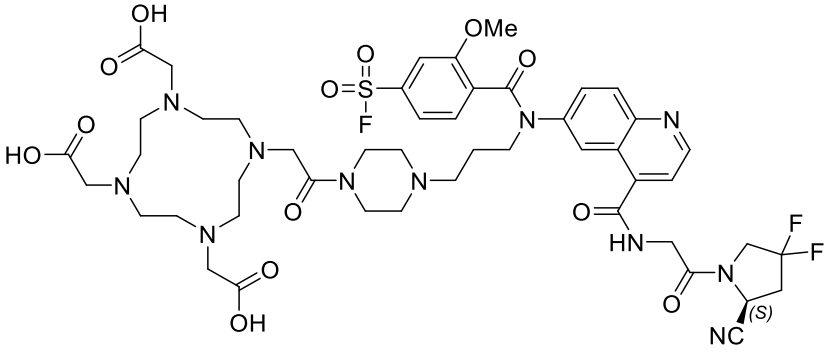


S18、

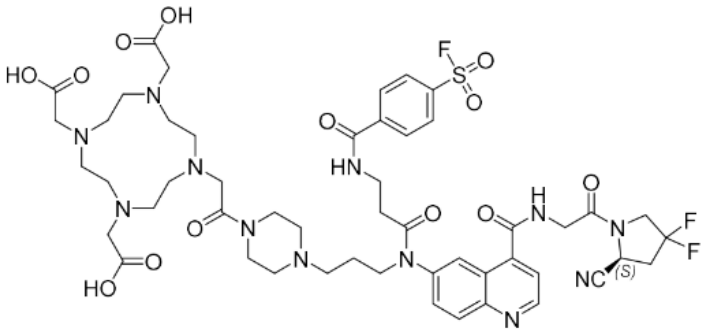
Claims



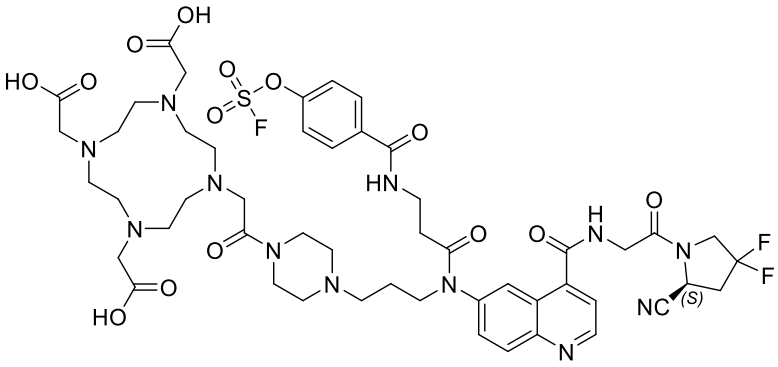
S19、



S20、

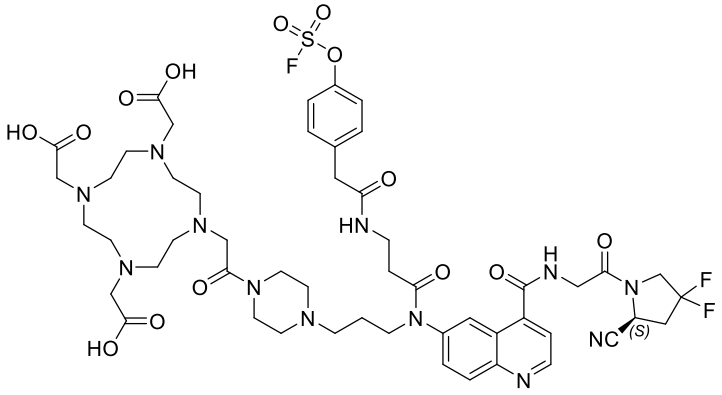


S3、



S21、

Claims



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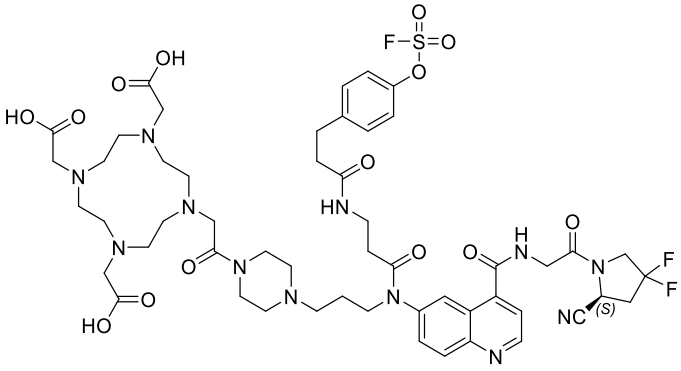

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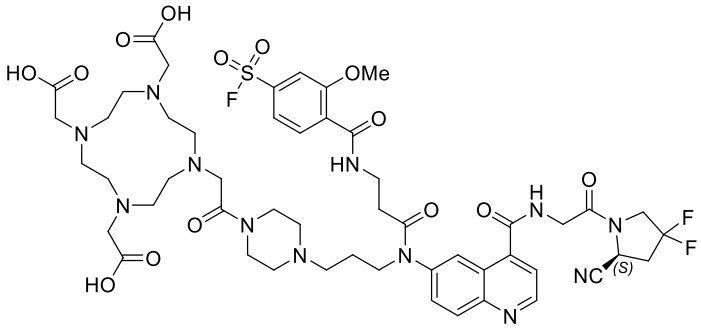

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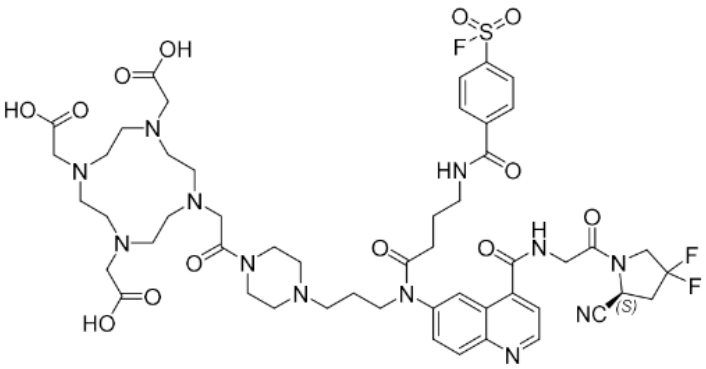

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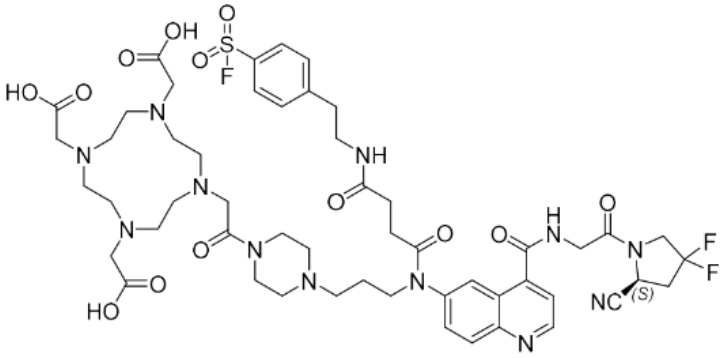
Claims



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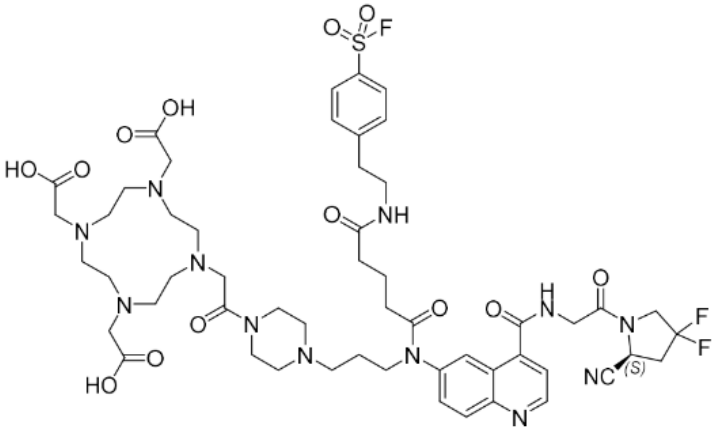

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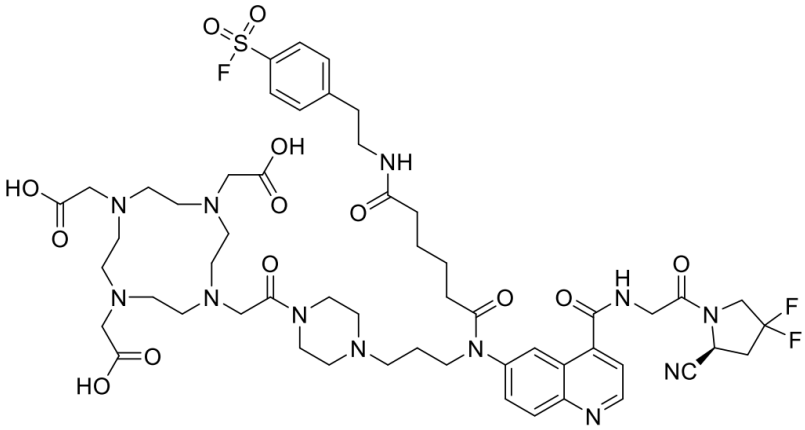

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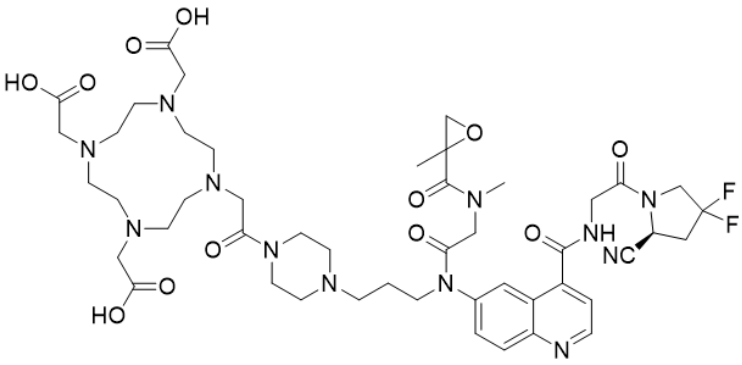

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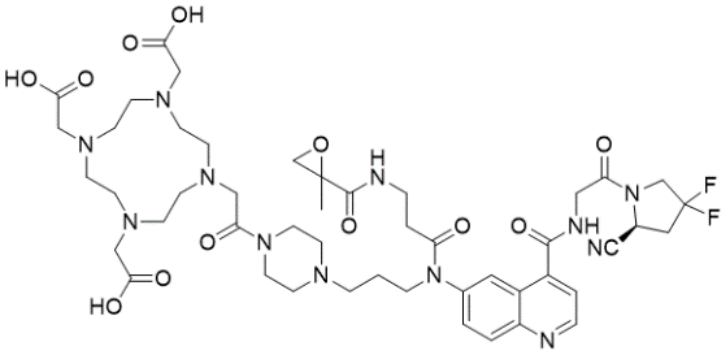
Claims



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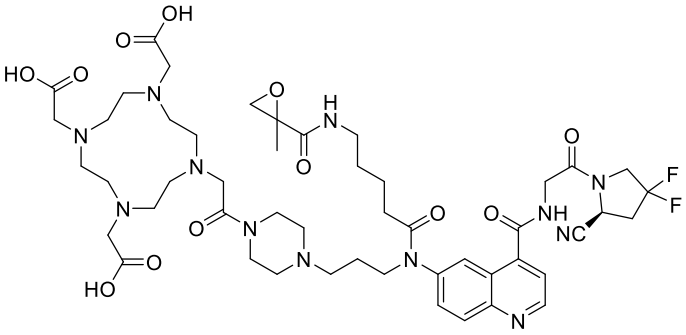

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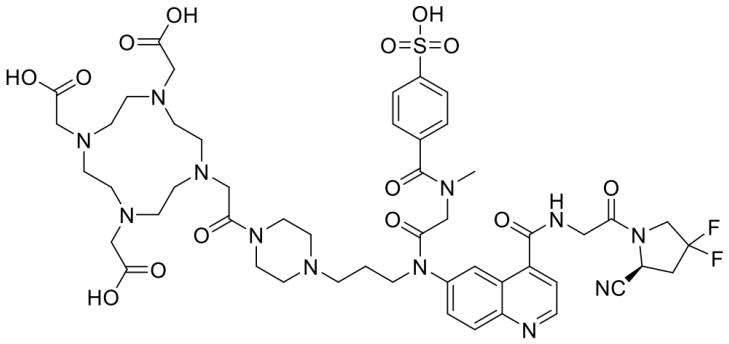

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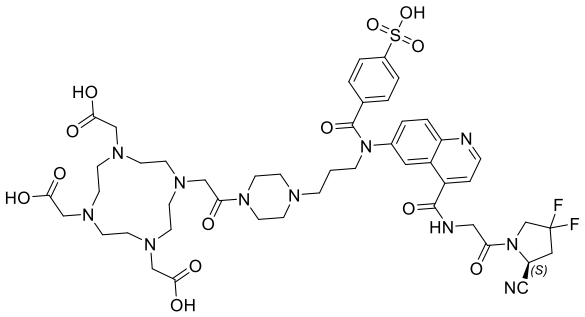

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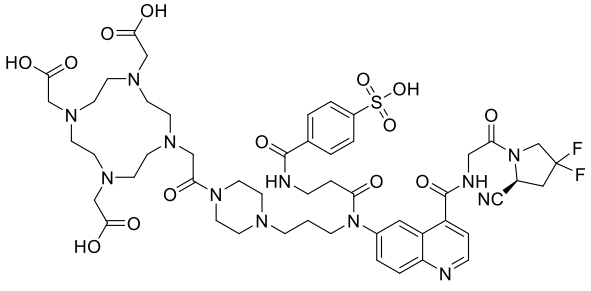

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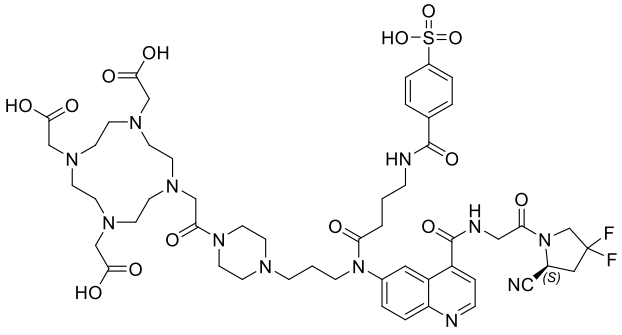
Claims



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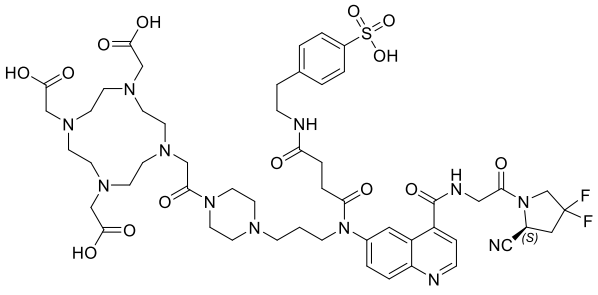

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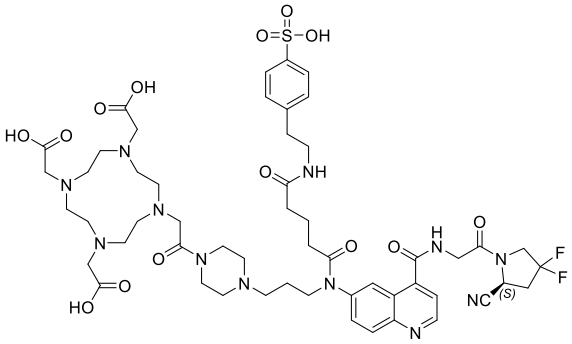

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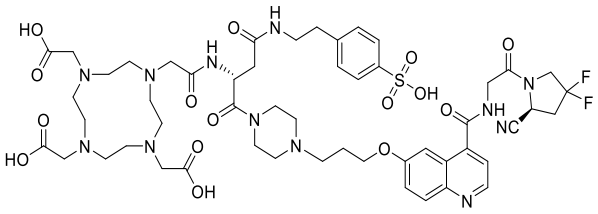

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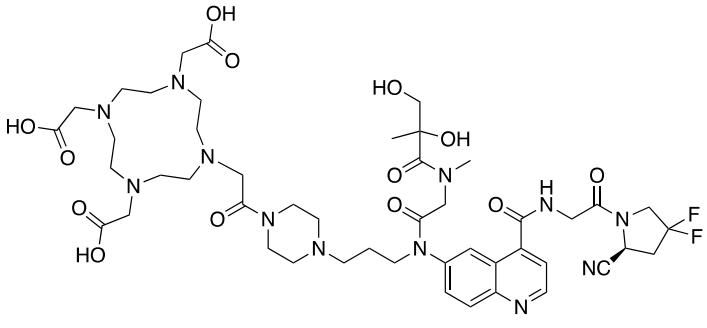

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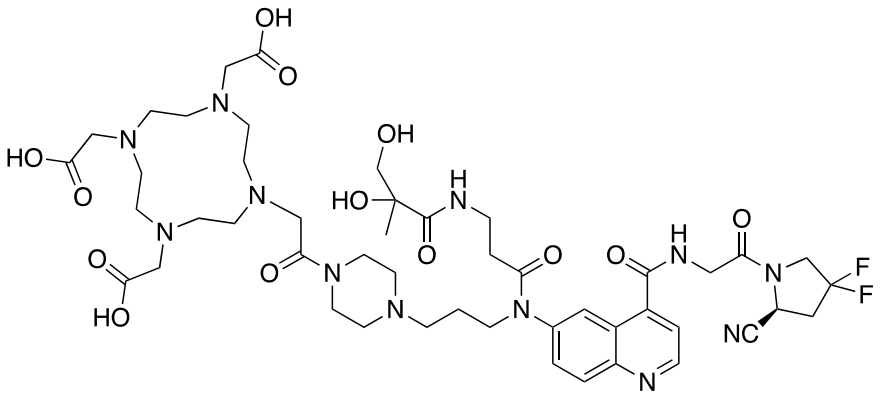
Claims



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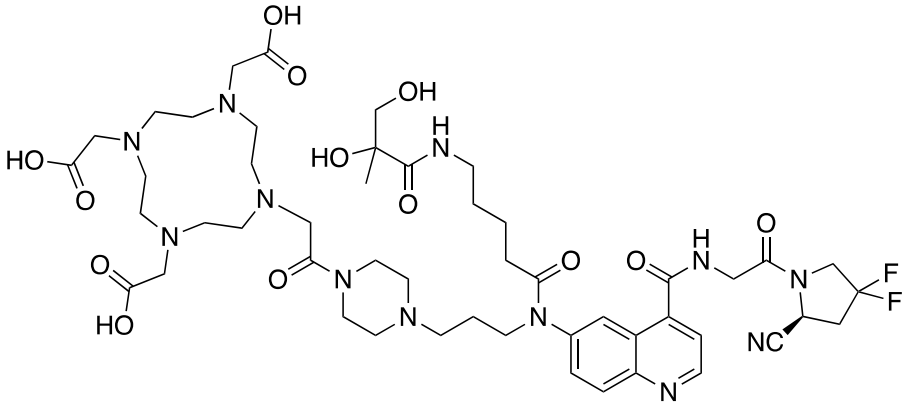

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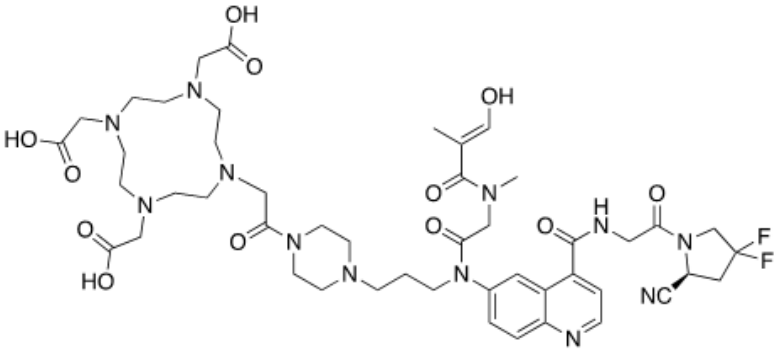

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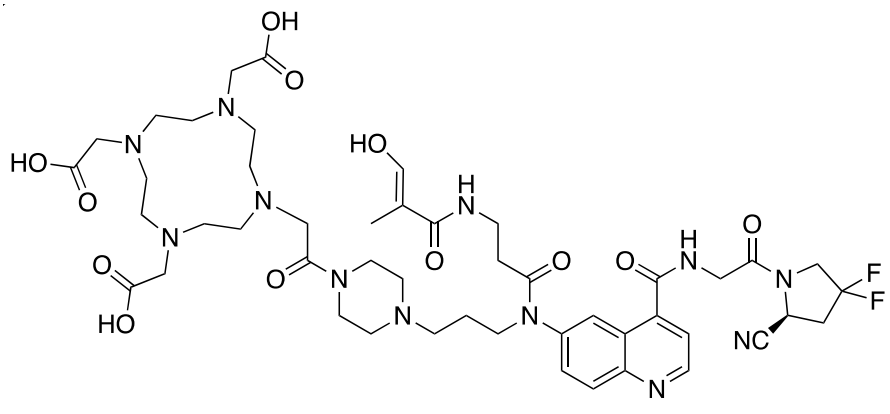
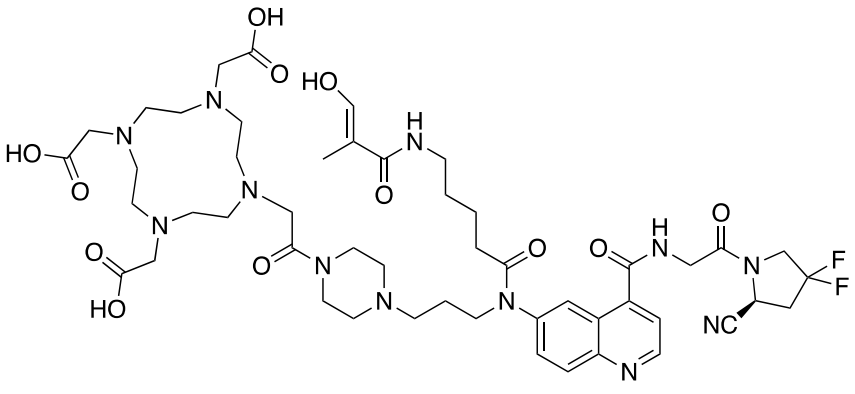


S35,

Claims



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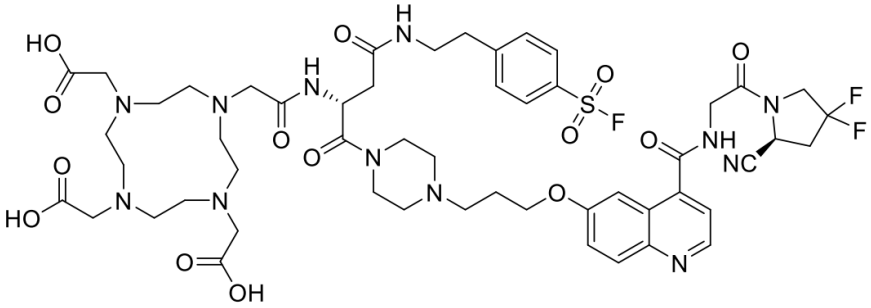

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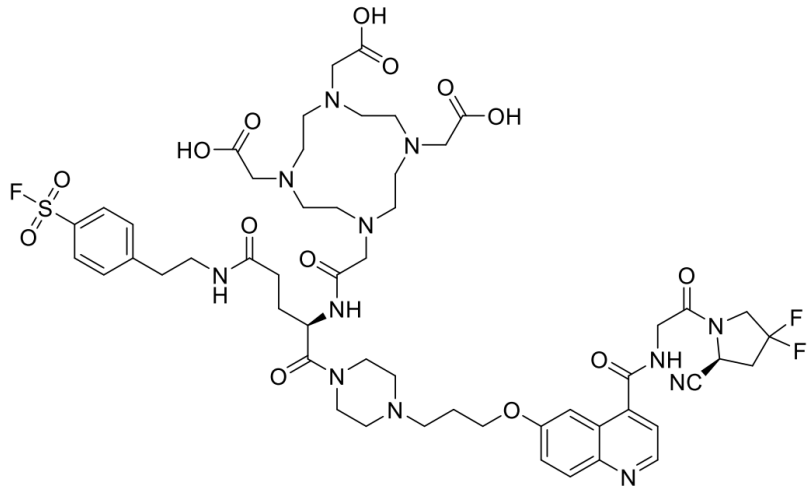

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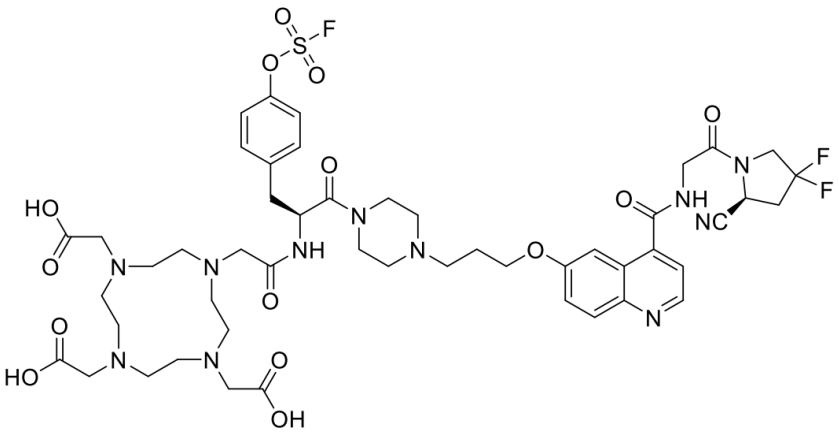
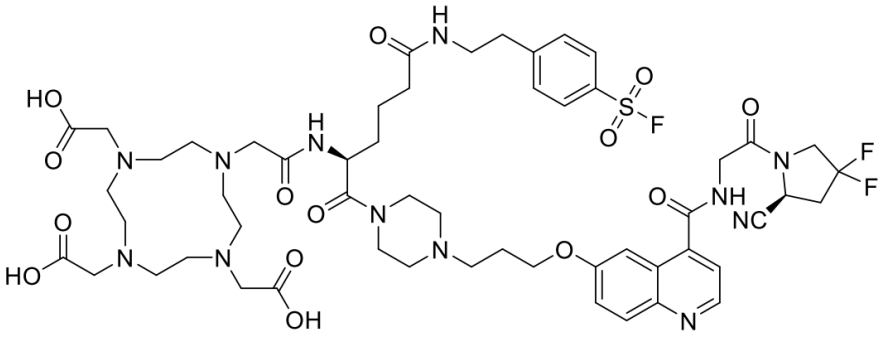


S12 、

Claims



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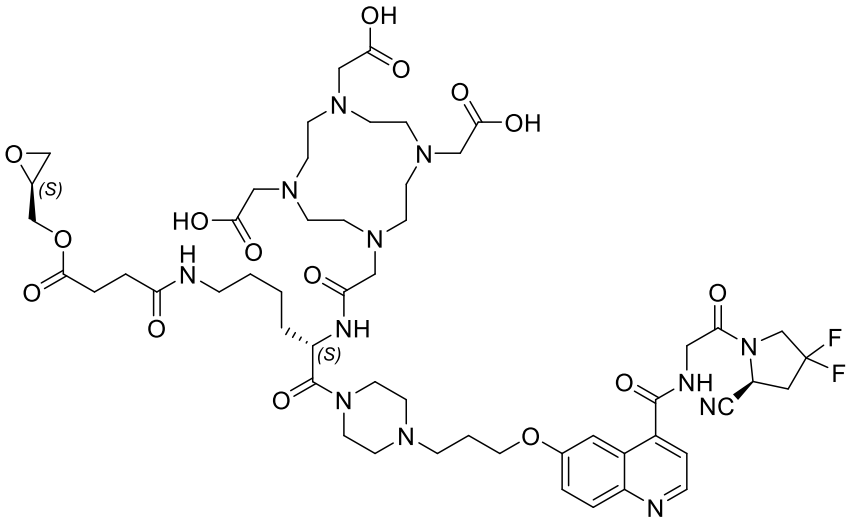
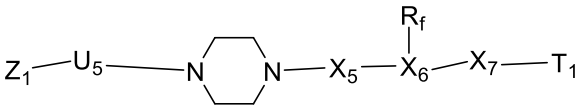


S14.

10. A compound represented by Formula (B), or a stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof, characterized in that:

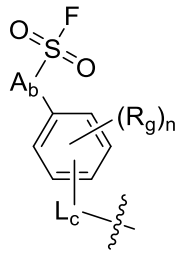


Formula (B)

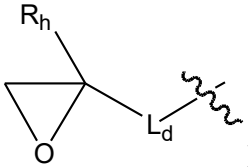
wherein Z_1 is a payload, T_1 is a targeting moiety,

U_5, X_5, X_6, and X_7 are the same or different, and are each independently selected from a linking group;

R_f is selected from the structure represented by Formula (Q-2-2) or Formula (Q-5-1) below:



Formula (Q-2-2)



Formula (Q-5-1),

L_c, L_d, and A_b are the same or different, and are each independently selected from a linking group,

n is the same or different, and is each independently selected from an integer of 0 to 6 (e.g., 0, 1, 2, 3, 4, 5, 6),

R_g and R_h are the same or different, and are each independently selected from hydrogen, halogen, -OH, cyano, nitro, amino, C_{1-20} alkyl, C_{1-20} alkoxy, and halogenated C_{1-20} alkyl;

 denotes the attachment site of the group.

11. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 10, characterized in that:

X_6 is selected from a trivalent linking group; preferably, X_6 is each independently selected from N, C_{1-20} alkanetriyl (C_{1-10} alkanetriyl, C_{1-6} alkanetriyl, C_{1-4} alkanetriyl) optionally substituted with one or more R_0, and any combination thereof;

preferably, U_5, X_5, X_7, L_c, L_d, and A_b are the same or different, and are each independently selected from a divalent linking group; preferably, U_5, X_5, X_7, L_c, L_d, and A_b are each independently selected from a bond, -O-, -S-, -P-, -O-(HO-P=O)-O-, -N(R_0)-, -CO-, C_{1-20} alkylene (C_{1-10} alkylene, C_{1-6} alkylene, C_{1-4} alkylene) optionally substituted with one or more R_0, and any combination thereof;

preferably, A_b is selected from a bond;

preferably, R_g and R_h are the same or different, and are each independently selected from hydrogen, halogen, hydroxy, cyano, nitro, amino, C_{1-20} alkyl, C_{1-20} alkoxy, and halogenated C_{1-20} alkyl;

preferably, each R_0 is the same or different, and is each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-10} alkyl, C_{1-10} alkoxy, halogenated C_{1-10} alkyl, and halogenated C_{1-10} alkoxy; preferably, each R_0 is the same or different, and is each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-6} alkyl, C_{1-6} alkoxy, halogenated C_{1-6} alkyl, and halogenated C_{1-6} alkoxy; further preferably, each R_0 is the same or different, and is each independently selected from hydrogen, halogen, hydroxyl, cyano, nitro, amino, C_{1-4} alkyl, C_{1-4} alkoxy, halogenated C_{1-4} alkyl, and halogenated C_{1-4} alkoxy.

12. The compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to claim 11, characterized in that:

U_5 is selected from a bond, -CO-, and -C_{1-4} alkyl CO-;

X_7 is selected from a bond;

X_6 is selected from N;

X_5 is selected from C_{1-10} alkylene, preferably C_{1-6} alkylene, C_{1-4} alkylene, and C_3 alkylene;

L_c and L_d are the same or different, and are each independently selected from -CO-, -C_{1-6} alkylene-, -CO-C_{1-6} alkylene-, -C_{1-6} alkylene-CO-N(R_0)-, -C_{1-6} alkylene-N(R_0)-CO-, -CO-C_{1-6} alkylene-N(R_0)-CO-C_{1-6} alkylene-, -CO-C_{1-6} alkylene-CO-N(R_0)-C_{1-6} alkylene-, -C_{1-6} alkylene-CO-N(R_0)-C_{1-6} alkylene-, -C_{1-6} alkylene-N(R_0)-CO-C_{1-6} alkylene-, -C_{1-6} alkylene-N(R_0)-CO-C_{1-6} alkylene-COO-C_{1-6} alkylene-, -C_{1-6} alkylene-CO-N(R_0)-C_{1-6} alkylene-COO-C_{1-6} alkylene-, -CO-C_{1-6} alkylene-N(R_0)-CO-C_{1-6} alkylene-COO-C_{1-6} alkylene-, -CO-C_{1-6} alkylene-CO-N(R_0)-C_{1-6} alkylene-COO-C_{1-6} alkylene-, etc; preferably, L_c and L_d are each independently selected from -C_{1-3} alkylene-, -CO-C_{1-3} alkylene-, -C_{1-3} alkylene-CO-N(R_0)-, -C_{1-3} alkylene-N(R_0)-CO-, -CO-C_{1-3} alkylene-N(R_0)-CO-C_{1-3} alkylene-, -CO-C_{1-3} alkylene-CO-N(R_0)-C_{1-3} alkylene-, -C_{1-3} alkylene-CO-N(R_0)-C_{1-3} alkylene-, -C_{1-3} alkylene-N(R_0)-CO-C_{1-3} alkylene-, -C_{1-3} alkylene-N(R_0)-CO-C_{1-3} alkylene-COO-C_{1-3} alkylene-, -C_{1-3} alkylene-CO-N(R_0)-C_{1-3} alkylene-COO-C_{1-3} alkylene-, -CO-C_{1-3} alkylene-N(R_0)-CO-C_{1-3} alkylene-COO-C_{1-3} alkylene-, -CO-C_{1-3} alkylene-CO-N(R_0)-C_{1-3} alkylene-COO-C_{1-3} alkylene-;

R_0 is selected from C_{1-4} alkyl, such as methyl;

R_g is selected from hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy;

R_h is selected from hydrogen, C_{1-6} alkyl, and C_{1-6} alkoxy;

A_b is selected from a bond and oxygen;

preferably, R_g is selected from H and methoxy.

13. A FAP-targeted nuclide probe, wherein the nuclide probe is the compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to any one of claims 1-12 labeled with a radionuclide, and the radionuclide is a diagnostic radionuclide or a therapeutic radionuclide,

preferably, the diagnostic radionuclide is at least one of ^{68}Ga, ^{67}Ga, ^{64}Cu, ^{18}F, ^{86}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{11}C, ^{203}Pb, ^{123}I, ^{125}I, ^{124}I, and $Al^{18}F$;

preferably, the therapeutic radionuclide is at least one of ^{177}Lu, ^{90}Y, ^{125}I, ^{131}I, ^{211}At, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{225}Ac, ^{227}Th, ^{223}Ra, ^{213}Bi, ^{212}Bi, and ^{212}Pb.

Claims

14. Use of the Compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to any one of claims 1-12, or the FAP-targeted nuclide probe according to claim 13 in the preparation of a FAP-targeted imaging agent and/or therapeutic agent.

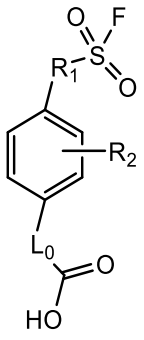
15. Use of the Compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to any one of claims 1-12, or the FAP-targeted nuclide probe according to claim 13, in the manufacture of a medicament for diagnosing and/or treating a disease, wherein the disease is a disease characterized by overexpression of fibroblast activation protein (FAP).

16. A kit, comprising the compound, or the stereoisomer, tautomer, isotopically labeled form, pharmaceutically acceptable salt, or prodrug thereof according to any one of claims 1-12, or the FAP-targeted nuclide probe according to claim 13; and instructions for diagnosing and/or treating a disease characterized by overexpression of fibroblast activation protein (FAP);

preferably, the disease characterized by overexpression of fibroblast activation protein (FAP) is selected from cancer, chronic inflammation, atherosclerosis, fibrosis (e.g., pulmonary fibrosis), tissue remodeling, scarring disease, rheumatoid arthritis, osteoarthritis, liver cirrhosis, and liver disease;

preferably, the cancer is selected from breast cancer, pancreatic cancer, small intestine cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, esophageal cancer, hypopharyngeal cancer, nasopharyngeal cancer, laryngeal cancer, myeloma cell, bladder cancer, cholangiocarcinoma, clear cell renal carcinoma, neuroendocrine tumor, carcinogenic osteomalacia, sarcoma, CUP(cancer of unknown primary), thymic cancer, glioma, neuroglioma, astrocytoma, cervical cancer, and prostate cancer.

17. A compound represented by Formula (M-1):

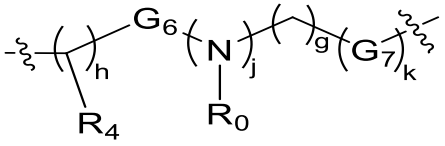


(M-1)

wherein R_1 is selected from a bond and O;

R_2 is selected from hydrogen, C_{1-10} alkyl, and C_{1-10} alkoxy;

L_0 comprises the structure represented by Formula (L-X):



(L-X),

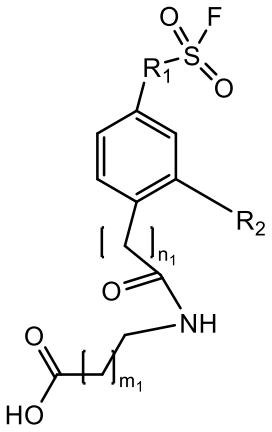
wherein h is selected from 0, 1, and 2; j is 0 or 1; g is selected from 0, 1, 2, 3, and 4; and k is 0, 1, or 2;

G_6 or G_7 is independently $-CH_2-$ or carbonyl, and they are not $-CH_2-$ at the same time;

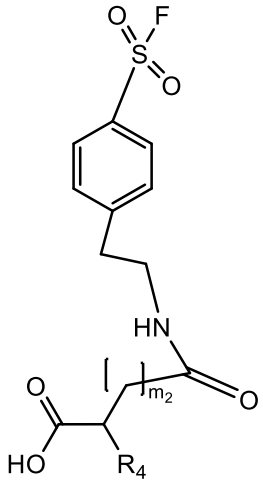
R_4 is H, $-NH_2$ or amino group protected by a protecting group.

18. The compound according to claim 17, characterized in that

the compound of Formula (M-1) is selected from the compounds represented by Formula (M-2) and Formula (M-3):



(M-2),



(M-3),

wherein R_2 is hydrogen or methoxy,

R_1 is a bond or oxygen,

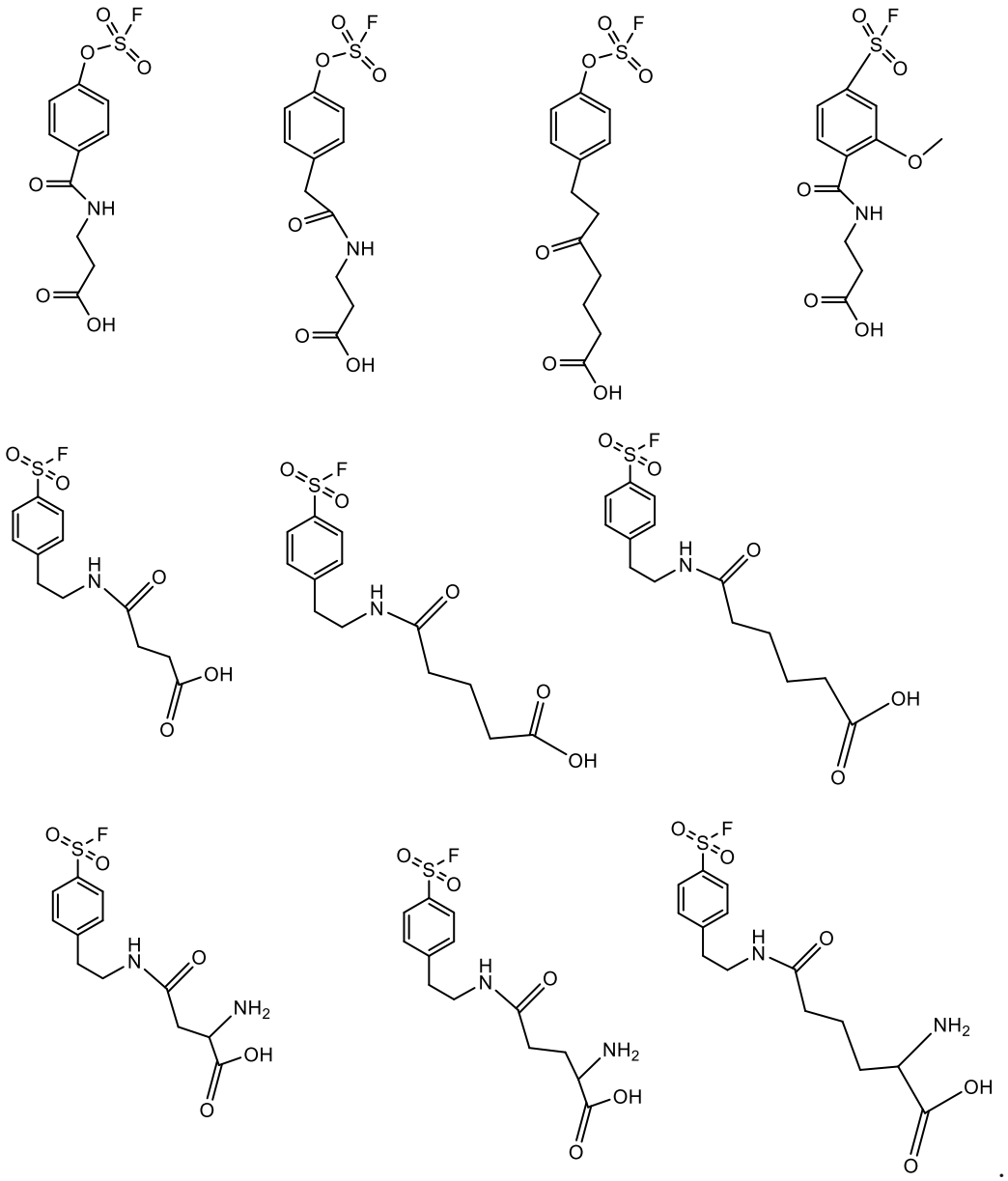
n_1 is an integer of 0 to 2,

m_1 is an integer of 1 to 3,

m_2 is an integer of 1 to 3.

19. The compound according to claim 17, characterized in that it is selected from the compounds shown below:

Claims



20. Use of the compound according to any one of claims 17 to 19 in the preparation of a radiopharmaceutical.