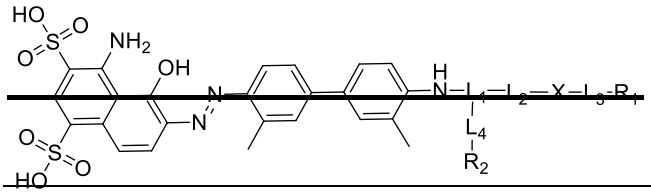
CLAIMS

1. A truncated Evans Blue modified fibroblast activation protein inhibitor compound or a pharmaceutically available salt thereof, wherein the molecular structure of the compound ~~is formed by connecting truncated Evans Blue, a fibroblast activation protein inhibitor and a nuclide chelating group by means of linker groups L_1, L_2, L_3, L_4 and X, and the compound has the following structure shown in Formula (I):~~



~~Formula (I)~~

~~wherein~~

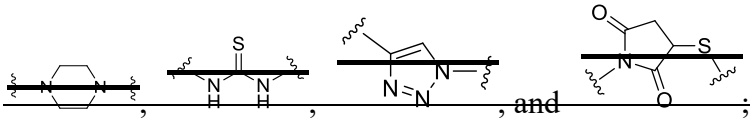
~~L_1 is lysine, glutamic acid, or a derivative compound containing a lysine or glutamic acid structure;~~

~~L_2 is $-(CH_2)_n-$, wherein n is an integer from 0 to 30, wherein each $-CH_2-$ may be individually substituted or unsubstituted with -O-, -NH-, -(CO)-, -NH(CO)-, or -(CO)-NH-, provided that no two adjacent $-CH_2-$ groups are substituted;~~

~~L_3 is $-(CH_2)_m-$, wherein m is an integer from 0 to 30, wherein each $-CH_2-$ may be individually substituted or unsubstituted with -O- or -(CO)-, provided that no two adjacent $-CH_2-$ groups are substituted;~~

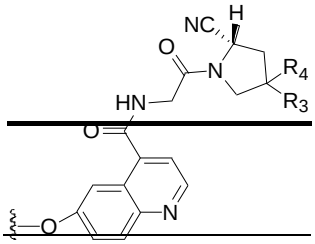
~~L_4 is $-(CH_2)_p-$, wherein p is an integer from 0 to 30, wherein each $-CH_2-$ may be individually substituted or unsubstituted with -O-, -NH-, -(CO)-, -NH(CO)-, or -(CO)-NH-, provided that no two adjacent $-CH_2-$ groups are substituted;~~

~~X is selected from N, C, O, S, or any one of the following structures:~~

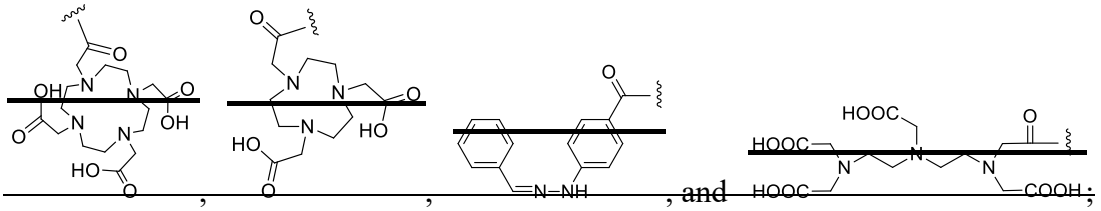


~~, , , and ;~~

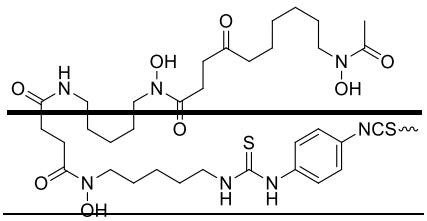
~~R_1 is the following structure of a fibroblast activation protein inhibitor:~~



~~R_2 is a nuclide chelating group, and is selected from any one of the following structures:~~



~~, , , and ;~~

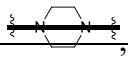


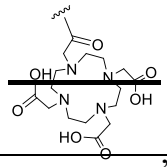
~~and R_3 R_4 are the same or different, and are independently selected from H or F.~~

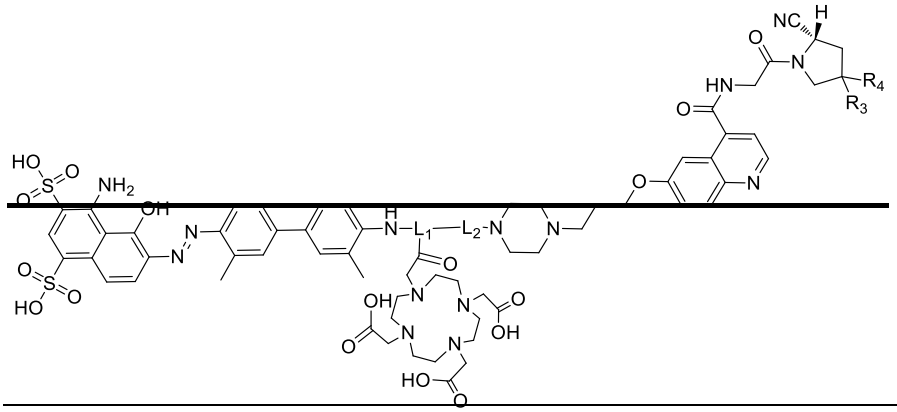
~~2. The compound according to claim 1, wherein the L_2 in Formula (I) is $-(CH_2)n-$; n is an integer from 0 to 16, is more preferably an integer from 0 to 12, and is further preferably 0, 3, or 10; wherein each $-CH_2-$ may be individually substituted or unsubstituted with $-O-$, $-NH-$, or $-(CO)-$, provided that no two adjacent $-CH_2-$ groups are substituted.~~

~~3. The compound according to claim 1, wherein the L_3 in Formula (I) is $-(CH_2)_m-$; m is an integer from 0 to 20, is more preferably an integer from 1 to 6, and is further preferably 2 or 3; wherein each $-CH_2-$ may be individually substituted or unsubstituted with $-O-$, provided that no two adjacent $-CH_2-$ groups are substituted.~~

~~4. The compound according to claim 1, wherein the L_4 in Formula (I) is $-(CH_2)_p-$; p is an integer from 0 to 20, is more preferably an integer from 0 to 12, is further preferably 3, 4, 9, or 12, and is most preferably 3; wherein each $-CH_2-$ may be individually substituted or unsubstituted with $-O-$, $-NH-$, $-(CO)-$, $-NH(CO)-$, or $-(CO)NH-$, provided that no two adjacent $-CH_2-$ groups are substituted.~~

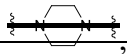
~~5. The compound according to claim 1, wherein the X in Formula (I) is~~  ~~, the L_3 is $-(CH_2)_3-$,~~

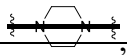
the L_4 is $-(CH_2)_0-$, and the R_2 is , namely the compound has the following structure shown in Formula (II):



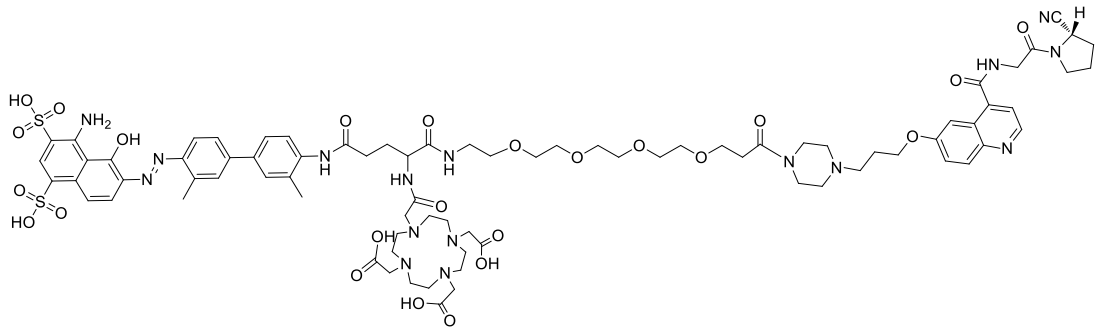
Formula (II)

wherein R_3 and R_4 are both H or both F, L_1 is a glutamic acid or lysine structure, and L_2 is $-(CH_2)_0-$, $-NH-CH_2-(CO)-$, $-NH-CH_2-(CH_2OCH_2)_2-CH_2-(CO)-$, $-NH-CH_2-(CH_2OCH_2)_4-CH_2(CO)-$, $-(CO)-CH_2-(CO)-$, $-(CO)-(CH_2)_2-(CO)-$, $-(CO)-CH_2-(CH_2OCH_2)_2-CH_2(CO)-$, or $-(CO)-CH_2-(CH_2OCH_2)_4-CH_2(CO)-$.

6. The compound according to claim 1, wherein the X in Formula (I) is , the L_1 is a glutamic acid structure, the L_2 is $-(CH_2)_0-$, $-NH-CH_2-(CO)-$, $-NH-CH_2-(CH_2OCH_2)_2-CH_2-(CO)-$, or $-NH-CH_2-(CH_2OCH_2)_4-CH_2(CO)-$, the L_3 is $-(CH_2)_3-$, the L_4 is $-(CH_2)_0-$, the R_2 is DOTA, and the R_3 and R_4 are both H or both F.

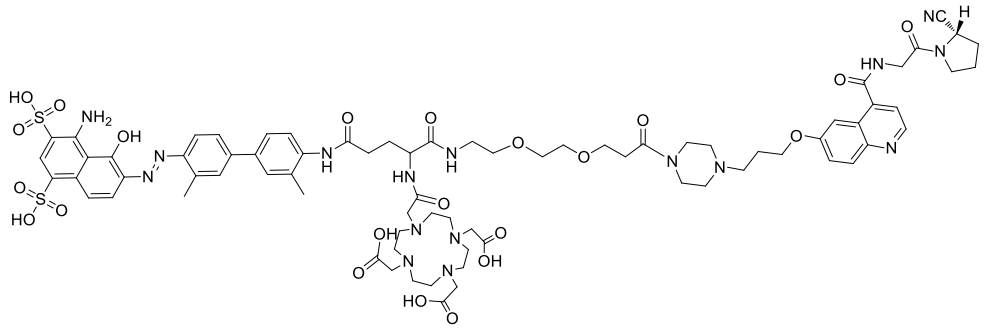
7. The compound according to claim 1, wherein the X in Formula (I) is , the L_1 is a lysine structure, the L_2 is $-(CO)-CH_2-$, $-(CO)-$, $-(CO)-(CH_2)_2-(CO)-$, $-(CO)-CH_2-(CH_2OCH_2)_2-CH_2(CO)-$, or $-(CO)-CH_2-(CH_2OCH_2)_4-CH_2(CO)-$, the L_3 is $-(CH_2)_3-$, the L_4 is $-(CH_2)_0-$, the R_2 is DOTA, and the R_3 and R_4 are both H or both F.

8. The compound according to claim 1, wherein the compound has any one of the following structures shown in Formula (II-1) to Formula (II-16):

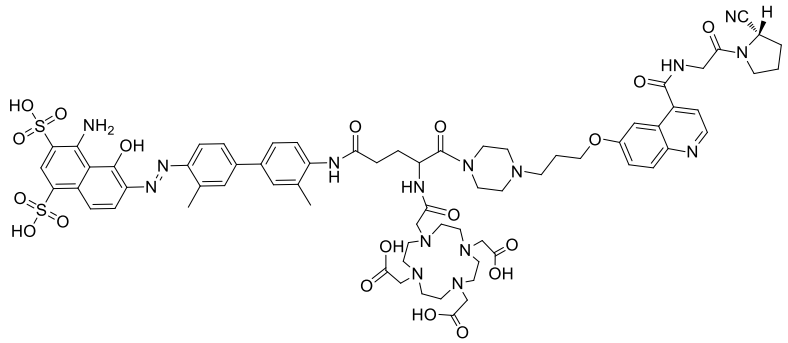


Formula (II-1)~~,~~.

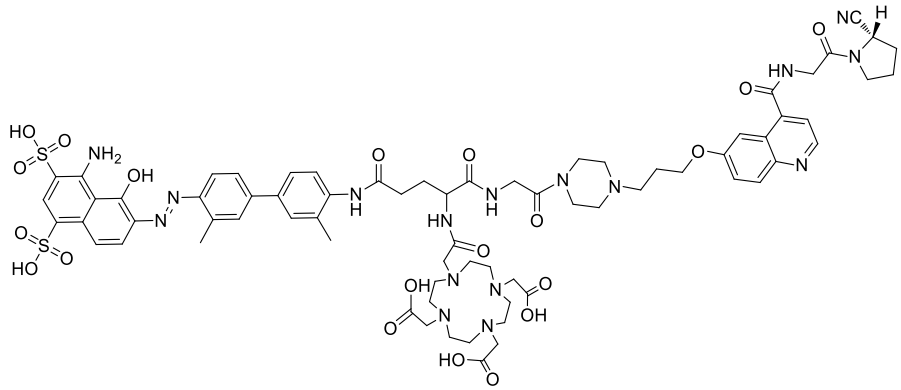
2. A truncated Evans Blue modified fibroblast activation protein inhibitor compound or a pharmaceutically available salt thereof, wherein the molecular structure of the compound has any one of the following structures shown in Formula (II-2) to Formula (II-16)



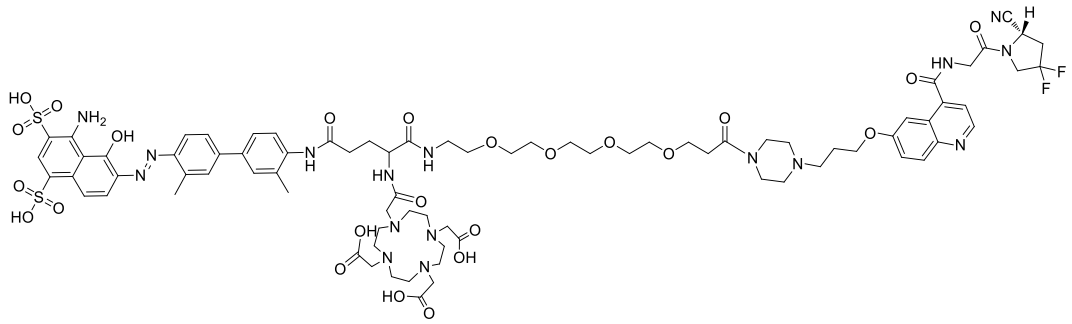
Formula (II-2),



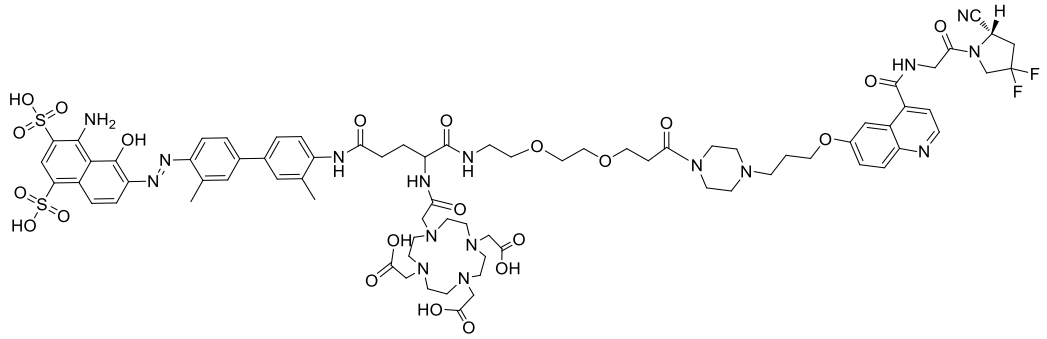
Formula (II-3),



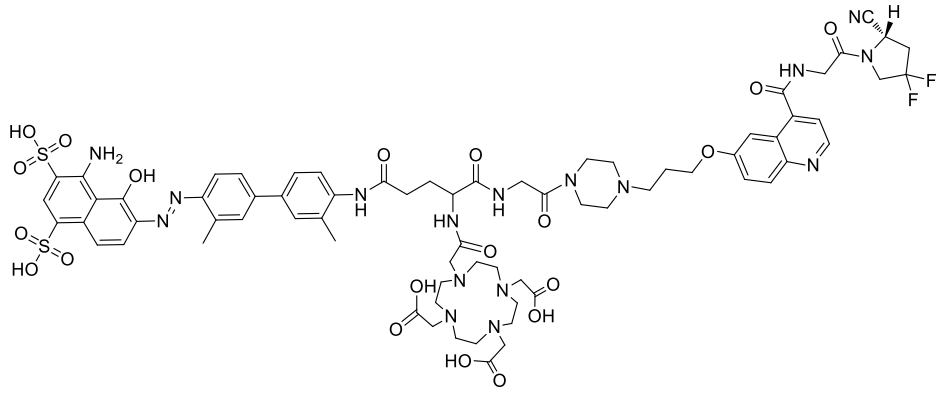
Formula (II-4),



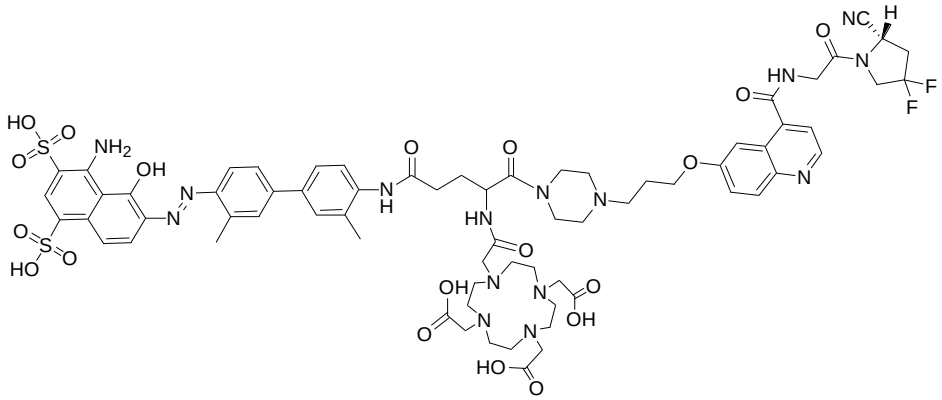
Formula (II-5),



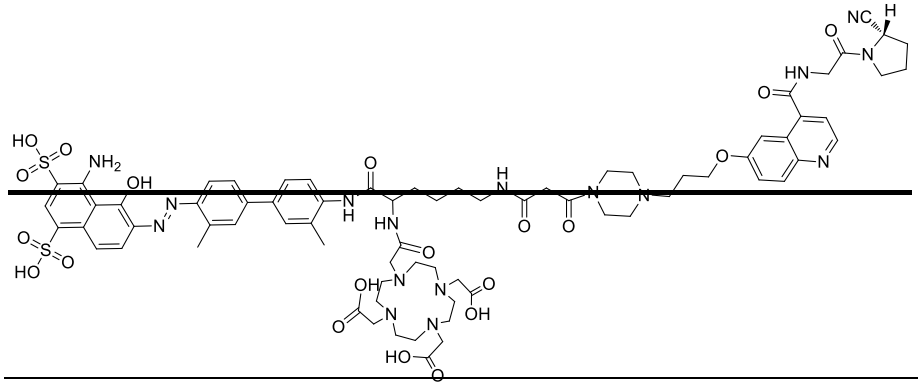
Formula (II-6),



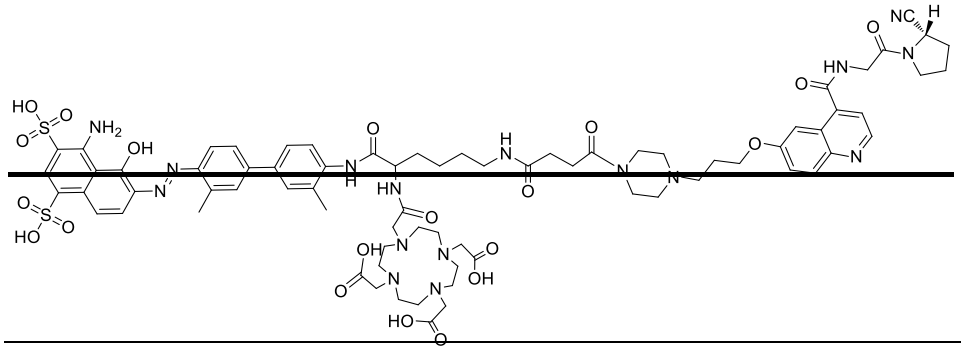
Formula (II-7), or



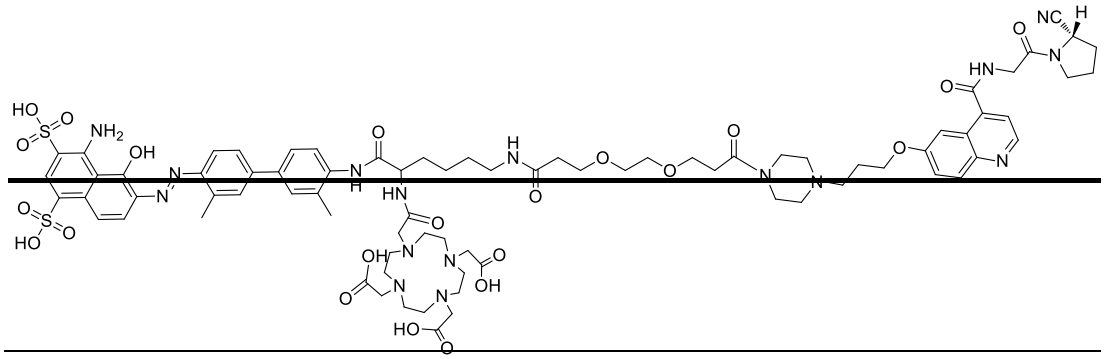
Formula (II-8),



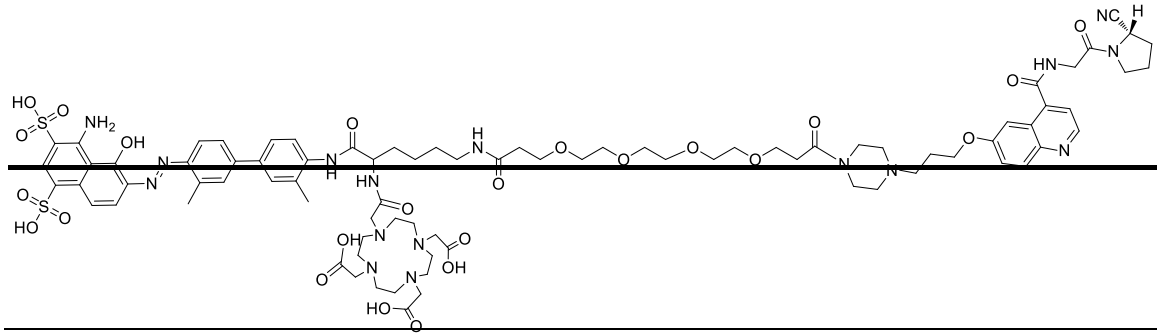
~~Formula (II-9),~~



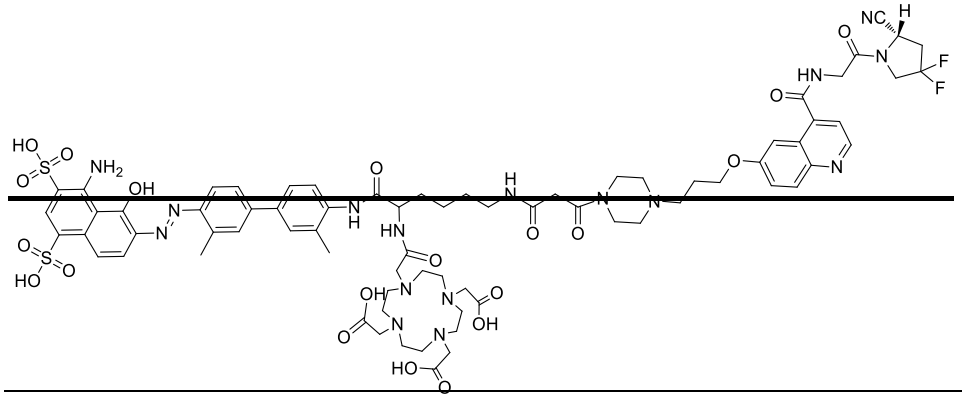
~~Formula (II-10),~~



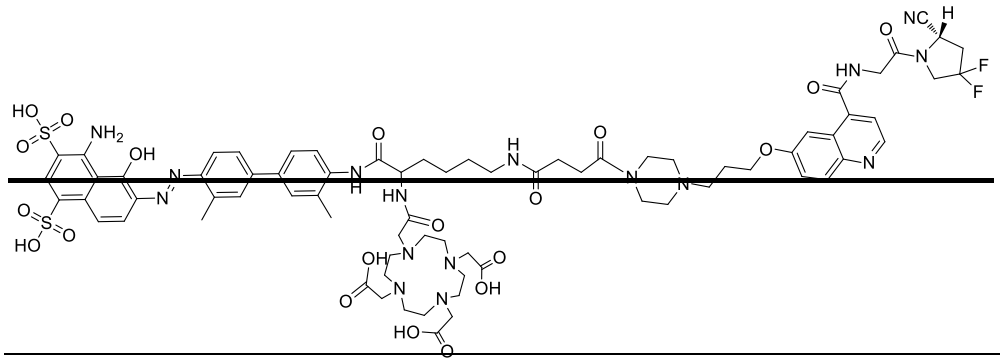
~~Formula (II-11),~~



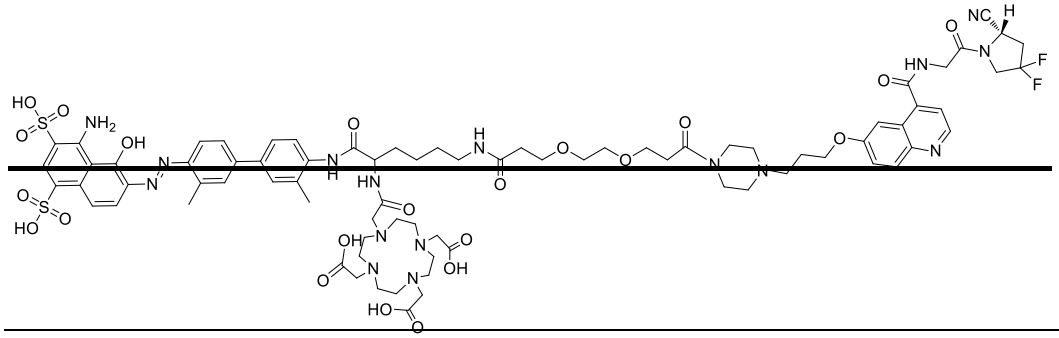
~~Formula (II-12),~~



~~Formula (II-13),~~

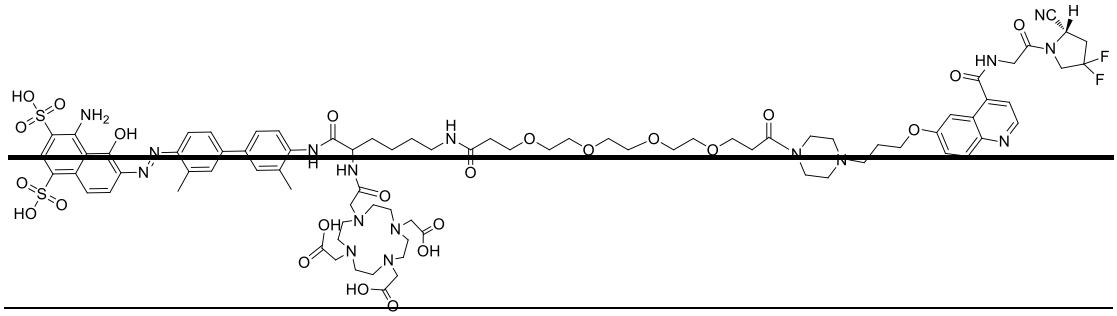


~~Formula (II-14),~~



~~Formula (II-15),~~

~~or~~



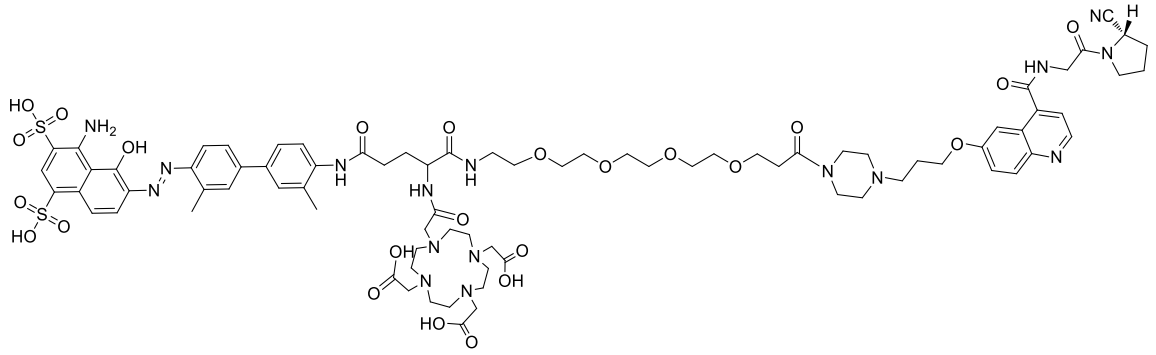
~~Formula (II-16)~~.

39. A method for preparing a truncated Evans Blue modified fibroblast activation protein inhibitor, comprising the following steps:

(1) reacting 6-hydroxy-4-quinolinecarboxylic acid with tert-butyl glycinate by amide condensation, followed by reactions with 1-bromo-3-chloropropane and tert-butyl 1-piperazinecarboxylate in sequence; then, removing Boc and tert-butyl protective groups under the action of TFA, and introducing a Boc protective group to amino, followed by an amide condensation reaction with (S)-pyrrolidene-2-carbonitrile hydrochloride; then, removing the Boc protective group using p-toluenesulfonic acid, followed by a condensation reaction with 5,8,11,14-tetraoxa-2-azaheptadecanedioic acid-1-tert-butyl ester; and removing the Boc protective group again under the action of p-toluenesulfonic acid to obtain an intermediate compound A;

(2) introducing a Boc protective group to one end of 4,4'-diamino-3,3'-dimethyl biphenyl, followed by a reaction with monosodium 1-amino-8-naphthol-2,4-disulfonate to prepare a truncated Evans Blue derivative; removing the Boc protective group, followed by an amide condensation reaction with N-tert-butyloxycarbonyl-L-glutamic acid-1-tert-butyl ester; then, removing Boc and tert-butyl protective groups under the action of TFA; and then carrying out a reaction with di-tert-butyl dicarbonate, and introducing a Boc protective group to amino to obtain an intermediate compound B; and

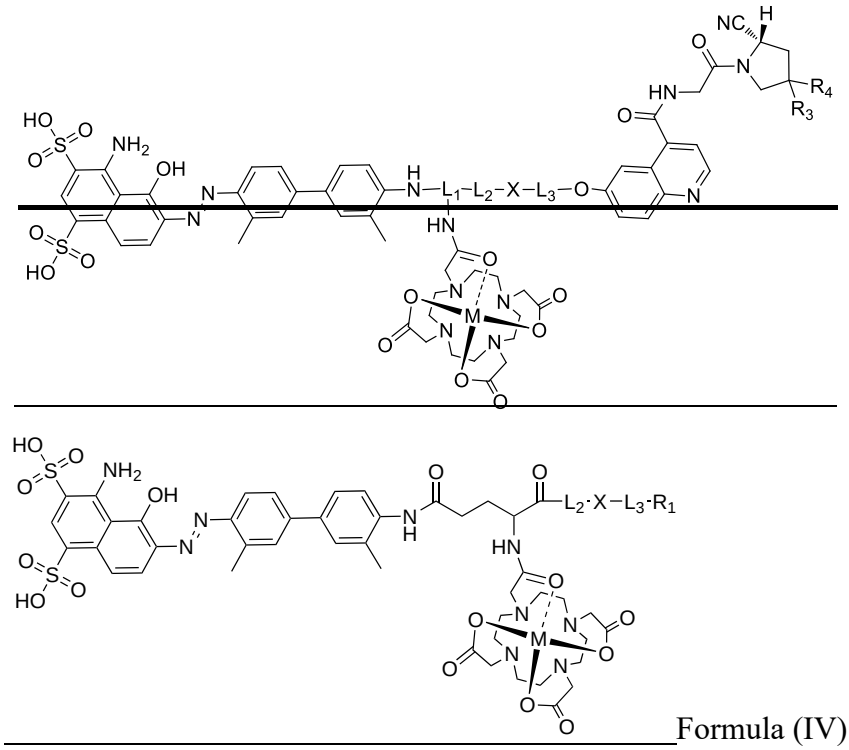
(3) reacting the intermediate compound A obtained in step (1) with the intermediate compound B obtained in step (2) by amide condensation; then removing the Boc protective group using p-toluenesulfonic acid; and finally, carrying out a reaction with DOTA-NHS to obtain a truncated Evans Blue modified fibroblast activation protein inhibitor compound having the following structure shown in Formula (II-1)



Formula (II-1).

~~10. A radiolabeled complex of truncated Evans Blue modified fibroblast activation protein inhibitor, wherein the complex is obtained by using the compound shown in Formula (I) according to claim 1 as a ligand and labeling the ligand with a radionuclide; the radionuclide is preferably any one of ^{177}Lu, ^{90}Y, ^{18}F, ^{64}Cu, ^{68}Ga, ^{62}Cu, ^{67}Cu, ^{86}Y, ^{89}Zr, ^{99m}Tc, ^{89}Sr, ^{153}Sm, ^{149}Tb, ^{161}Tb, ^{186}Re, ^{188}Re, ^{212}Pb, ^{213}Bi, ^{223}Ra, ^{225}Ac, ^{226}Th, ^{227}Th, ^{131}I, ^{211}At, or ^{111}In; and the radionuclide is further preferably ^{68}Ga, ^{177}Lu, or ^{90}Y.~~

~~11~~4. A radiolabeled complex of truncated Evans Blue modified Fibroblast activation protein inhibitor, having the following structure shown in Formula (IV):



Formula (IV)

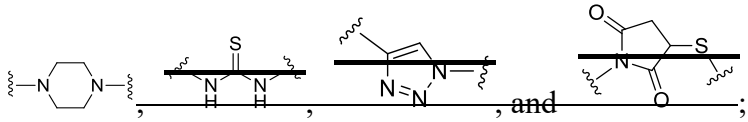
wherein

~~L_1 is a lysine or glutamic acid structure, or a derivative compound structure containing a lysine or glutamic acid structure;~~

L_2 is -$(CH_2)_0$-、-NH-CH_2-(CO)-、-NH-CH_2-(OCH_2CH_2)-O-CH_2(CO)-或 NH-CH_2-$(OCH_2CH_2)_3$-O-CH_2(CO)-~~-$(CH_2)_n$-~~, ~~wherein n is an integer from 0 to 30, and wherein each CH_2 may be individually substituted or unsubstituted with -O-, -NH-, -(CO)-, -NH(CO)-, or -(CO)-NH-, provided that no two adjacent CH_2 groups are substituted~~;

L_3 is -$(CH_2)_3$-~~-$(CH_2)_m$-, wherein m is an integer from 0 to 30, and wherein each CH_2 may be individually substituted or unsubstituted with -O- or -(CO)-, provided that no two adjacent CH_2 groups are substituted~~;

X is~~ selected from N, C, O, S, or the following structures:~~



~~, , , and~~ ;

R_3 and R_4 are~~ the same or different, and are independently selected from~~ both H or both F;

and M is a radionuclide selected from any one of ^{68}Ga, ^{177}Lu, or ^{90}Y.

~~12. The complex according to claim 11, wherein the L_2 in Formula (IV) is -$(CH_2)_n$-; n is an integer from 0 to 16, is more preferably an integer from 0 to 12, and is further preferably 0, 3, or 10; and wherein each -CH_2- may be individually substituted or unsubstituted with -O-, -NH-,~~

~~or -(CO)-, provided that no two adjacent -CH_2- groups are substituted.~~

~~13. The complex according to claim 11, wherein the L_2 in Formula (IV) is -$(CH_2)_0$-, -NH-CH_2-(CO)-, -NH-CH_2-$(CH_2OCH_2)_2$-CH_2-(CO)-, -NH-CH_2-$(CH_2OCH_2)_4$-CH_2(CO)-, -(CO)-CH_2-(CO)-, -(CO)-$(CH_2)_2$-(CO)-, -(CO)-CH_2-$(CH_2OCH_2)_2$-CH_2(CO)-, or -(CO)-CH_2-$(CH_2OCH_2)_4$-CH_2(CO)-.~~

~~14. The complex according to claim 11, wherein the L_3 in Formula (IV) is -$(CH_2)_m$-; m is an integer from 0 to 20, is more preferably an integer from 1 to 6, and is further preferably 2 or 3; and wherein each -CH_2- may be individually substituted or unsubstituted with -O-, provided that no two adjacent -CH_2- groups are substituted.~~

~~15. The compound according to claim 11, wherein the L_3 in Formula (IV) is -$(CH_2)_3$-.~~

~~16~~5. A method for preparing a radiolabeled complex of truncated Evans Blue modified Fibroblast activation protein inhibitor, comprising the following steps: dissolving the compound shown in Formula (II-1) according to claim 1 or the compound shown in Formula (II-2) ~ Formula (II-8) according to claim 2 in a buffer solution or deionized water; and adding a radionuclide solution to the obtained solution for a reaction under closed conditions for 5-40 min to produce a radionuclide labeled complex.~~,~~

~~17. A method for preparing a radiolabeled complex of truncated Evans Blue modified Fibroblast activation protein inhibitor~~or, comprising the following steps: dissolving the compound shown in Formula (II-1) according to claim 1 or the compound shown in Formula (II-2) ~ Formula (II-8) according to claim 2 in a buffer solution or deionized water; treating the obtained solution by aseptic filtration, followed by loading into a container, freeze-drying and sealing with a stopper to obtain a freeze-dried medicine box; and then adding an appropriate amount of an acetic acid solution or a buffer solution to the freeze-dried medicine box for dissolution, and adding a corresponding radionuclide solution for a reaction under closed conditions for 5-40 min to produce a radionuclide labeled complex.

~~18~~6. Application of the compound according to any one of claims 1-2~~8~~ or a pharmacologically acceptable salt thereof in preparation of medicines in nuclide therapy or imaging of tumors with high expression of FAP.

~~19~~7. Application of the complex according to ~~any one of~~ claims ~~10-15~~4 in nuclide therapy or imaging of tumors with high expression of FAP.

~~20~~8. The application according to any one of claims ~~18-19~~6-7, wherein the compound or the complex is formulated as an injection and then intravenously injected into patients with tumors with high expression of FAP; and the tumors with high expression of FAP comprise, but are not limited to, breast cancer, ovarian cancer, lung cancer, colorectal cancer, gastric cancer or

pancreatic cancer.