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(54) **Titre : COMPOSE A DOUBLE CIBLAGE, SON PROCEDE DE PREPARATION ET SON UTILISATION**
(54) **Title: DUAL-TARGETING COMPOUND AND PREPARATION METHOD AND APPLICATION THEREOF**

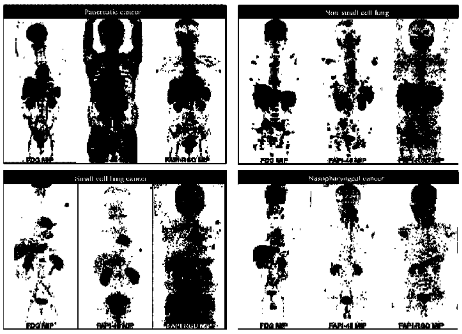
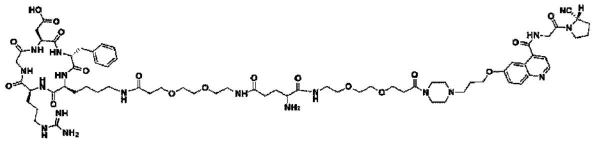


FIG 16



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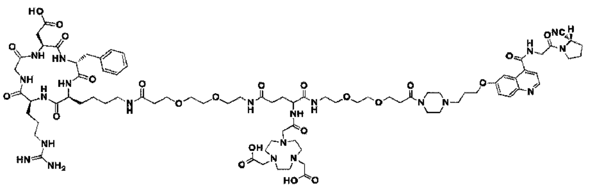
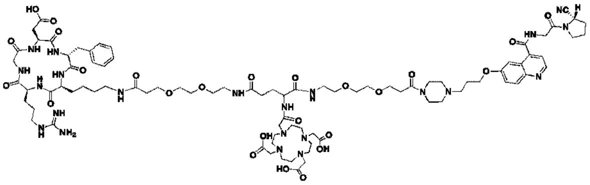


(I-1)



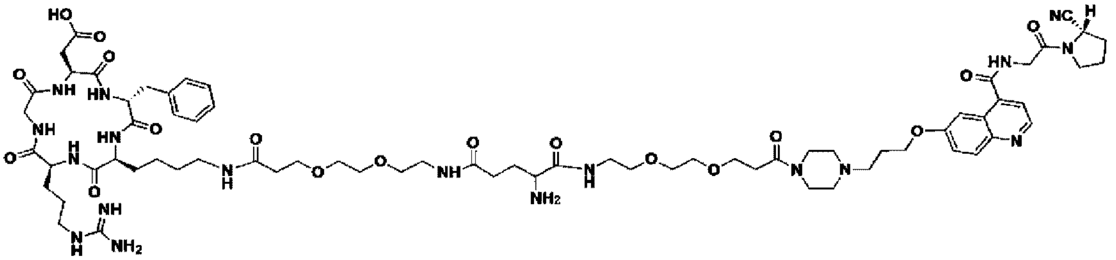
(I-2)

(57) **Abrégé/Abstract:**

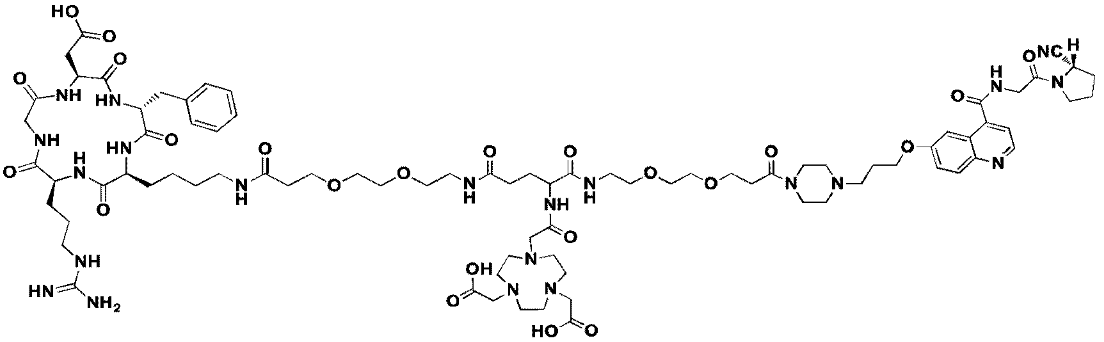
A dual-targeting compound, and a preparation method therefor and the use thereof, which relate to the fields of nuclear medicine and molecular imaging. A radionuclide-labeled dual-targeting compound, having a structure as shown in formula (I-1) or formula (I-2). The dual-targeting compound has a high affinity to both an FAP target and an integrin $\alpha_V\beta_3$ target, can synergistically target the FAP target and the integrin $\alpha_V\beta_3$ target in tumors, and exhibits a high uptake and a long retention time in tumors. Provided are a radionuclide-labeled dual-targeting compound based on the dual-targeting compound, and a preparation method therefor and the use thereof in the preparation of a drug for diagnosing and treating diseases characterized by overexpression of FAP and/or integrin $\alpha_V\beta_3$.

ABSTRACT

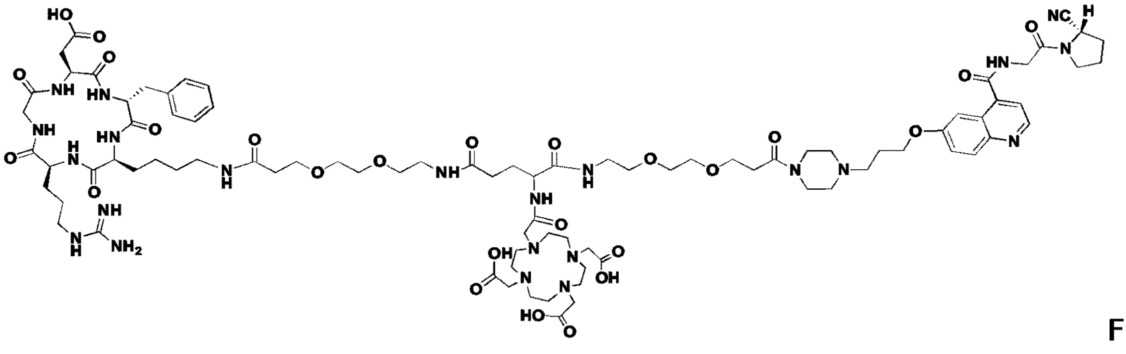
The present disclosure relates to the fields of nuclear medicine and molecular imaging, and specifically relates to a dual-targeting compound and a preparation method and application thereof. The dual-targeting compound has the following structure shown in Formula (I). The present disclosure also provides a dual-targeting compound capable of being labeled with a radionuclide, and the compound has the following structure shown in Formula (I-1) or Formula (I-2). The dual-targeting compound of the present disclosure has high affinity for an FAP target and an integrin $\alpha_v\beta_3$ target, can realize synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors, and has high uptake in tumors and long retention time in tumors. The present disclosure also provides a radionuclide labeled dual-targeting compound based on the dual-targeting compound, and a preparation method and application thereof in preparation of medicines for diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$.



(I)



Formula (I-1)



Formula (I-2)

DESCRIPTION

DUAL-TARGETING COMPOUND AND PREPARATION METHOD AND APPLICATION THEREOF

TECHNICAL FIELD

The present disclosure relates to the fields of nuclear medicine and molecular imaging, and specifically relates to a radionuclide labeled dual-targeting compound targeting a fibroblast activation protein (FAP) and an integrin $\alpha_v\beta_3$ and a preparation method and use of the compound in diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$.

BACKGROUND

A fibroblast activation protein (FAP) is a membrane serine peptidase that is expressed on the surface of a tumor stroma activated fibroblast and plays an important role in generation and development processes of tumors. Previous studies show that the FAP is generally not expressed in normal human tissues, but selectively highly expressed on surfaces of stromal fibroblasts of more than 90% of epithelial malignant tumors, including breast cancer, ovarian cancer, lung cancer, colorectal cancer, gastric cancer and pancreatic cancer. An integrin $\alpha_v\beta_3$ is a heterodimer receptor located on surfaces of cells, which is rarely expressed in endothelial and epithelial cells of normal blood vessels, but is highly expressed on surfaces of a variety of solid tumor cells such as lung cancer, osteosarcoma, neuroblastoma, breast cancer, prostate cancer, bladder cancer, glioblastoma and invasive melanoma. Moreover, the integrin $\alpha_v\beta_3$ is highly expressed in endothelial cell membranes of new blood vessels in all tumor tissues, indicating that the integrin $\alpha_v\beta_3$ plays a key role in growth, invasion and metastasis of tumors. A polypeptide containing an arginine-glycine-aspartic acid (RGD) sequence can specifically bind to the integrin $\alpha_v\beta_3$. In view of widespread expression and important role of the FAP and the integrin $\alpha_v\beta_3$ in tumors, the FAP and the integrin $\alpha_v\beta_3$ have become important targets for imaging and therapy of tumors.

In order to further improve the diagnosis and therapy efficiency of tumors, dual-targeting probes having affinity for the two targets have already been developed in the prior art. For example, a dual-targeting probe having affinity for both a prostate specific membrane antigen (PSMA) and a gastrin releasing peptide receptor (GRPR) was reported by Anna Orlova et al.. Due to high expression of the PSMA and GRPR in the prostate gland, the dual-targeting probe has the disadvantage that it can only be applied to radiodiagnosis and therapy of prostate cancer, and cannot be applied to other tumors.

SUMMARY

Due to main distribution in tumor stromal cells and new blood vessels, FAP and integrin $\alpha_v\beta_3$ are highly expressed in a variety of tumor types at the same time, and are ideal targets for development of a dual-targeting probe for "extensive tumors". Considering the heterogeneity of tumors, in order to further improve the diagnosis and therapy efficiency of tumors, a targeting compound capable of targeting the two targets FAP and integrin $\alpha_v\beta_3$ is required to be developed. The dual-targeting compound requires high affinity for the two targets at the same time to realize synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors, as well as excellent pharmacokinetic properties in the body to increase the uptake in tumors and prolong the retention time in tumors. A radionuclide labeled dual-targeting compound based on the dual-targeting compound can utilize the FAP target and the integrin $\alpha_v\beta_3$ target at the same time to increase the number of effective receptors in tumors and improve the utilization efficiency, so that the problem of improving the detection efficiency and/or therapy efficiency of positive tumors is solved.

In order to solve the above problems, a primary purpose of the present disclosure is to develop a novel compound structure capable of realizing synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors to improve the uptake of a medicine in tumors and prolong the retention time.

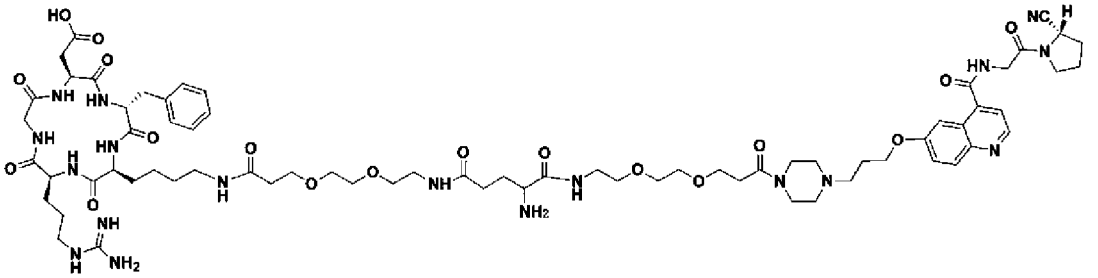
Another purpose of the present disclosure is to provide a method for preparing the novel compound. The compound capable of realizing synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors is synthesized by a convenient and available synthetic route.

Another purpose of the present disclosure is to provide application of the compound in diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$.

DESCRIPTION

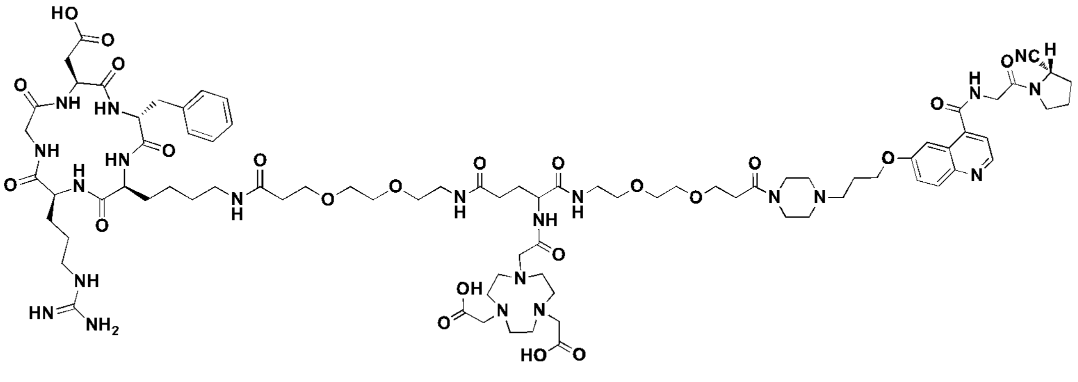
The above purposes of the present disclosure are realized by adopting the following technical solutions.

In the first aspect, the present disclosure provides a dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$. The compound structurally contains ligand structures specifically binding to FAP and integrin $\alpha_v\beta_3$ at the same time, and the compound has the following structure shown in Formula (I):



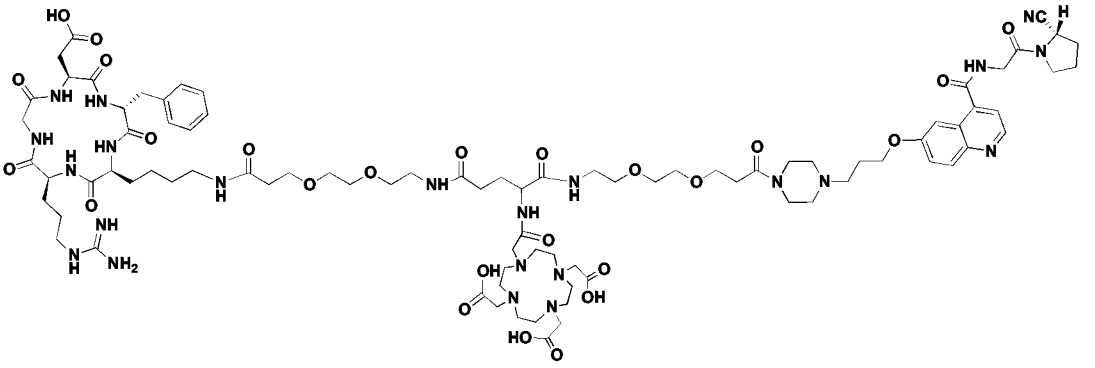
(I).

In the second aspect, the present disclosure also provides a dual-targeting compound capable of being labeled with a radionuclide for targeting FAP and integrin $\alpha_v\beta_3$. The compound structurally contains ligand structures specifically binding to FAP and integrin $\alpha_v\beta_3$ at the same time and a nuclide chelating structure. The structure of the compound is denoted as an FAPI-RGD structure in the present disclosure, and the compound has the following structure shown in Formula (I-1) or Formula (I-2):



Formula (I-1);

DESCRIPTION



Formula (I-2).

In the third aspect, the present disclosure provides a radionuclide labeled dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$. The compound is obtained by labeling the compound as described in the second aspect of the present disclosure with a radionuclide.

In the solution of the present disclosure, the radionuclide may be selected from an α-ray emitting isotope, a β-ray emitting isotope, a γ-ray emitting isotope, an auger electron emitting isotope, or an X-ray emitting isotope, such as any one of ^{18}F, ^{51}Cr, ^{67}Ga, ^{68}Ga, ^{111}In, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{139}La, ^{140}La, ^{175}Yb, ^{153}Sm, ^{166}Ho, ^{86}Y, ^{90}Y, ^{149}Pm, ^{165}Dy, ^{169}Er, ^{177}Lu, ^{47}Sc, ^{142}Pr, ^{159}Gd, ^{212}Bi, ^{213}Bi, ^{72}As, ^{72}Se, ^{97}Ru, ^{109}Pd, ^{105}Rh, ^{101m}Rh, ^{119}Sb, ^{128}Ba, ^{123}I, ^{124}I, ^{131}I, ^{197}Hg, ^{211}At, ^{151}Eu, ^{153}Eu, ^{169}Eu, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{64}Cu, ^{67}Cu, ^{198}Au, ^{225}Ac, ^{227}Th, ^{89}Zr, or ^{199}Ag; and the radionuclide is more preferably ^{18}F, ^{64}Cu, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{188}Re, or ^{225}Ac.

In the fourth aspect, the present disclosure provides a method for preparing the dual-targeting compound as described in the second aspect and a radionuclide labeled compound thereof (namely the dual-targeting compound as described in the third aspect of the present disclosure). The preparation method provided by the present disclosure includes:

(1) reacting 6-hydroxyquinoline-4-carboxylic acid with amino of tert-butyl glycinate first by condensation; then connecting Boc-protected piperazinyl at hydroxyl position of an amide condensation product by an alkyl chain; removing Boc protective groups and tert-butyl protective groups under acidic conditions, and introducing a Boc protective group to piperazine ring of the condensation product, followed by an amide condensation reaction with (S)-pyrrolidene-2-carbonitrile hydrochloride; after removing the Boc protective group,

carrying out a condensation reaction with N-Boc-3-[2-(2-aminoethoxy)ethoxy]propionic acid; next, removing the Boc protective group, and carrying out a reaction with Fmoc-O-tert-butyl-L-glutamic acid; after removing tert-butyl ester, preparing an activated ester, followed by a reaction with c(RGDfK) with amino-dipolyethylene glycol to obtain a dual-targeting compound; then after removing an Fmoc protective group, carrying out a reaction with a nuclide chelating agent, where the nuclide chelating agent is 1,4,7,10-tetraazacyclododecane-N,N',N,N'-tetraacetic acid or 1,4,7-triazacyclononane-1,4,7-triacetic acid; and finally, removing a tert-butyl protective group on a chelating group to obtain a dual-targeting compound capable of being labeled with a radionuclide, namely the dual-targeting compound as described in the second aspect of the present disclosure; and

(2) reacting the dual-targeting compound capable of being labeled with a radionuclide obtained in step (1) with compound containing a radionuclide by a prior art of wet labeling or freeze-drying labeling to obtain the radionuclide labeled dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$ as described in the third aspect of the present disclosure.

In the fifth aspect, the present disclosure provides a pharmaceutical composition. The pharmaceutical composition includes the dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$ as described in the first aspect of the present disclosure, the dual-targeting compound capable of being labeled with a radionuclide for targeting FAP and integrin $\alpha_v\beta_3$ as described in the second aspect of the present disclosure, the radionuclide labeled dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$ as described in the third aspect, or any pharmaceutically acceptable tautomer, racemate, hydrate, solvate or salt thereof.

In the sixth aspect, the present disclosure also provides application of the dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$ as described in the first aspect of the present disclosure, the dual-targeting compound capable of being labeled with a radionuclide for targeting FAP and integrin $\alpha_v\beta_3$ as described in the second aspect, the radionuclide labeled dual-targeting compound capable of targeting FAP and integrin $\alpha_v\beta_3$ as described in the third aspect, or the pharmaceutical composition as described in the fifth aspect in preparation of medicines for diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$ in animals or human persons.

In the application of the present disclosure, the diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$ include, but are not limited to: cancer, chronic inflammation, atherosclerosis, fibrosis, tissue remodeling and cicatricial diseases; and preferably, the cancer is further selected from breast cancer, pancreatic cancer, small bowel cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, esophageal cancer, hypopharyngeal cancer, nasopharyngeal cancer, laryngeal cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal cell carcinoma, neuroendocrine carcinoma, carcinogenic osteomalacia, sarcoma, CUP (cancer of unknown primary), thymic carcinoma, glioma, neuroglioma, astrocytoma, cervical cancer, or prostate cancer.

The structure of the FAPI-RGD compound provided by the present disclosure has high affinity for the FAP target and the integrin $\alpha_v\beta_3$ target, can realize synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors, exhibits high uptake in tumors and long retention time in tumors, and is expected to be applied to diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$.

In addition, the preparation method of the FAPI-RGD compound provided by the present disclosure has simple reaction route, simple operation, cheap and readily available raw materials and low production cost, and is suitable for industrial production.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 is a diagram showing nuclear magnetic hydrogen spectrum of compound 7.

FIG. 2 is a diagram showing nuclear magnetic carbon spectrum of compound 7.

FIG. 3 is a diagram showing mass spectrum of compound 7.

FIG. 4 is a diagram showing mass spectrum of compound 8.

FIG. 5 is a diagram showing mass spectrum of compound 9.

FIG. 6 is a diagram showing mass spectrum of compound 12.

FIG. 7 is a diagram showing mass spectrum of compound 13.

FIG. 8 is a diagram showing mass spectrum of compound 14.

FIG. 9 is a diagram showing mass spectrum of compound 15.

FIG. 10 is a diagram showing experimental results of the stability of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) of the present disclosure in normal saline.

FIG. 11 is a diagram showing experimental results of cell uptake and cell binding of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) of the present disclosure.

FIG. 12 is a diagram showing MicroPET imaging results of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) of the present disclosure and monomers ^{68}GA-FAPI-02 and ^{68}Ga-C(RGDfK) in HT1080-FAP tumor-bearing mice.

FIG. 13 is a diagram showing MicroPET imaging results and statistics of uptake results in tumors and vital organs 30 min after co-injection of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) of the present disclosure and C(RGDfK) and/or FAPI-02.

FIG. 14 is a diagram showing SPECT imaging results of ^{177}Lu-FAPI-RGD complex prepared in Example 4 of the present disclosure in HT1080-FAP tumor-bearing mice.

FIG. 15 is a diagram showing the molecular structure of a complex of ^{68}GA labeled control compound FAPI-RGD, MicroPET imaging results 30 min and 2 h after the control compound is injected into HT1080-FAP tumor-bearing mice, and statistics of uptake results in tumors and vital organs.

FIG. 16 is a diagram showing PET/CT imaging results 3 h after ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) of the present disclosure, ^{18}F-FDG and ^{68}Ga-FAPI46 are intravenously injected into patients with pancreatic cancer, non-small cell lung cancer, small cell lung cancer and nasopharyngeal carcinoma.

DETAILED DESCRIPTION OF EMBODIMENTS

Technical solutions of the present disclosure are further explained and described below in conjunction with specific embodiments and attached drawings.

Example 1: Preparation of compound (I-1)

Synthesis of compound 2:

Compound 1 (6-hydroxyquinoline-4-carboxylic acid, 1.89 g, 10.0 mmol), tert-butyl glycinate (1.89 g, 10.0 mmol), HATU (3.8 g, 10.0 mmol) and N,N-diisopropylethylamine (2.6 g, 20.0 mmol) were sequentially put into 30 mL of N,N-dimethylformamide in a 100 mL flask. A reaction mixture was stirred overnight, and reduced pressure distillation was conducted to remove the solvent to obtain a crude product. Then purification was conducted with a silica gel column (ratio of dichloromethane to methanol was 30:1) to obtain white solid compound 2 with a yield of 87%.

Synthesis of compound 3:

Compound 2 (1.51 g, 5.0 mmol), 1-bromo-3-chloropropane (1.55 g, 10.0 mmol) and potassium carbonate (1.38 g, 10.0 mmol) were sequentially put into 50 mL of N,N-dimethylformamide in a 100 mL flask. The system was heated to 60 °C and stirred overnight at 60 °C, and reduced pressure distillation was conducted to remove the solvent to obtain a crude product. Then purification was conducted with a silica gel column (ratio of dichloromethane to methanol was 50:1) to obtain white solid compound 3 with a yield of 63%.

Synthesis of compound 4:

Compound 3 (0.76 g, 2.0 mmol), tert-butyl 1-piperazinecarboxylate (0.55 g, 3.0 mmol) and potassium iodide (0.49 g, 3.0 mmol) were sequentially put into 30 mL of acetonitrile in a 100 mL flask. The system was heated to 60 °C and stirred overnight at 60 °C, and reduced pressure distillation was conducted to remove the solvent to obtain a crude product. Then purification was conducted with a silica gel column (ratio of dichloromethane to methanol was 30:1) to obtain white solid compound 4 with a yield of 58%.

Synthesis of compound 5:

Compound 4 (0.52 g, 1.0 mmol) was dissolved in 10 mL of a mixed solution of dichloromethane and trifluoroacetic acid (at a volume ratio of 9:1) in an ice bath. The system was heated to room temperature for reaction for 2 h, and after the reaction was completed, reduced pressure distillation was conducted to remove the solvent. Then resulting product was dissolved in 10 mL of N,N-dimethylformamide to obtain compound 5 for later use.

Synthesis of compound 6:

Di-tert-butyl dicarbonate (0.22 g, 1.0 mmol) and N,N-diisopropylethylamine (0.39 g, 3.0 mmol) were separately added to an N,N-dimethylformamide solution of compound 5. The system was stirred overnight at room temperature, and reduced pressure distillation was conducted to remove the solvent to obtain a crude product. Then purification was conducted with a silica gel column (ratio of dichloromethane to methanol was 10:1) to obtain white solid compound 6 with a yield of 72%.

Synthesis of compound 7:

Compound 6 (0.47 g, 1.0 mmol), (S)-pyrrolidene-2-carbonitrile hydrochloride (0.13 g, 1.0 mmol), HATU (0.38 g, 1.0 mmol) and N,N-diisopropylethylamine (0.26 g, 2.0 mmol) were sequentially put into 10 mL of N,N-dimethylformamide in 100 mL flask. A reaction mixture was stirred at room temperature until a reaction was completed, and reduced pressure distillation was conducted to remove the solvent to obtain a crude product. Then purification was conducted with a silica gel column (ratio of dichloromethane to methanol was 50:1) to obtain white solid compound 7 with a yield of 85%. FIG. 1 shows the magnetic hydrogen spectrum of compound 7. FIG. 2 shows the nuclear magnetic carbon spectrum of compound 7. FIG. 3 is a diagram showing the mass spectrum of compound 7.

Synthesis of compound 8:

Compound 7 (2.50 g, 4.5 mmol), p-toluenesulfonic acid monohydrate (2.58 g, 13.6 mmol) and 25 mL of acetonitrile were added to a reaction flask for a reaction at 65 °C for 1 h. After monitoring by TLC (ratio of methanol to dichloromethane was 5:1) that compound 7 was completely reacted, evaporation to dryness was conducted under reduced pressure at 40 °C. 14 ml of DMF and DIPEA (3.05 g, 23.6 mmol) were added and stirred at 25 °C for a reaction (1), during which a protective group was removed from piperazinyl of compound 7, to obtain an intermediate. N-tert-butoxycarbonyl-dipolyethylene glycol-carboxylic acid (1.62 g, 4.8 mmol), HATU (2.60 g, 6.8 mmol) and 10 mL of DMF were added to another reaction flask for a reaction (2) at 25 °C for 30 min. A reaction solution system obtained after the reaction (2) was added dropwise to a reaction system (1) for a reaction for 1 h. Evaporation to dryness was conducted under reduced pressure at 40 °C. 50 mL of purified water was added, and extraction was conducted for two times with 50 mL of DCM each time. The DCM was combined, and drying was conducted with anhydrous sodium sulfate, followed by filtration and evaporation to dryness to obtain a crude product. The crude product was purified by column chromatography to obtain 1.68 g of a target compound. The theoretical molecular weight was 709.3799, the measured molecular weight was 709.38801, and the mass spectrum results were consistent with that of the target compound. FIG. 4 is a diagram showing the mass spectrum of compound 8.

Synthesis of compound 9:

Compound 8, p-toluenesulfonic acid monohydrate (1.61 g, 8.5 mmol) and 20 mL of acetonitrile were added to a reaction flask for a reaction at 65 °C for 1 h, and evaporation to dryness was conducted under reduced pressure at 40 °C. 20 ml of DMF and DIPEA (1.83 g, 14.2 mmol) were added and stirred for a reaction (1) at 25 °C. Fmoc-o-tert-butyl-L-glutamic acid (1.43 g, 3.4 mmol), HATU (1.29 g, 3.4 mmol) and 20 mL of DMF were added to another reaction flask for a reaction (2) at 25 °C for 30 min. A reaction solution system obtained after the reaction (2) was added dropwise to a reaction system (1) for a reaction for 1 h. Evaporation to dryness was conducted under reduced pressure at 40 °C to obtain a crude product, and the crude product was purified by column chromatography to obtain 1.19 g of target compound. The theoretical molecular weight was 1016.5008, the measured molecular weight was 1016.51094, and the mass spectrum results were consistent with that of the target compound. FIG. 5 is a diagram showing the mass spectrum of compound 9.

Synthesis of compound 12:

c(RGDfK) (1.00 g, 1.7 mmol), tert-butyl amino-dipolyethylene glycol-succinimide (0.74 g, 1.9 mmol), DIPEA (0.44 g, 3.4 mmol) and 20 mL of DMF were added to a reaction flask for a reaction at 30 °C for 20 h. Evaporation to dryness was conducted under reduced pressure at 40 °C, 10 mL of methanol was added, and 60 mL of MTBE was added dropwsie for precipitating solid to obtain an intermediate 11. Next, suction filtration was conducted, followed by vacuum drying at 40 °C for 2 h. The solid intermediate 11 was added to the reaction flask, and 30 mL of TFA and 1.5 mL of purified water were added for a reaction at 30 °C for 1 h, followed by cooling to 0-5 °C. Then, 200 mL of MTBE was added dropwise and stirred at 0-5 °C for 30 min, followed by suction filtration, rinsing with MTBE and vacuum drying at 40 °C to obtain a product. The theoretical molecular weight was 762.4024, the measured molecular weight was 762.40768, and the mass spectrum results were consistent with that of the target compound. FIG. 6 is a diagram showing the mass spectrum of compound 12.

Synthesis of compound 13:

Compound 9, p-toluenesulfonic acid monohydrate (0.34 g, 1.8 mmol) and 20 mL of acetonitrile were added to a reaction flask for a reaction at 65 °C for 4 h, and evaporation to dryness was conducted under reduced pressure at 40 °C. 20 mL of DMF, DIPEA (0.36 g, 2.8 mmol), DCC (0.14 g, 0.7 mmol) and NHS (0.08 g, 0.7 mmol) were added for a reaction at 35 °C for 15-20 h to obtain an intermediate 10, followed by cooling to 25 °C. Compound 12 was added for a reaction for 1 h, and evaporation to dryness was conducted under reduced pressure at 40 °C to obtain a crude product. The crude product was purified by a preparative liquid phase to obtain 66.5 mg of target compound. The theoretical molecular weight was 1704.8300, the measured molecular weight was 1704.84518, and the mass spectrum results were consistent with that of the target compound. FIG. 7 is a diagram showing the mass spectrum of compound 13.

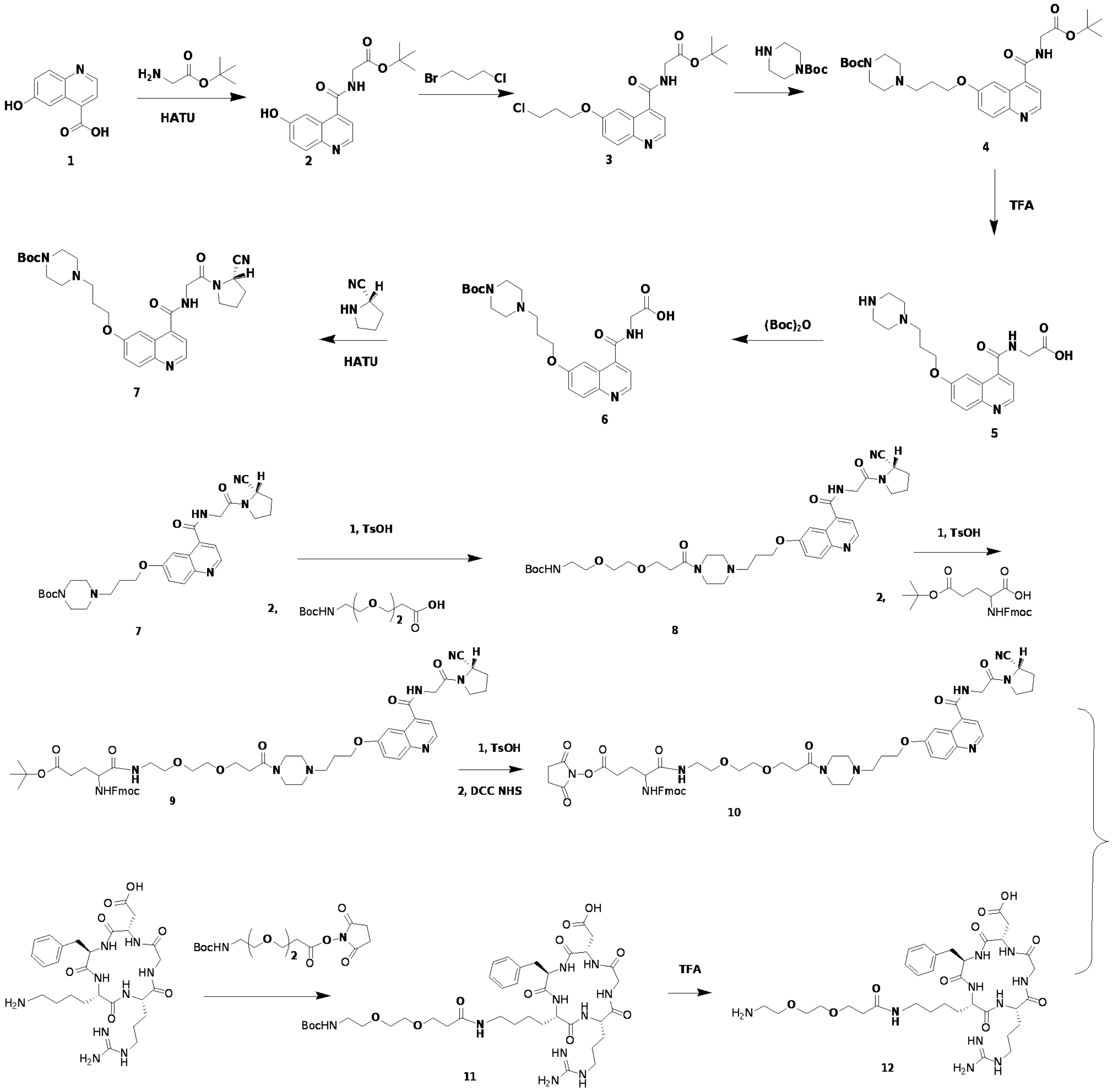
Synthesis of compound 14:

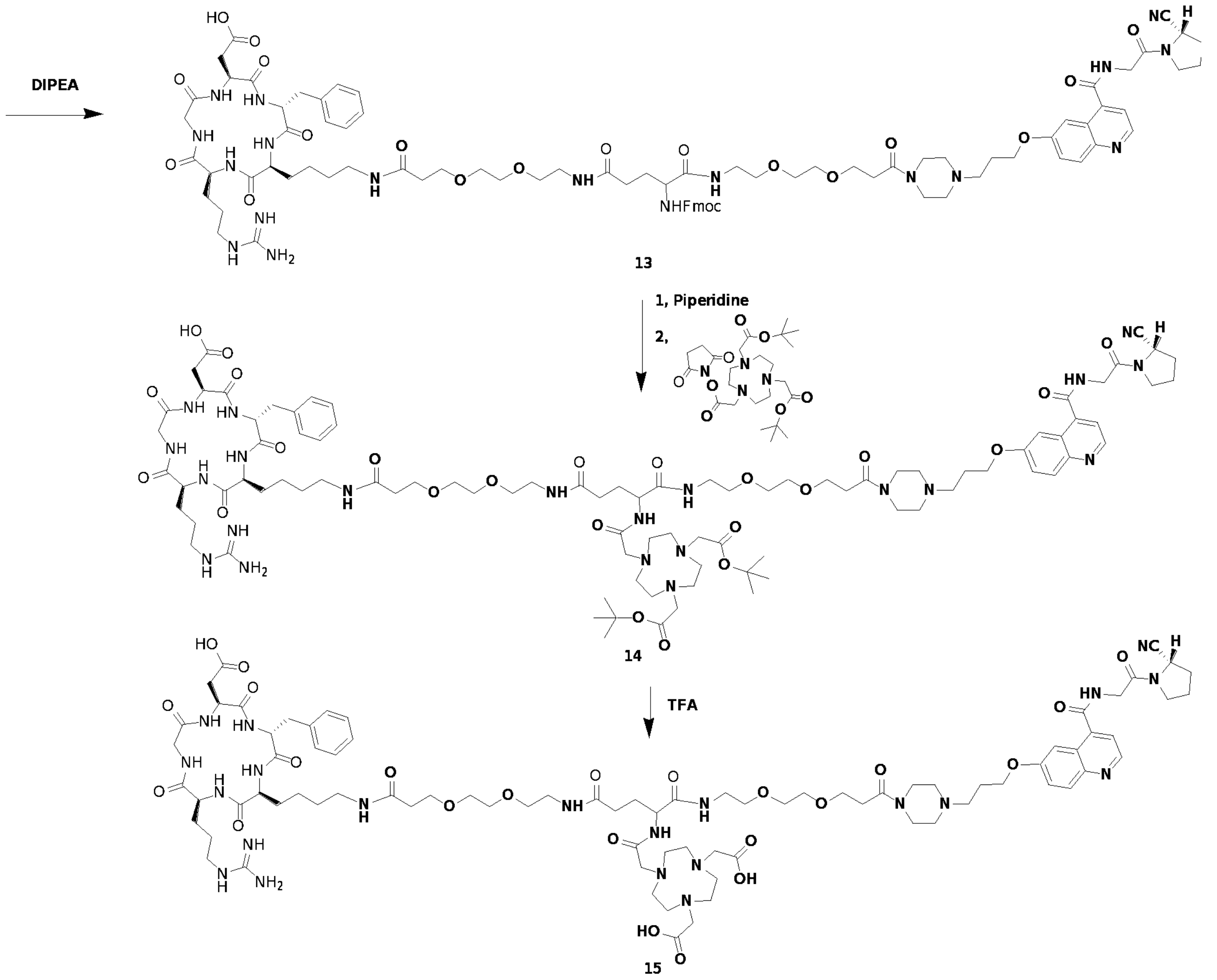
Compound 13, 0.5 mL of piperidine and 2 mL of DMF were added to a reaction flask for a reaction at 25 °C for 1 h, 10 mL of ethyl acetate was added dropwise for crystallization, stirring was conducted for 30 min, followed by suction filtration to obtain a solid, and the solid was subjected to vacuum drying at 40 °C for 2 h to obtain 50.8 mg of a product. Compound 13 without an FMOc protective group was dissolved in 2 mL of DMF, NOTA-2-tert-butyl-NHS-activated ester and DIPEA (0.010 g, 0.08 mmol) were added for a reaction at 25 °C for 1 h, and evaporation to dryness was conducted under reduced pressure at 40 °C. 2 mL of ethyl acetate and 2 mL of MTBE were added for crystallization, and stirring was conducted for 20 min, followed by suction filtration and vacuum drying at 40 °C to obtain 43.2 mg of product. The theoretical molecular weight was 1880.0196, the measured molecular weight was 1880.0369, and the mass spectrum results were consistent with that of the target compound. FIG. 8 is a diagram showing the mass spectrum of compound 14.

Synthesis of compound 15:

Compound 14 and 2 mL of trifluoroacetic acid were added to a reaction flask for a reaction at 25 °C for 1 h, and evaporation to dryness was conducted under reduced pressure at 40 °C to obtain a crude product. The crude product was purified by a preparative liquid phase and then freeze-dried to obtain product compound 15 with a yield of 42%. The theoretical molecular weight was 1767.8944, the measured molecular weight was 1767.91036, and the mass spectrum results were consistent with that of the target compound. FIG. 9 is a diagram showing the mass spectrum of compound 15.

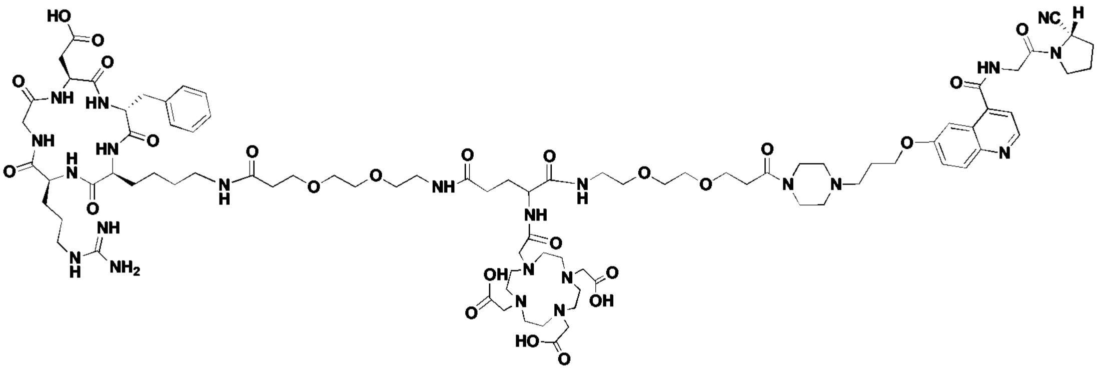
A synthesis route in the above steps is as follows:





Example 2

The preparation method in Example 2 can refer to the preparation method in Example 1. The NOTA-2-tert-butyl-NHS-activated ester in the above example was substituted with NOTA-3-tert-butyl-NHS-activated ester to obtain the following structure:



Formula (I-2).

Example 3: Preparation of a radioactive ^{68}Ga labeled FAPI-RGD complex (^{68}Ga-FAPI-RGD) shown in Formula (I-1)

Wet method: A hydrochloric acid solution of about 18.5-1,850 MBq of $^{68}GaCl_3$ (rinsed with a germanium-gallium generator) was added to an acetic acid-acetate solution (1.0 g/L) containing 0.5 mL of compound having the structure shown in Formula (I-1) prepared in Example 1 in a centrifuge tube, and a reaction was carried out at 37 °C for 20 min. A small C18 separation column was taken, slowly rinsed with 10 mL of anhydrous ethanol first, and then rinsed with 10 mL of water. The obtained labeled solution was diluted with 10 mL of water, and then sampled to the separation column. Unlabeled ^{68}Ga ions were removed with 10 mL of water, and rinsing was conducted with 0.3 mL of 10 mM ethanol solution of HCl to obtain a ^{68}Ga labeled FAPI-RGD complex. The rinsed solution was diluted with normal saline, followed by aseptic filtration to obtain injection of the ^{68}Ga labeled FAPI-RGD complex.

Freeze-drying method: A hydrochloric acid solution of about 18.5-1,850 MBq of $^{68}GaCl_3$ (rinsed with a germanium-gallium generator) was added to a freeze-dried medicine box containing compound shown in Formula (I-1), and uniformly mixed for a reaction at 37 °C for 20 min. A small C18 separation column was taken, slowly rinsed with 10 mL of anhydrous ethanol first, and then rinsed with 10 mL of water. Resulting labeled solution was diluted with 10 mL of water, and then sampled to the separation column. Unlabeled ^{68}Ga ions were removed with 10 mL of water, and rinsing was conducted with 0.3 mL of 10 mM ethanol solution of HCl to obtain rinsed solution of a complex. The rinsed solution was diluted with normal saline, followed by aseptic filtration to obtain an injection of the ^{68}Ga labeled FAPI-RGD complex.

Example 4: Preparation of a radioactive ^{177}Lu labeled FAPI-RGD complex (^{177}Lu-FAPI-RGD) shown in Formula (I-2)

Preparation of a buffer solution with a pH of 5.5: 57.6 mg of acetic acid, 189 mg of gentianic acid and 525 mg of sodium acetate trihydrate were weighed and dissolved in 48 ml of pure water, and the pH was adjusted to 5.5 with a sodium hydroxide solution. 200 µg of compound having the structure shown in Formula (I-2) prepared in Example 2 was fully dissolved in 200 µL of the buffer solution (pH was 5.5), and then 5 ml of the buffer solution (pH was 5.5) and a hydrochloric acid solution of about 150 mCi of $^{177}LuCl_3$ were added. A mixture was shaken uniformly and heated for a reaction at 80 °C for 20 min. After the reaction was completed, cooling was conducted to room temperature. Then reaction solution was diluted with normal saline, followed by aseptic filtration to obtain an injection of 10 mCi/mL ^{177}Lu labeled FAPI-RGD complex.

Experimental Example: Analysis and application effect

1. Analysis of the stability of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1)

20 μL of a solution of ^{68}Ga-FAPI-RGD (having an activity of 3.7 MBq/20 μL) prepared in Example 3 was added to a centrifuge tube containing 100 μL of normal saline or PBS (pH was 7.4) for co-incubation at 37 °C for 0.5 h, 1 h and 4 h to obtain co-incubation solution. 20 μL of the co-incubation solution was filtered with a 0.22 μm needle filter membrane, and then the radiochemical purity was analyzed by HPLC. Test results are shown in FIG. 10. After incubation in the normal saline, the ^{68}Ga-FAPI-RGD is not obviously decomposed, and the radiochemical purity is greater than 99%, indicating that the ^{68}Ga-FAPI-RGD prepared by the present disclosure has excellent stability.

2. Analysis of a cell experiment of the ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1)

A cell uptake experiment of ^{68}Ga-FAPI-RGD was carried out in HT1080-FAP tumor cells, and test results are shown in the part A of FIG. 11. The ^{68}Ga-FAPI-RGD has rapid cell uptake, and the maximum uptake is reached after incubation for 30 min and remained at similar uptake level for 2 h. In addition, it is proven by a blocking experiment that the cell uptake of the ^{68}Ga-FAPI-RGD can be partially inhibited by C(RGDfK) or FAPI-02, and can be completely blocked by FAPI-RGD (with reference to the part A of FIG. 11). A cell binding experiment was carried out in HT1080-FAP and U87MG tumor cells, and test results are shown in the part B and the part C of FIG. 11 respectively. According to the cell experiment of HT1080-FAP, the IC_{50} value of ^{68}Ga-FAPI-RGD and ^{68}Ga-FAPI-02 was 11.17 nM and 4.14 nM, respectively after measurement. According to the cell experiment of HT1080-FAP, the IC_{50} value of ^{68}Ga-FAPI-RGD and ^{68}Ga-C(RGDfK) was 18.93 nM and 11.49 nM, respectively after measurement. The experimental results show that compared with corresponding monomers, the FAPI-RGD has similar affinity for corresponding receptors FAP and integrin

$\alpha_v\beta_3$.

3. MicroPET imaging of ^{68}Ga labeled FAPI-RGD complex shown in Formula (I) in tumor-bearing mice

^{68}Ga-FAPI-RGD was prepared according to the method in Example 3. 7.4 MBq of the ^{68}Ga-FAPI-RGD, ^{68}Ga-FAPI-02 and ^{68}Ga-C(RGDfK) were intravenously injected into tails of HT1080-FAP tumor-bearing mice which were randomly divided into groups, and after anaesthetization with isoflurane, MicroPET imaging was conducted on the ^{68}Ga-FAPI-RGD group after administration for 0-240 min and on the other groups after administration for 0-120 min. Results are shown in FIG. 12. In FIG. 12, the part A, the part C and the part E show maximum-density MicroPET projection images of HT1080-FAP tumor-bearing mice (n was 3) at different time points after intravenous injection in the above three groups of mice, respectively. The part B, the part D and the part F show the uptake in various organs or tissues (including blood, liver, kidneys, tumors and muscles) of the above three groups of mice at different time points after injection, respectively. Three dose uptakes in each group from left to right correspond to 0.5 h, 1 h and 2 h after injection, respectively. FIG. 12 shows that tumors are clearly visible at the time points of imaging acquisition, and the ^{68}Ga-FAPI-RGD has higher uptake in tumors than the monomers ^{68}Ga-FAPI-02 and ^{68}Ga-C(RGDfK). A specific binding property of the ^{68}Ga-FAPI-RGD to integrin $\alpha_v\beta_3$ and FAP in vivo is confirmed by a blocking experiment. The above ^{68}Ga-FAPI-RGD and C(RGDfK) or FAPI-02 were co-injected into HT1080-FAP tumor-bearing mice. MicroPET imaging results and organ uptake results are shown in FIG. 13. In FIG. 13, four images in the part A correspond to images obtained after single injection of ^{68}Ga-FAPI-RGD, co-injection of ^{68}Ga-FAPI-RGD and C(RGDfK), co-injection of ^{68}Ga-FAPI-RGD and FAPI-02, and co-injection of ^{68}Ga-FAPI-RGD, C(RGDfK) and FAPI-02 from left to right, respectively. The part B and the part C respectively shows the uptake of ^{68}Ga-FAPI-RGD in various organs or tissues (including blood, liver, kidneys, tumors and muscles) and the target/non-target ratio of mice, after injection in different way of the above four groups. Four bar graphs for each organ or tissue in the part B and the part C correspond to the four injection ways in the part A from left to right, respectively. From FIG. 13, it can be seen that after co-injection of the

^{68}Ga-FAPI-RGD and RGD or FAPI-02, the uptake of the ^{68}Ga-FAPI-RGD in tumors can be reduced, and after co-injection of the ^{68}Ga-FAPI-RGD, C(RGDfK) and FAPI-02, the uptake of the ^{68}Ga-FAPI-RGD in tumors is further reduced. It is proven by a clocking experiment that the ^{68}Ga-FAPI-RGD can achieve specific targeting of tumors by binding to integrin $\alpha_v\beta_3$ and FAP in vivo.

4. SEPCT imaging of ^{177}Lu labeled FAPI-RGD complex shown in Formula (II) in tumor-bearing mice

^{177}Lu-FAPI-RGD was prepared according to the method in Example 4. 37 MBq of the ^{177}Lu-FAPI-RGD was intravenously injected into tails of HT1080-FAP tumor-bearing mice, and after anaesthetization with isoflurane, SPECT imaging was conducted after administration for 4 h. Results are shown in FIG. 14. It can be seen that tumors are clearly visible after 4 h of administration.

5. MicroPET imaging of complex of ^{68}Ga labeled FAPI-RGD (control compound) in tumor-bearing mice

As a control, a thiosuccinimide bond formed by maleimide and mercaptan was used as a connecting structure, compound shown in the part B of FIG. 15 was prepared, labeling with ^{68}Ga was conducted according to the method in Example 3, and MicroPET imaging study was carried out in HT1080-FAP tumor-bearing mice. Results are shown in FIG. 15. The part A of FIG. 15 shows that at the time points of imaging acquisition, major radioactive signals are concentrated in the liver and kidneys, and less uptake in tumors is achieved. The part C of FIG. 15 also shows high uptake in the liver and kidneys and low uptake in tumors. Therefore, when the thiosuccinimide bond is used as a connecting structure, the affinity of targeting group to targeted receptor may be reduced, leading to decrease of the uptake in target organ. Meanwhile, the uptake in non-target tissues is too high, leading to decrease of the target/non-target ratio, so that adverse reactions are more likely to be caused. A specific connecting structure of the present disclosure can not only ensure high affinity for receptor but also provide suitable pharmacokinetic properties, so that high absolute uptake in tumors and high target/non-target ratio are ensured.

6. PET/CT imaging of a ^{68}Ga labeled FAPI-RGD complex shown in Formula (I-1) in

patients with tumors

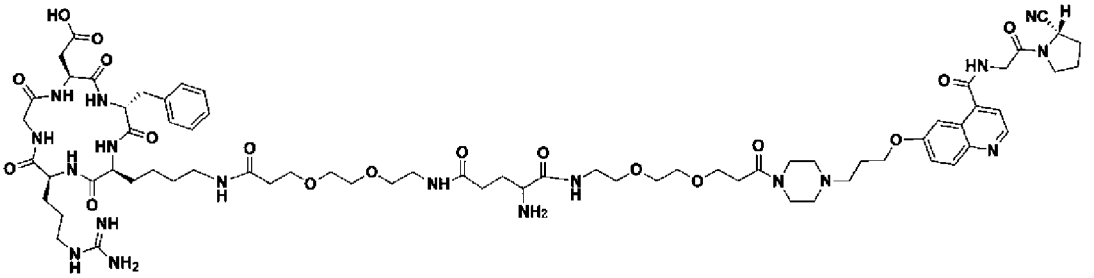
^{68}Ga-FAPI-RGD clinical trial was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Xiamen University. All subjects, including a patient with pancreatic cancer, a patient with non-small cell lung cancer, a patient with small cell lung cancer and a patient with nasopharyngeal cancer, signed a written informed consent. The dose of intravenous injection of ^{68}Ga-FAPI-RGD was calculated based on the body weight of every subject (1.8-2.2 MBq [0.05-0.06 mCi]/kg). A hybrid PET/CT scanner (Discovery MI, GE Healthcare, Milwaukee, WI, USA) was used to obtain data 3 h after the intravenous injection. Imaging results are shown in FIG. 16. The maximum standard uptake value (SUV_{max}) was calculated automatically by using the region of interest (ROI) drawn on a longitude image. The SUV_{max} of the ^{68}Ga-FAPI-RGD targeting dual targets in different types of tumors is higher than that of ^{68}Ga-FAPI-46 targeting single FAP target, and the SUV_{max} is increased by about 30-50%, proving that the design of targeting dual targets can improve the number of effective receptors in tumors and the utilization efficiency so as to improve the uptake in tumors.

In summary, an FAPI-RGD structure is developed by the present disclosure. The compound has high affinity for the FAP target and the integrin $\alpha_v\beta_3$ target, can realize synergistic targeting of the FAP target and the integrin $\alpha_v\beta_3$ target in tumors, has excellent pharmacokinetics, high uptake in tumors and long retention time in tumors, and is expected to be applied to diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$.

Although the present disclosure has been described in detail by general descriptions, specific embodiments and tests above, it is obvious to persons skilled in the field that some modifications or improvements can be made on the basis of the present disclosure. Therefore, all the modifications or improvements made without departing from the spirit of the present disclosure shall fall within the protection scope of the present disclosure.

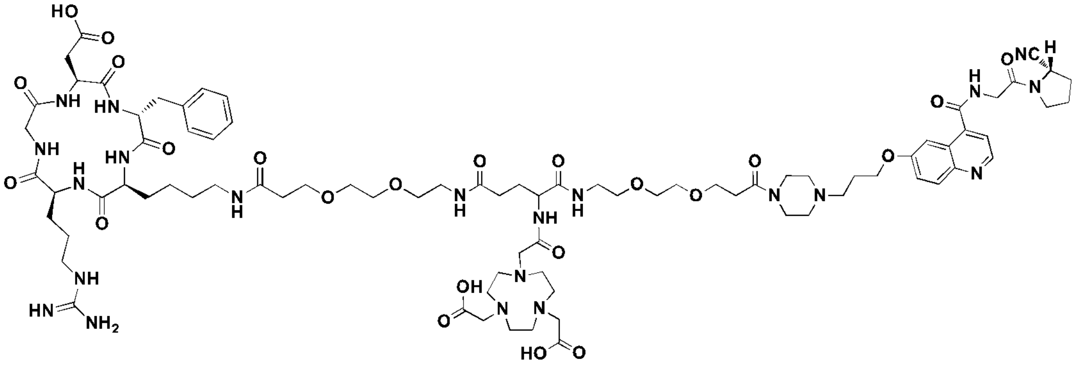
CLAIMS

1. A dual-targeting compound, wherein the compound structurally contains ligand structures specifically binding to FAP and integrin $\alpha_v\beta_3$ at the same time, and the compound has the following structure shown in Formula (I):

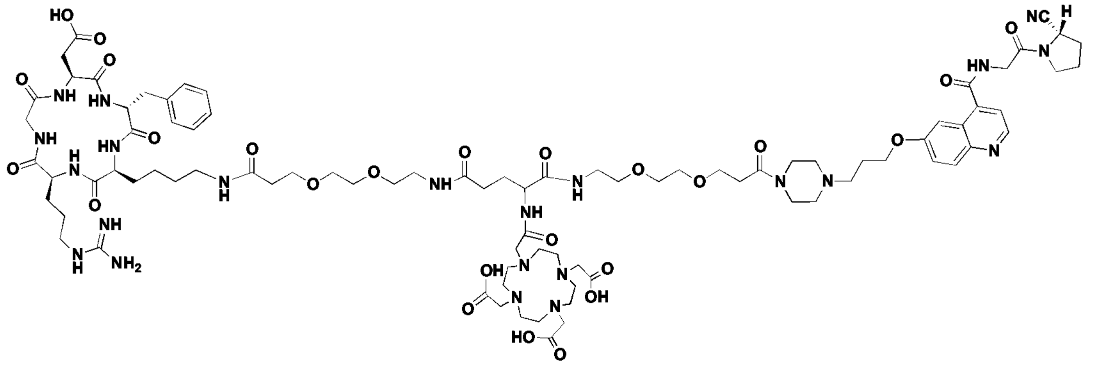


(I).

2. A dual-targeting compound capable of being labeled with a radionuclide, wherein the compound structurally contains ligands specifically binding to FAP and integrin $\alpha_v\beta_3$ at the same time and a nuclide chelating structure, and the compound has the following structure shown in Formula (I-1) or Formula (I-2):



(I-1),



(I-2).

3. A method for preparing the dual-targeting compound capable of being labeled with a radionuclide according to claim 2, comprising the following steps: firstly reacting 6-hydroxyquinoline-4-carboxylic acid with amino of tert-butyl glycinate by amide condensation; then connecting BoC-protected piperazinyl at hydroxyl position of an amide condensation

product by an alkyl chain; removing Boc protective groups and tert-butyl protective groups under acidic conditions, and introducing a Boc protective group to piperazine ring of the condensation product, followed by an amide condensation reaction with (S)-pyrrolidene-2-carbonitrile hydrochloride; after removing the Boc protective group, carrying out a condensation reaction with N-Boc-3-[2-(2-aminoethoxy)ethoxy]propionic acid; next, removing the Boc protective group, and carrying out a reaction with Fmoc-O-tert-butyl-L-glutamic acid; after removing tert-butyl ester, preparing an activated ester, followed by a reaction with c(RGDfK) with amino-dipolyethylene glycol to obtain a dual-targeting compound; then after removing an Fmoc protective group, carrying out a reaction with a nuclide chelating agent, wherein the nuclide chelating agent is 1,4,7,10-tetraazacyclododecane-N,N',N,N'-tetraacetic acid or 1,4,7-triazacyclononane-1,4,7-triacetic acid; and finally, removing a tert-butyl protective group on a chelating group to obtain a dual-targeting compound capable of being labeled with a radionuclide.

4. A radionuclide labeled dual-targeting compound, wherein the compound is obtained by labeling any one of the dual-targeting compounds capable of being labeled with a radionuclide according to claim 2 with a radionuclide; and the radionuclide is selected from an α-ray emitting isotope, a β-ray emitting isotope, a γ-ray emitting isotope, an auger electron emitting isotope, or an X-ray emitting isotope.

5. The radionuclide labeled dual-targeting compound according to claim 4, wherein the radionuclide is selected from any one of ^{18}F, ^{51}Cr, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{139}La, ^{140}La, ^{175}Yb, ^{153}Sm, ^{166}Ho, ^{86}Y, ^{90}Y, ^{149}Pm, ^{165}Dy, ^{169}Er, ^{177}Lu, ^{47}Sc, ^{142}Pr, ^{159}Gd, ^{212}Bi, ^{213}Bi, ^{72}As, ^{72}Se, ^{97}Ru, ^{109}Pd, ^{105}Rh, ^{101m}Rh, ^{119}Sb, ^{128}Ba, ^{123}I, ^{124}I, ^{131}I, ^{197}Hg, ^{211}At, ^{151}Eu, ^{153}Eu, ^{169}Eu, ^{201}Tl, ^{203}Pb, ^{212}Pb, ^{198}Au, ^{225}Ac, ^{227}Th, or ^{199}Ag.

6. The radionuclide labeled dual-targeting compound according to claim 4, wherein the radionuclide is selected from ^{18}F, ^{64}Cu, ^{68}Ga, ^{89}Zr, ^{90}Y, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{188}Re, or ^{225}Ac.

7. A method for preparing the radionuclide labeled dual-targeting compound according to claim 4, comprising: reacting the dual-targeting compound capable of being labeled with a radionuclide according to claim 2 with compound containing a radionuclide by a prior art of wet labeling or freeze-drying labeling to obtain the radionuclide labeled dual-targeting compound.

CLAIMS

8. A pharmaceutical composition, comprising the dual-targeting compound according to claim 1, the dual-targeting compound capable of being labeled with a radionuclide according to claim 2, the radionuclide labeled dual-targeting compound according to claim 4, or a pharmaceutically acceptable hydrate, solvate or salt thereof.

9. Application of any one of the dual-targeting compound according to claim 1, the dual-targeting compound capable of being labeled with a radionuclide according to claim 2, the radionuclide labeled dual-targeting compound according to claim 4, or a pharmaceutically acceptable hydrate, solvate or salt thereof, or the pharmaceutical composition according to claim 8 in preparation of medicines for diagnosis or therapy of diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$ in animals or human persons.

10. The application according to claim 9, wherein the diseases characterized by overexpression of FAP and/or integrin $\alpha_v\beta_3$ comprise, but are not limited to: cancer, chronic inflammation, atherosclerosis, or cicatricial diseases.

11. The application according to claim 10, wherein the cancer is selected from breast cancer, pancreatic cancer, small bowel cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, esophageal cancer, hypopharyngeal cancer, nasopharyngeal cancer, laryngeal cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal cell carcinoma, neuroendocrine carcinoma, carcinogenic osteomalacia, sarcoma, cancer of unknown primary, thymic carcinoma, glioma, neuroglioma, astrocytoma, cervical cancer, or prostate cancer.

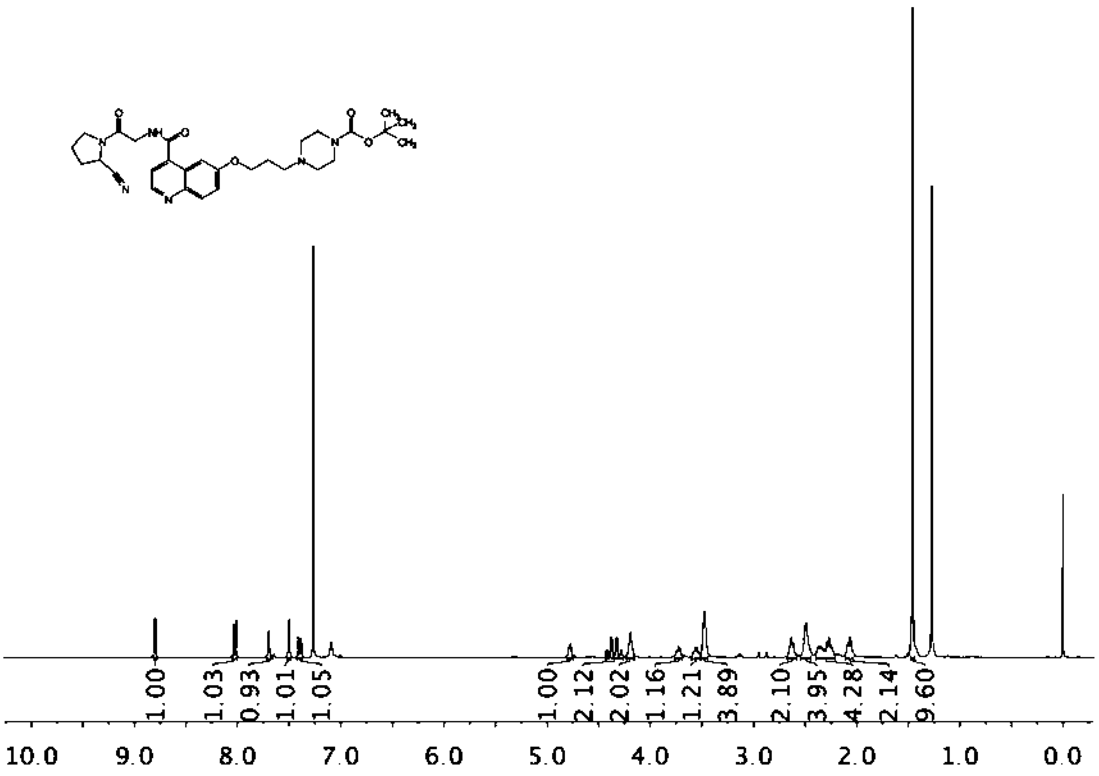

1.00
1.03
0.93
1.01
1.05
1.00
2.12
2.02
1.16
1.21
3.89
2.10
3.95
4.28
2.14
9.60
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

FIG. 1

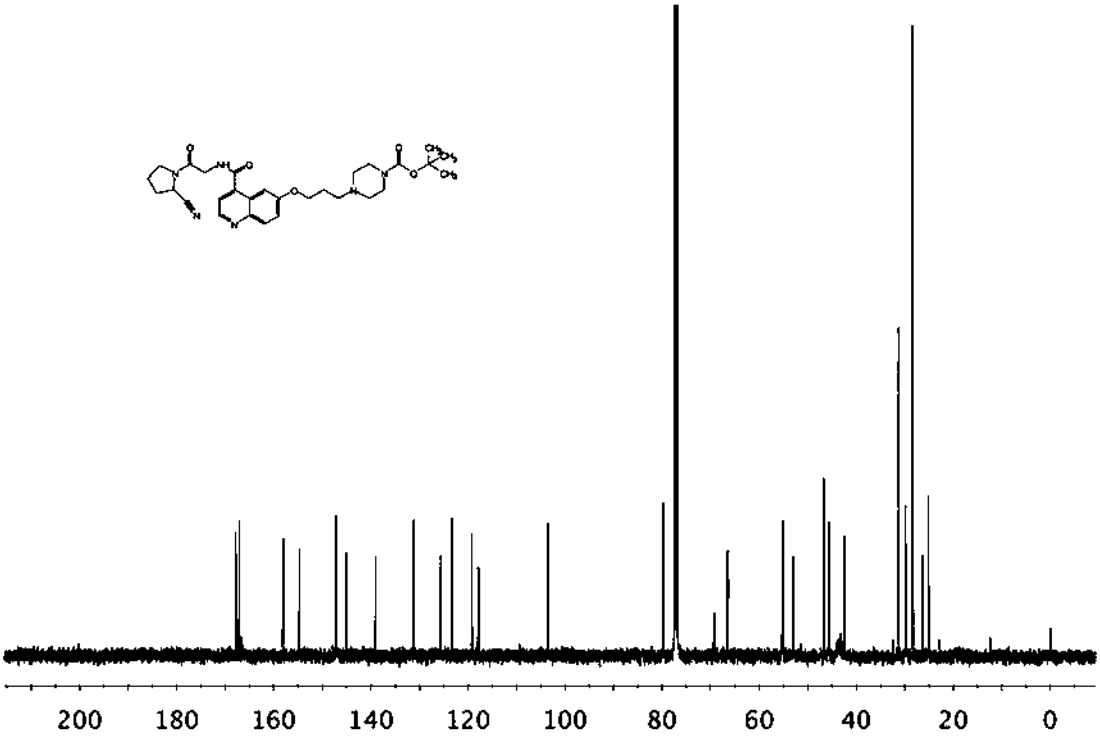

200
180
160
140
120
100
80
60
40
20
0

FIG. 2

DRAWINGS

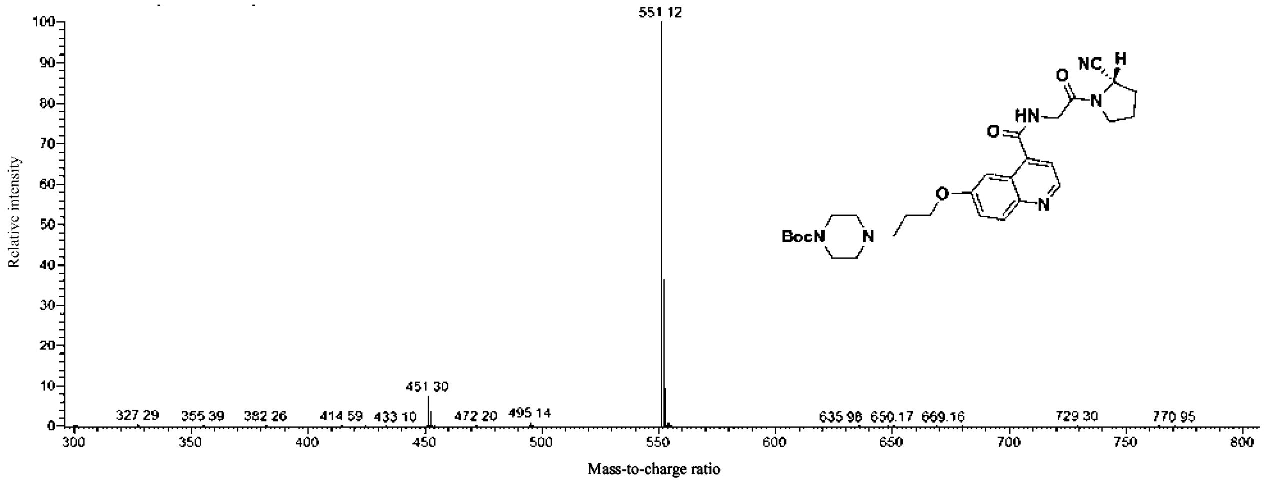


FIG. 3

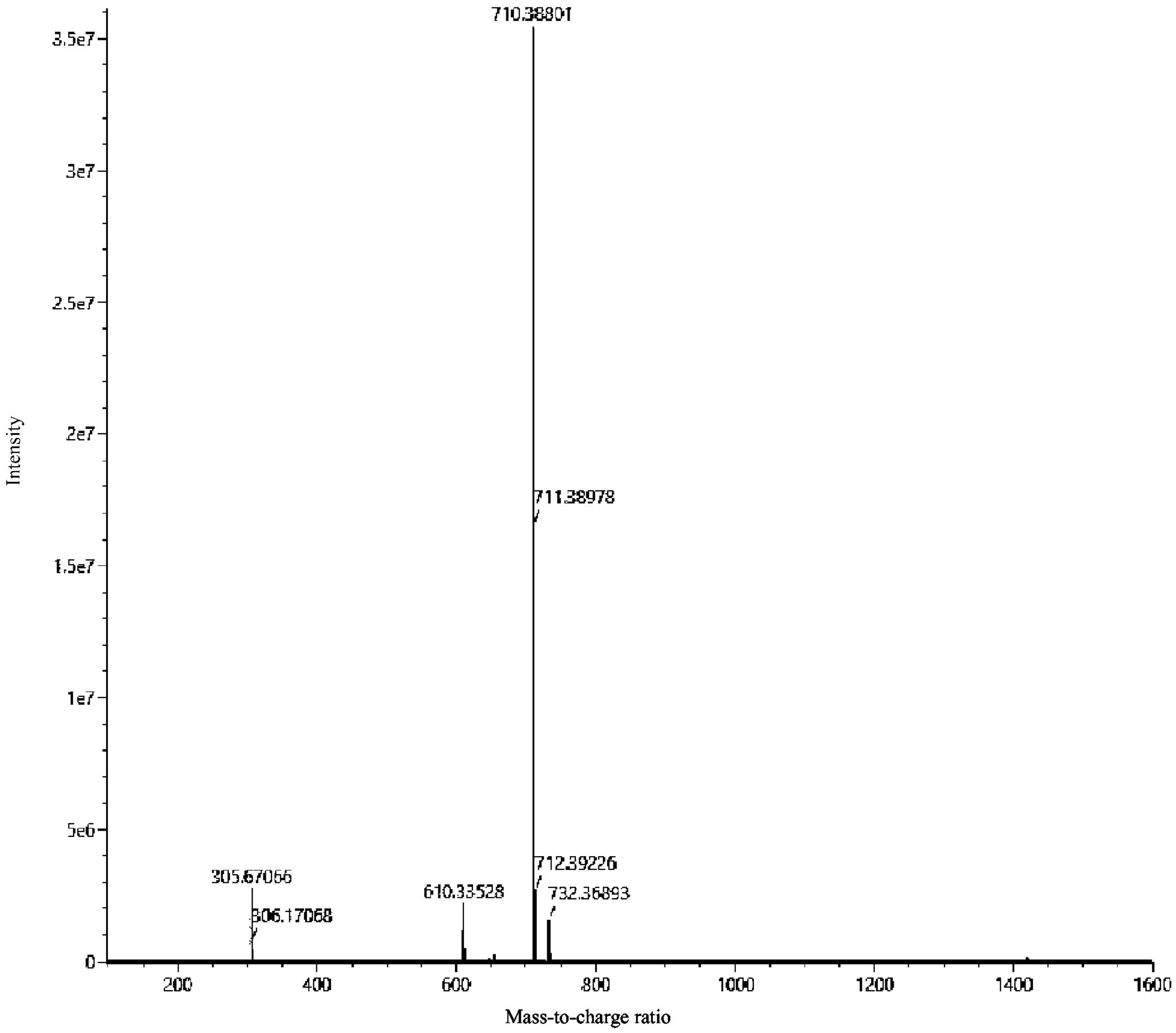


FIG. 4

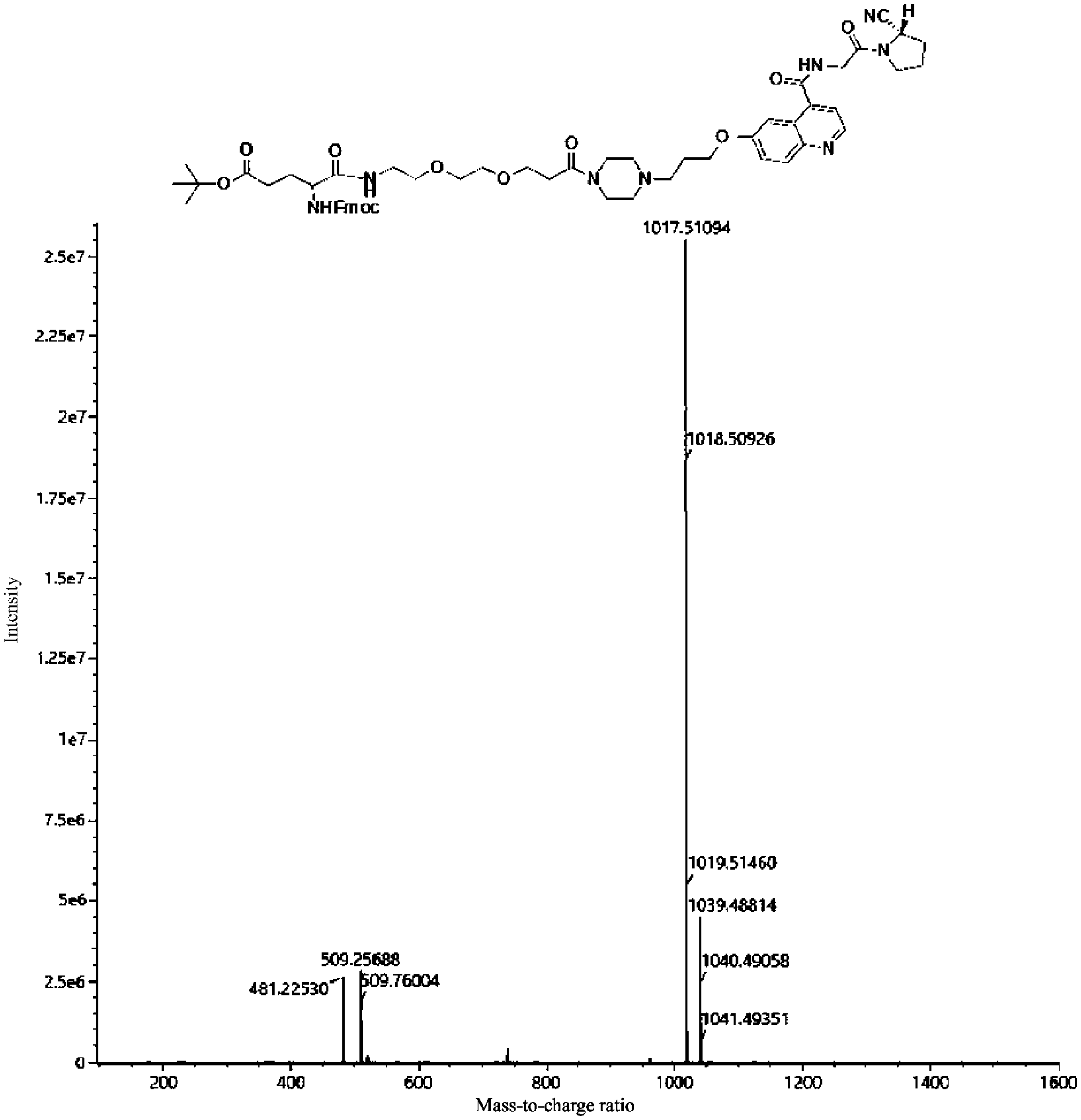

NC
H
O
HN
O
N
O
N
O
O
O
O
O
N
N
O
O
O
N
H
NHFmoc
1017.51094
1018.50926
1019.51460
1039.48814
1040.49058
1041.49351
509.25688
509.76004
481.22530
2.5e7
2.25e7
2e7
1.75e7
1.5e7
1.25e7
1e7
7.5e6
5e6
2.5e6
0
Intensity
200
400
600
800
1000
1200
1400
1600
Mass-to-charge ratio

FIG. 5

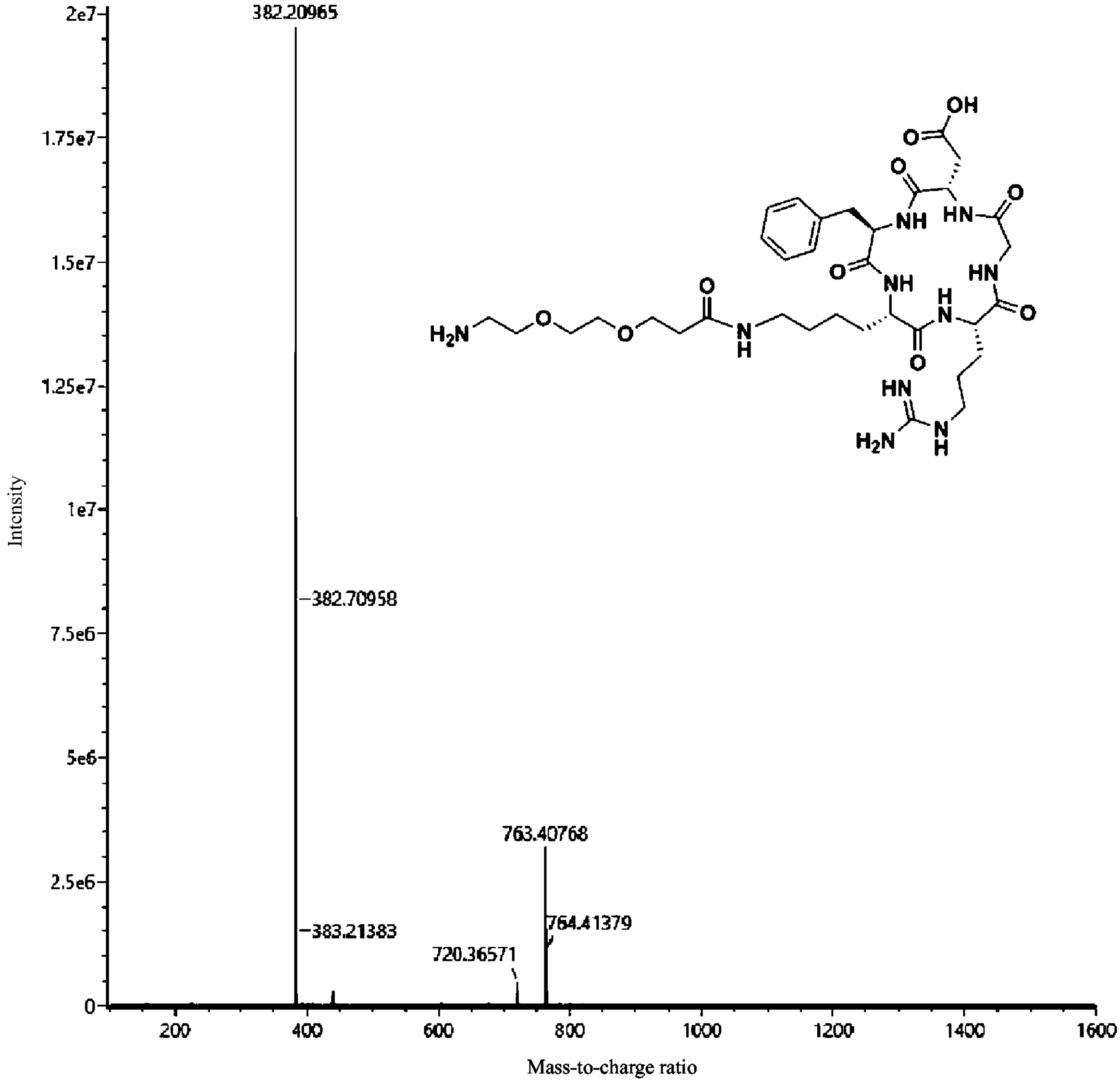

382.20965
−382.70958
−383.21383
763.40768
764.41379
720.36571
2e7
1.75e7
1.5e7
1.25e7
1e7
7.5e6
5e6
2.5e6
0
Intensity
200
400
600
800
1000
1200
1400
1600
Mass-to-charge ratio
OH
O
NH
HN
HN
NH
H
N
H_2N
HN
H_2N
N
H

FIG. 6

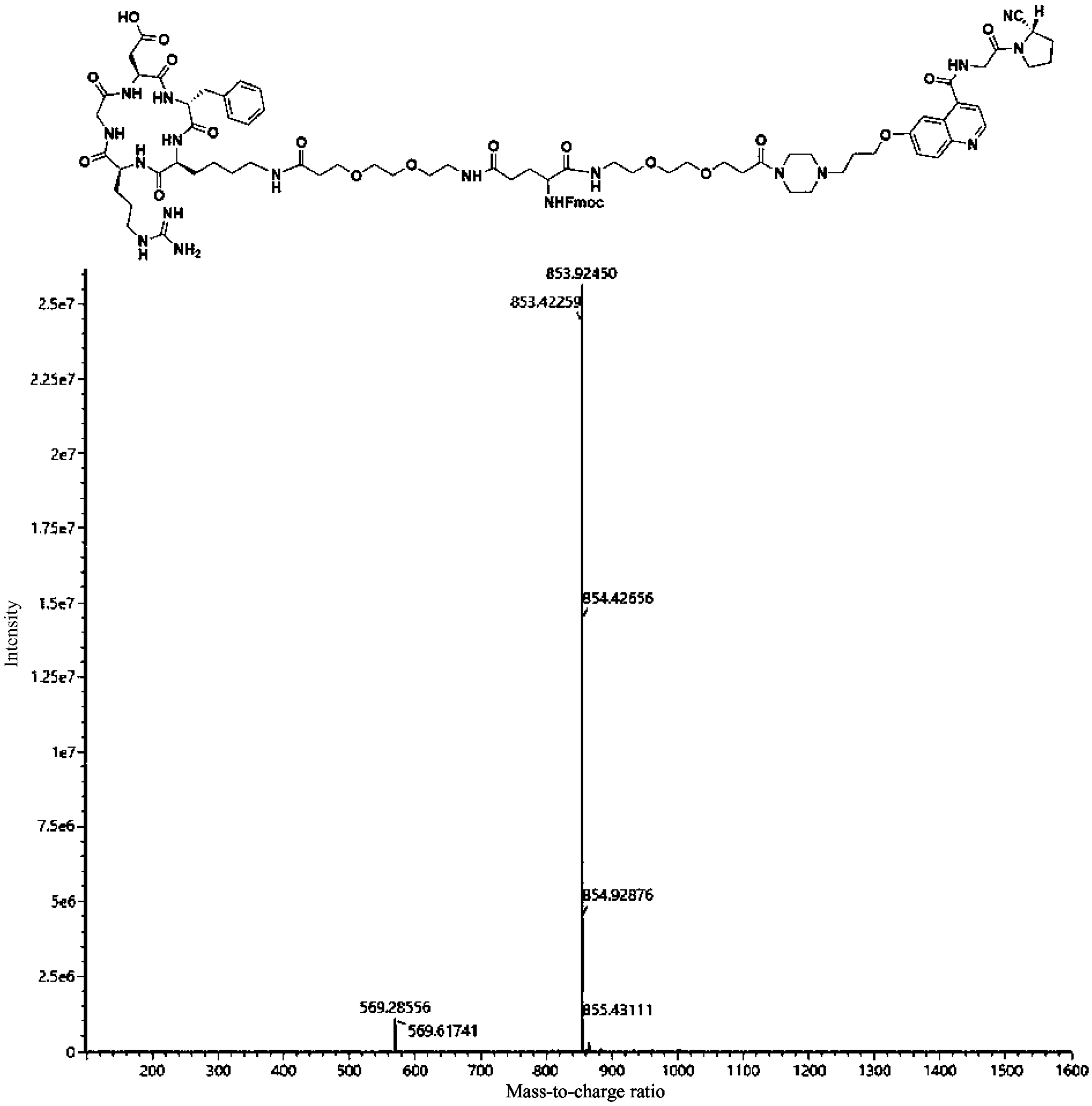

HO
O
O
O
NH
HN
NH
HN
O
O
H
N
O
O
NH
N
H
NH2
O
N
H
O
O
NH
O
O
N
H
NHFmoc
O
O
O
N
N
O
N
O
HN
O
N
NC
H
2.5e7
2.25e7
2e7
1.75e7
1.5e7
1.25e7
1e7
7.5e6
5e6
2.5e6
0
Intensity
853.92450
853.42259
854.42656
854.92876
855.43111
569.28556
569.61741
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
Mass-to-charge ratio

FIG. 7

DRAWINGS

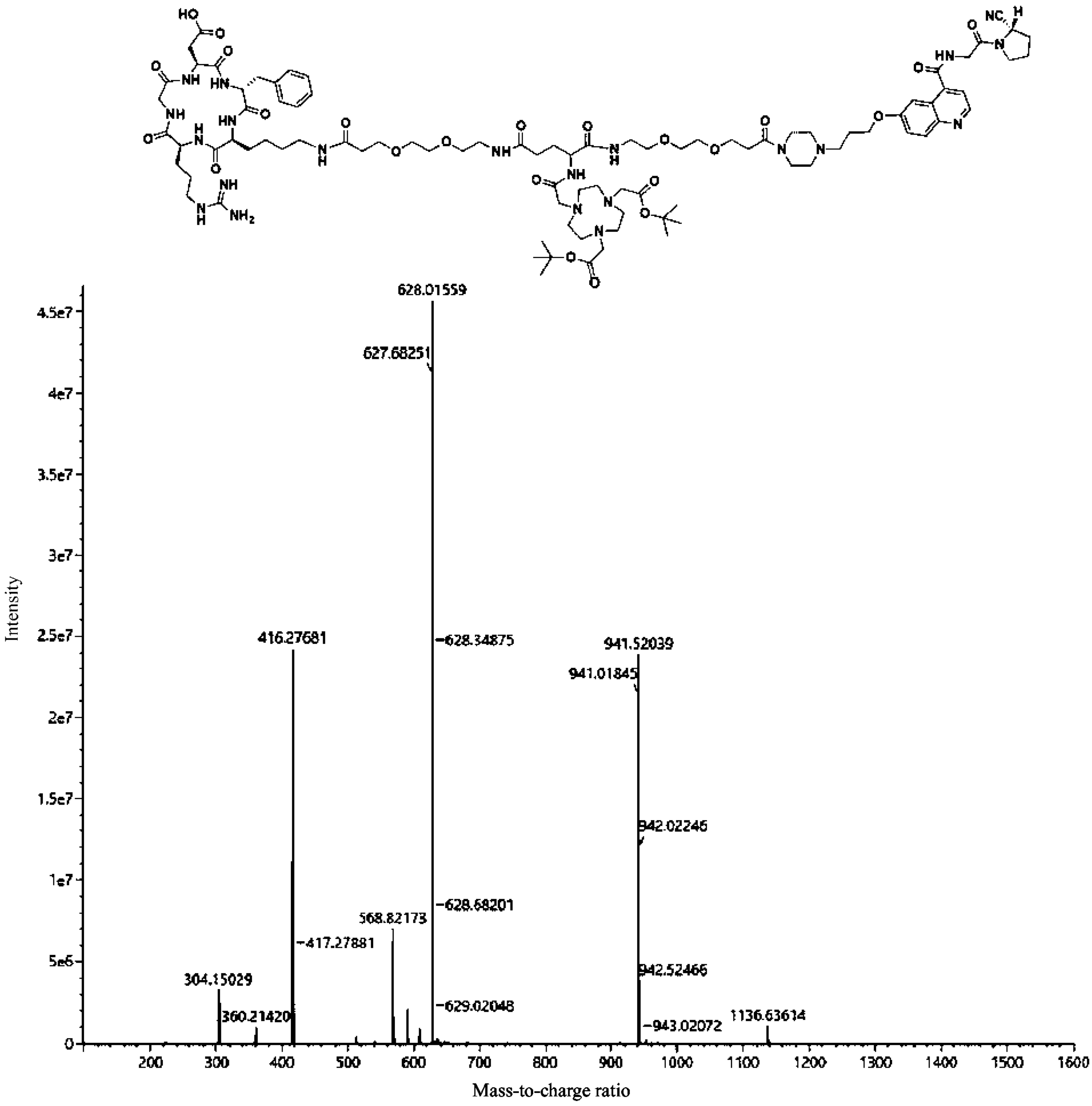


FIG. 8

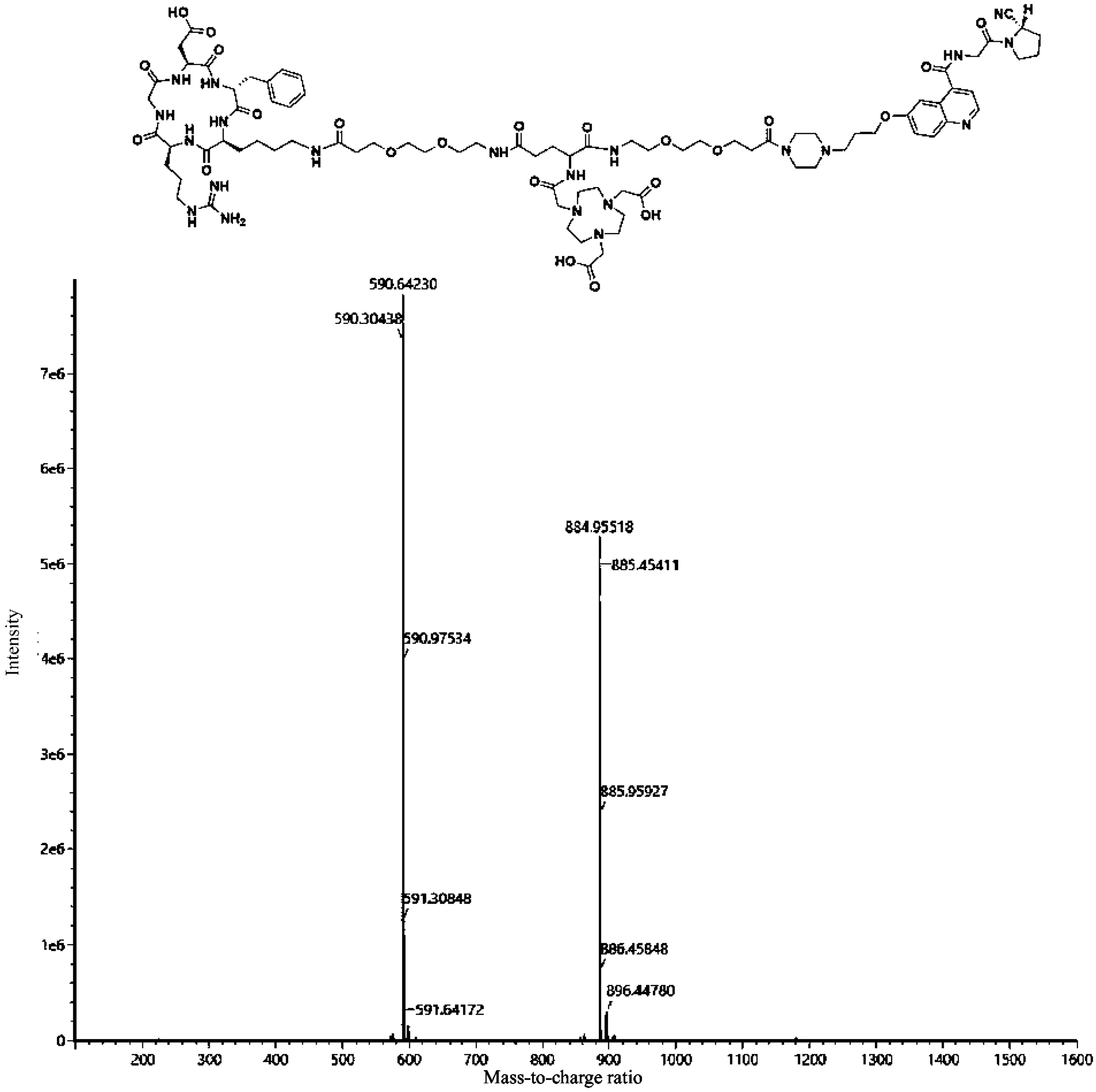
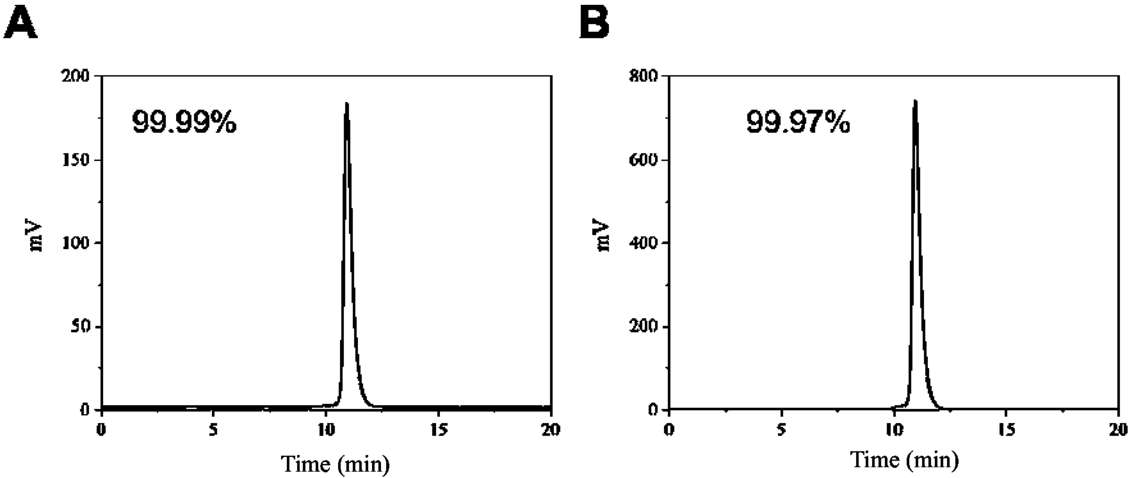
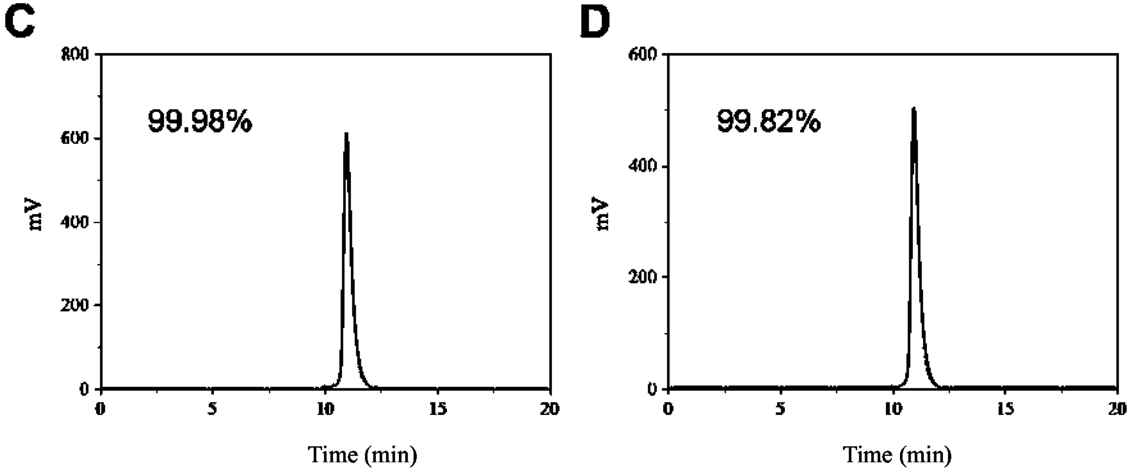

590.64230
590.30438
590.97534
591.30848
591.64172
884.95518
885.45411
885.95927
886.45848
896.44780
7e6
6e6
5e6
4e6
3e6
2e6
1e6
0
Intensity
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
Mass-to-charge ratio

FIG. 9



Normal saline (0.5 h)



Normal saline (1 h)

Normal saline (4 h)

FIG. 10

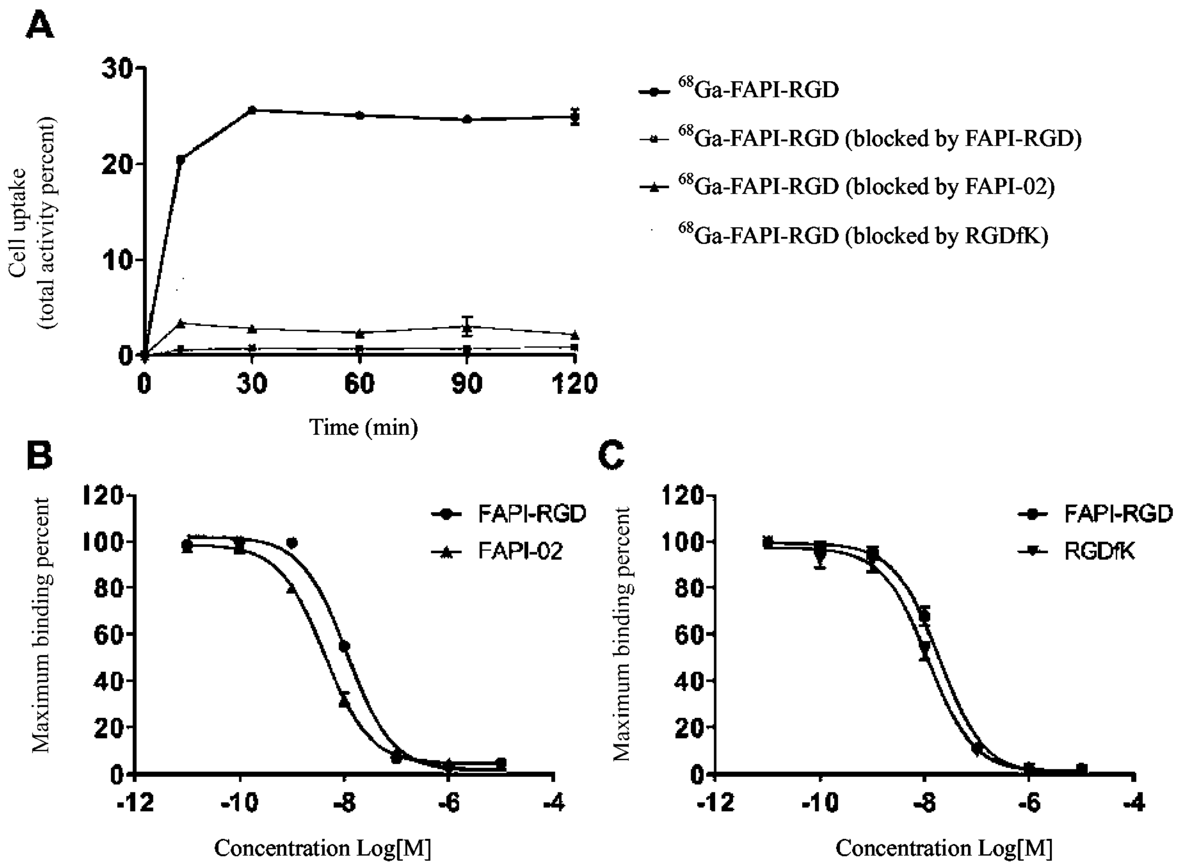

A
Cell uptake (total activity percent)
30
20
10
0
0
30
60
90
120
Time (min)
^{68}Ga-FAPI-RGD
^{68}Ga-FAPI-RGD (blocked by FAPI-RGD)
^{68}Ga-FAPI-RGD (blocked by FAPI-02)
^{68}Ga-FAPI-RGD (blocked by RGDfK)
B
Maximum binding percent
120
100
80
60
40
20
0
-12
-10
-8
-6
-4
Concentration Log[M]
FAPI-RGD
FAPI-02
C
Maximum binding percent
120
100
80
60
40
20
0
-12
-10
-8
-6
-4
Concentration Log[M]
FAPI-RGD
RGDfK

FIG. 11

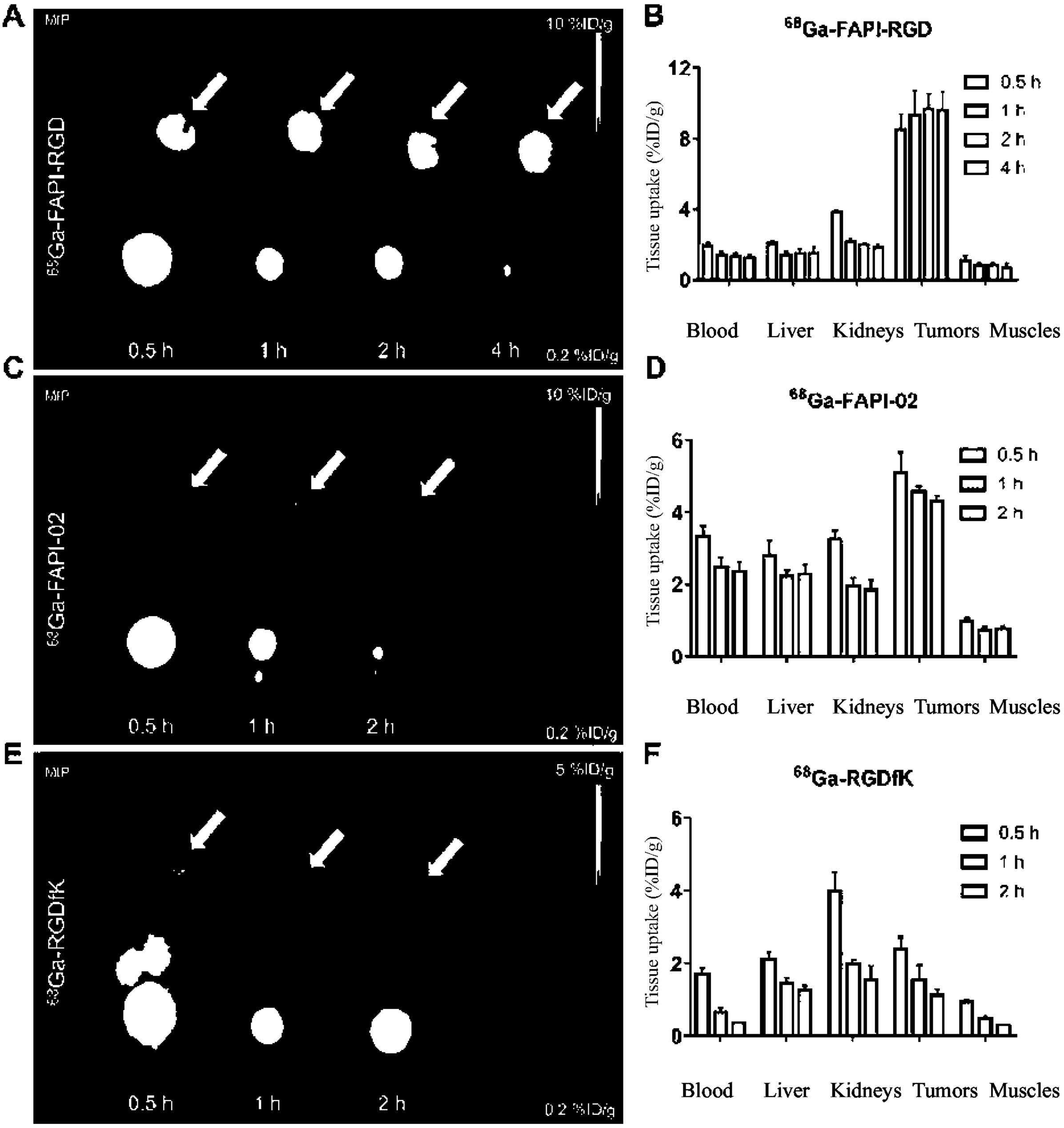

A
MIP
10 %ID/g
⁶⁸Ga-FAPI-RGD
0.5 h
1 h
2 h
4 h
0.2 %ID/g
B
⁶⁸Ga-FAPI-RGD
Tissue uptake (%ID/g)
0
4
8
12
0.5 h
1 h
2 h
4 h
Blood
Liver
Kidneys
Tumors
Muscles
C
MIP
10 %ID/g
⁶⁸Ga-FAPI-02
0.5 h
1 h
2 h
0.2 %ID/g
D
⁶⁸Ga-FAPI-02
Tissue uptake (%ID/g)
0
2
4
6
0.5 h
1 h
2 h
Blood
Liver
Kidneys
Tumors
Muscles
E
MIP
5 %ID/g
⁶⁸Ga-RGDfK
0.5 h
1 h
2 h
0.2 %ID/g
F
⁶⁸Ga-RGDfK
Tissue uptake (%ID/g)
0
2
4
6
0.5 h
1 h
2 h
Blood
Liver
Kidneys
Tumors
Muscles

FIG. 12

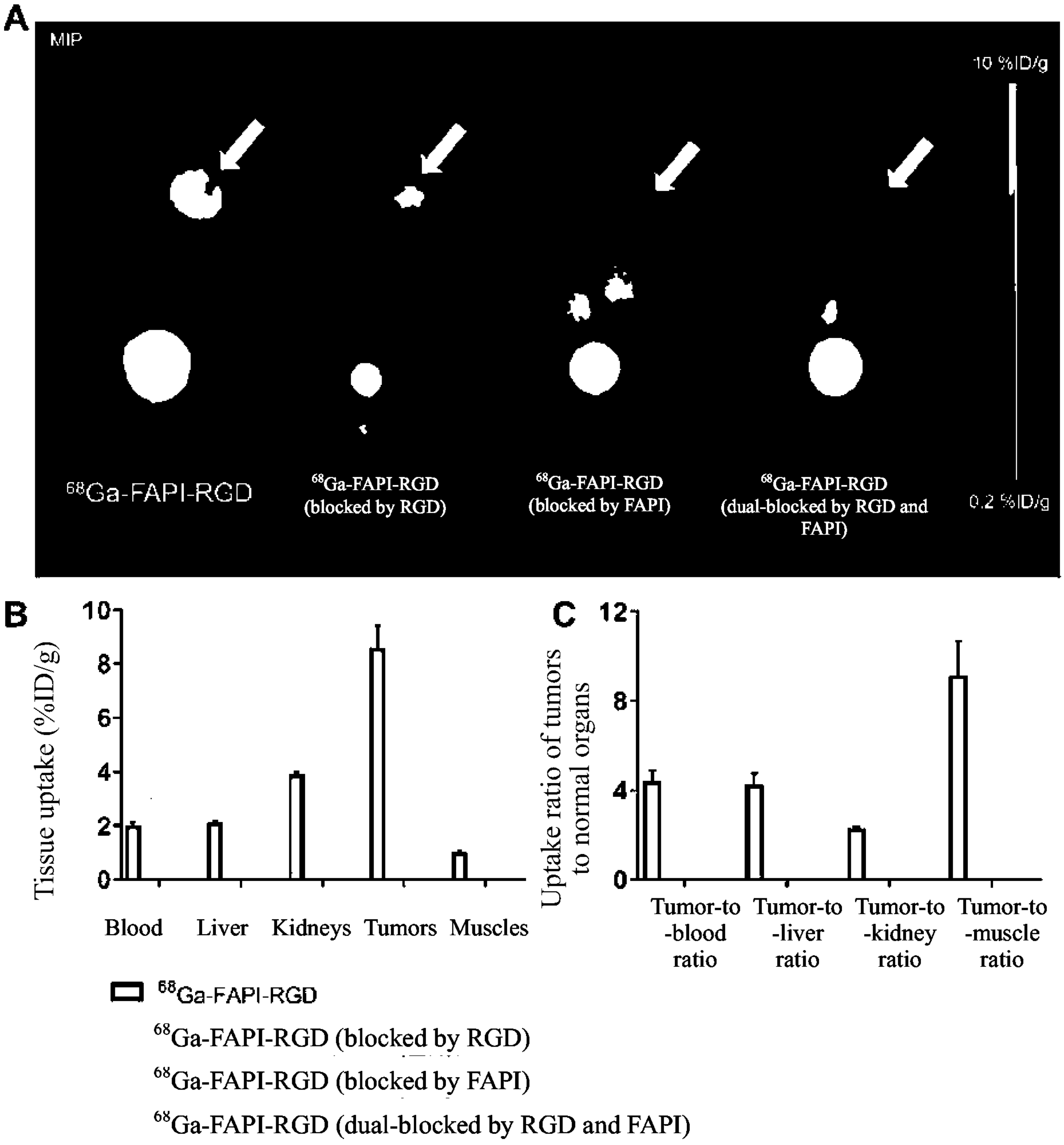

A
MIP
10 %ID/g
0.2 %ID/g
^{68}Ga-FAPI-RGD
^{68}Ga-FAPI-RGD (blocked by RGD)
^{68}Ga-FAPI-RGD (blocked by FAPI)
^{68}Ga-FAPI-RGD (dual-blocked by RGD and FAPI)
B
Tissue uptake (%ID/g)
0
2
4
6
8
10
Blood
Liver
Kidneys
Tumors
Muscles
C
Uptake ratio of tumors to normal organs
0
4
8
12
Tumor-to-blood ratio
Tumor-to-liver ratio
Tumor-to-kidney ratio
Tumor-to-muscle ratio
^{68}Ga-FAPI-RGD
^{68}Ga-FAPI-RGD (blocked by RGD)
^{68}Ga-FAPI-RGD (blocked by FAPI)
^{68}Ga-FAPI-RGD (dual-blocked by RGD and FAPI)

FIG. 13

DRAWINGS

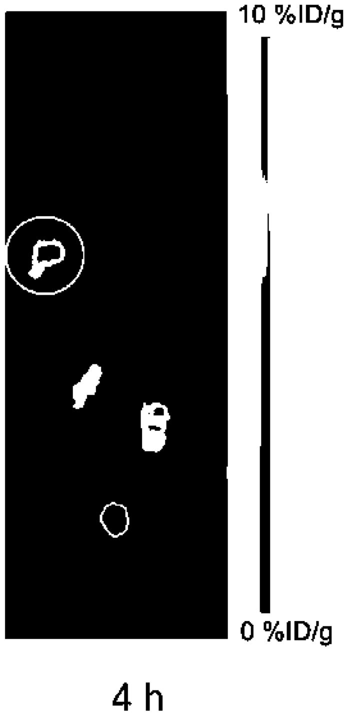


FIG. 14

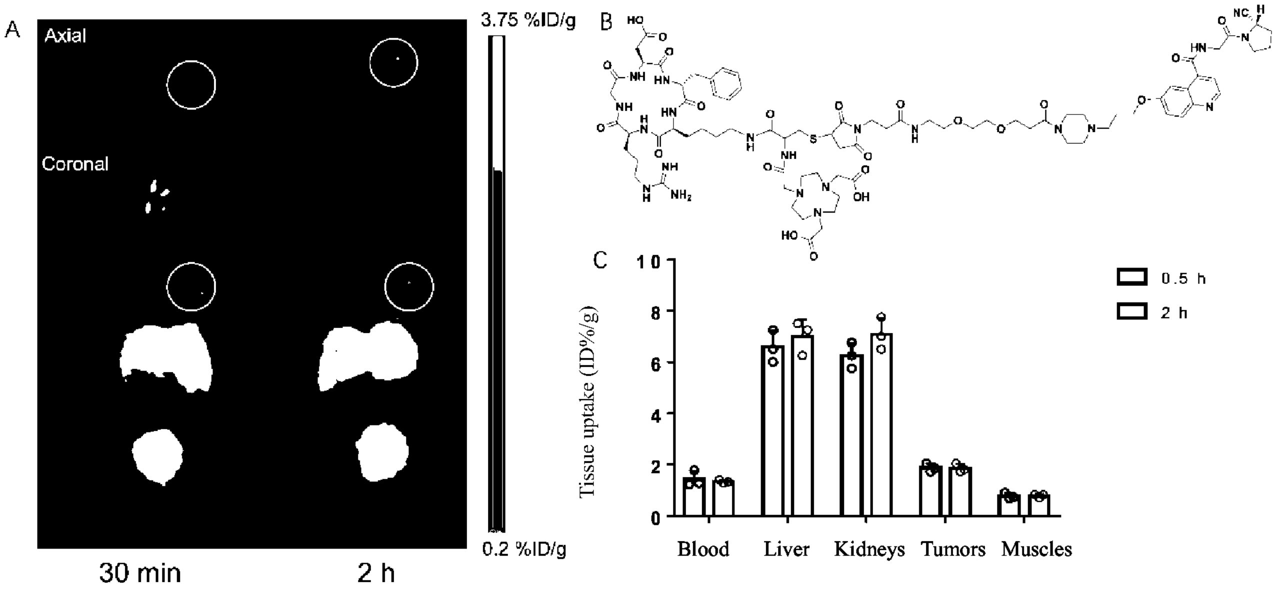


FIG. 15

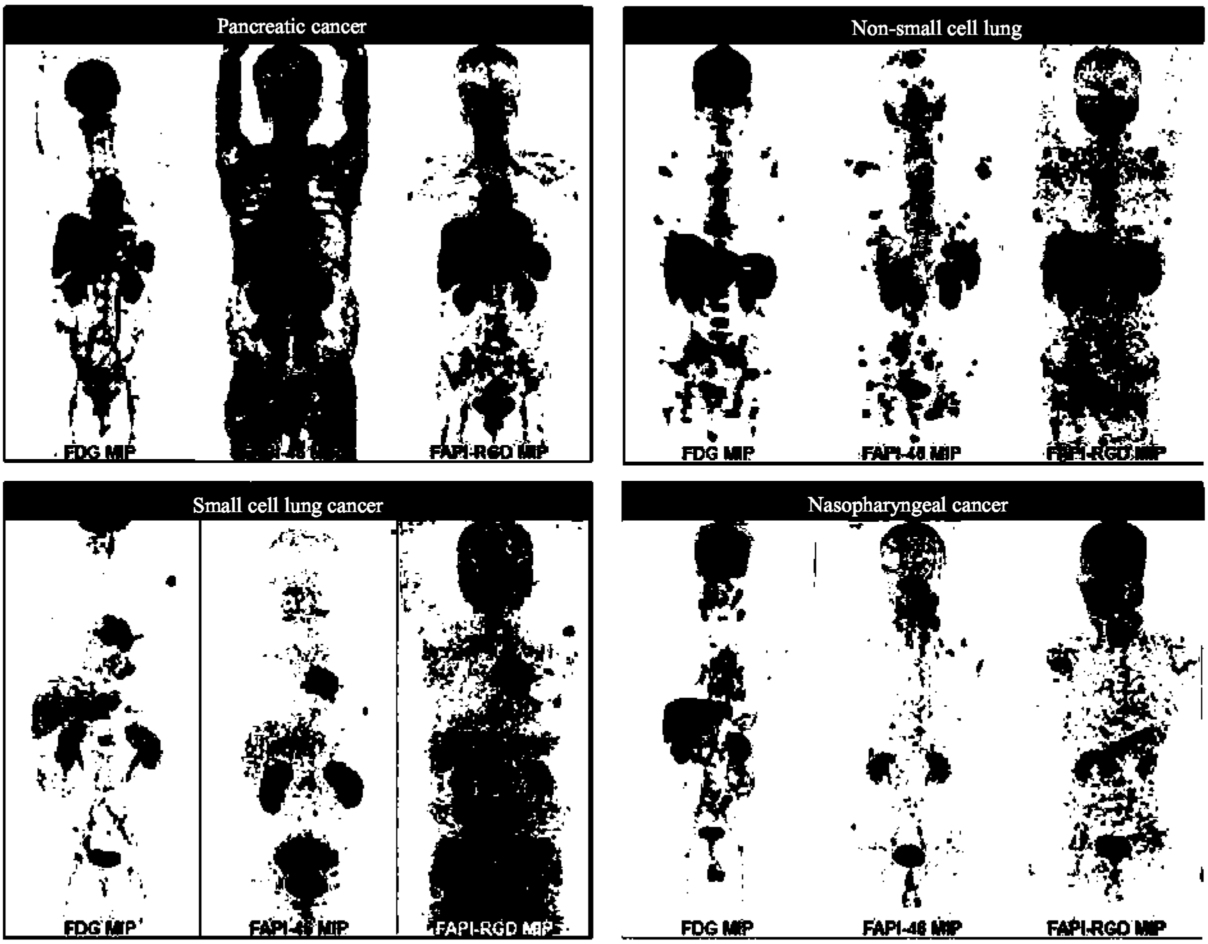

Pancreatic cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Non-small cell lung
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Small cell lung cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Nasopharyngeal cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP

FIG. 16

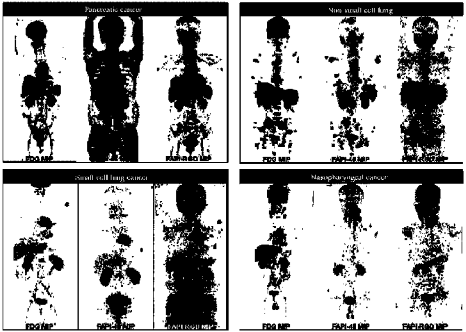
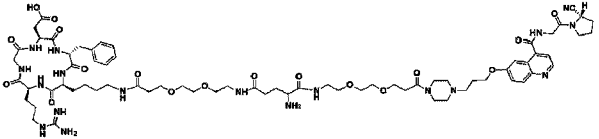
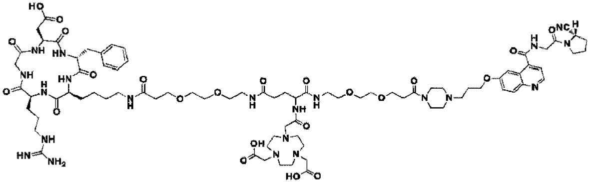

Pancreatic cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Non small cell lung
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Small cell lung cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP
Nasopharyngeal cancer
FDG MIP
FAPI-46 MIP
FAPI-RGD MIP

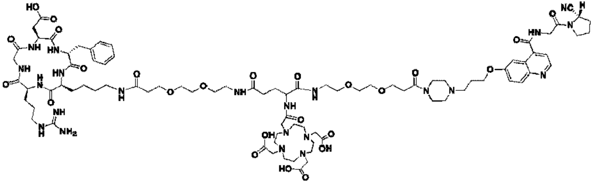
FIG 16



(I)



(I-1)



(I-2)