Radiolabeled compound, and precursor compound thereof, preparation method therefor, and application thereof

Technical Field

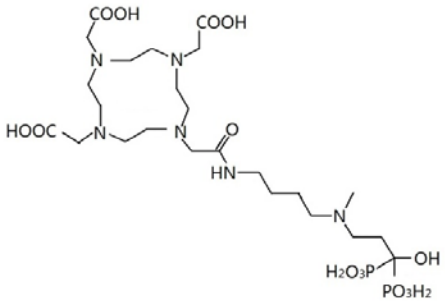
The present disclosure belongs to the technical field of nuclear medicine, and specifically relates to radiolabeled compounds, precursor compounds thereof, preparation methods thereof and applications thereof.

Background Art

Bone is a common site for distant metastasis of malignant tumors, and its incidence is second only to the lung and liver. Early diagnosis and treatment of metastatic bone tumors can effectively improve the prognosis and life quality of patients.

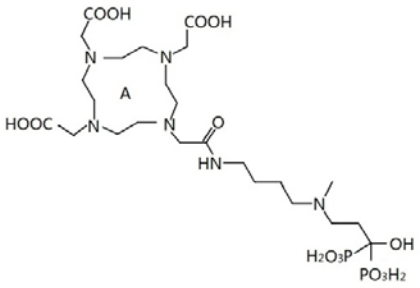
Current treatments for metastatic bone tumors mainly include radiotherapy, chemotherapy, radionuclide therapy, bisphosphonate therapy, analgesic therapy and palliative surgery. Targeted radionuclide therapy for metastatic bone tumors can significantly relieve bone pain, kill tumor cells, has few toxic side effects, and thus is a safe and effective treatment method. Currently, radiopharmaceuticals commonly used in China to treat metastatic bone tumors include $^{89}SrCl_2$ and ^{153}Sm-EDTMP. They can significantly relieve bone pain and reduce the incidence of skeletal-related events. However, both of them need to be produced by nuclear reactors and are relatively expensive, and it is difficult for $^{89}SrCl_2$ to be used for imaging and thus $^{89}SrCl_2$ is subjected to certain use restrictions. There is an urgent clinical need for more effective, inexpensive, and easily available therapeutic radiopharmaceuticals.

^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, and ^{211}At are all medical isotopes with excellent nuclear properties. ^{68}Ga is obtained through a ^{68}Ge/^{68}Ga generator, which is convenient in source and low in cost; it can emit β^+ rays and is used for PET imaging. ^{177}Lu, ^{225}Ac, ^{64}Cu, and ^{211}At are all purchased from abroad, and the supply channels are smooth and stable. ^{177}Lu has a half-life (T1/2) of 6.7d, emits three kinds of β-particles with energy of 497keV (78.6%), 384keV (9.1%), and 176keV (12.2%), respectively, which can be used for treatment, and also emits γ rays of 113keV (6.4%), and 208keV (11%), which are suitable for in vivo localization and imaging. ^{225}Ac emits α-rays, where α-ions have higher linear energy transfer, high ray energy, short range, and thus have higher relative biological effect and the strongest killing effect on tumor cells. ^{225}Ac has a half-life (T1/2) of 9.9d, and its daughter nuclide ^{213}Bi has a half-life (T1/2) of 46 minutes. ^{64}Cu nuclide has become a research hot spot in the fields of PET molecular probes and theranostic medicine due to its properties such as suitable half-life (12.7 h), unique decay properties (β^+ decay, β^- decay, electron capture), and ability to coordinate with a variety of ligands to form



Formula I.

The present disclosure provides a radiolabeled compound of a compound represented by Formula I or a pharmaceutically acceptable salt thereof, which has a structure represented by Formula II,



Formula II

wherein, A represents a nuclide, preferably ^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, or ^{211}At.

The present disclosure inventively binds the chelating agent DOTA with ibandronic acid to form a new compound, DOTA-ibandronic acid. When being labeled with radionuclides ^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, or ^{211}At, the amount of precursor used is much lower than that of ibandronic acid alone. We provide a variety of radionuclide-labeled DOTA-ibandronic acids, which are new drugs for both imaging and treatment of metastatic bone tumors. This kind of drugs can better exert the imaging and treatment effects of radionuclides ^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, ^{211}At and DOTA-ibandronic acid on metastatic bone tumors, thereby creating a synergistic effect of 1 plus 1 being greater than 2.

In some embodiments of the present disclosure, the radionuclide-labeled DOTA-ibandronic acids have a radiochemical purity of greater than or equal to 95%.

The present disclosure provides a preparation method of the precursor compound of the radiolabeled compound represented by Formula I, which comprises the following steps:

S1, reacting Compound 1 with tert-butyl acrylate to form Compound **2**;

for 5 minutes. The supernatants were respectively collected into 3 corresponding test tubes (numbered as C-①, C-②, C-③, respectively). The centrifugation and supernatant collection were repeated 3 times. The total radioactivity count of the precipitations in the centrifuge tubes and that of the supernatants in the test tubes were measured by a γ counter, respectively, and the plasma protein binding rate (PPB) was calculated.

The results show that the ^{68}Ga-DOTA-ibandronic acid of the present disclosure has a PPB of 81% after being incubated in plasma for 30 minutes. The high plasma protein binding rate indicates that the labeled compound will retain in the body for a long time, be less likely to be cleared, and can achieve good imaging effect.

Experimental Example 4

In this experimental example, the in vivo distribution of the ^{68}Ga-DOTA-ibandronic acid of the present disclosure in mice was investigated, and specified as follows:

Twenty healthy Kunming mice (body weight of 18-22g) were taken, and randomly divided into 5 groups, 4 in each group, half of them being male and half of them being female. 0.5mci/0.1ml freshly prepared ^{68}Ga-DOTA-ibandronic acid was injected via tail vein. The animals were decapitated after 15 min, 30 min, 1 h, 2 h, and 4h respectively. The carotid blood, brain, heart, liver, spleen, lung, kidney, stomach, small intestine, muscle, and femur tissues were weighed, and measured their radioactivity counts with a γ counter, from which, after time decay correction, the percent injected dose per gram of tissue (%ID/g) was calculated. The in vivo distribution results of ^{68}Ga-DOTA-ibandronic acid in mice were shown in Table 6 below:

Table 6: In vivo distribution results of ^{68}Ga-DOTA-ibandronic acid in mice

Tissue or organ	%ID/g				
	15min	30min	1h	2h	4h
Heart	1.037	0.557	0.349	0.216	0.159
Liver	0.526	0.658	0.498	0.418	0.325
Spleen	0.665	0.562	0.332	0.350	0.283
Lung	0.869	1.479	0.659	0.477	0.272
Kidney	4.658	5.391	3.774	2.414	1.023
Stomach	1.254	1.365	0.964	0.658	0.562
Blood	2.635	2.837	1.622	0.452	0.325

One New Zealand rabbit of about 2Kg was taken and injected with about 2.0mci/0.2ml of freshly prepared ^{177}Lu-DOTA-ibandronic acid via ear vein, and PET whole-body imaging was performed on 1d, 3d, 5d, and 7d after the injection, respectively (Figure 2).

Experimental Example 7

The imaging of ^{225}Ac-DOTA-ibandronic acid prepared according to the method of Example 7 in New Zealand rabbits at different time points was investigated, and specified as follows:

One New Zealand rabbit of about 2Kg was taken and injected with about 0.01mci/2ml of ^{225}Ac-DOTA-ibandronic acid freshly prepared under the above optimal labeling conditions via ear vein, and PET whole-body imaging was performed on 1d, 3d, and 5d after the injection, respectively (Figure 3).

Experimental Example 8

In this experimental example, the therapeutic effects of ^{177}Lu-DOTA-ibandronic acid of the present disclosure on tumor-bearing mice (PC-3, H1975, MDA-MB-231 bone metastasis models) were investigated. The ^{177}Lu-DOTA-ibandronic acid used in this experimental example was prepared according to the method of Example 6.

(1) Establishment of tumor-bearing mouse models: 8 SPF male nude mice and 4 SPF female nude mice were taken, and anesthetized with isoflurane. Then the skin around the left knee joint was disinfected, and the left hind limb was bent. An insulin needle (29G needle) was inserted into the tibia vertically from concave point of the articular fossa of the tibia, slowly rotated and inserted into the medullary cavity, to inject 25 μl of cell culture (approximately 2×10^6) of PC-3 (4 males), H1975 (4 males), and MDA-MB-231 (4 females). Then disinfection was carried out, and the holes were sealed with sterile bone wax. The animals were placed on a 37°C hot-plate for rewarming. After resuscitation, they were returned to the cage and continued to be raised.

(2) Testing of tumor-bearing mouse models: After 4 weeks of inoculation, 12 nude mice were scanned using Micro-CT, respectively. It was observed that the nude mice each had varying degrees of bone destruction, accompanied by varying degrees of soft tissue swelling, indicating that the bone metastasis models were successfully established.

(3) Methods of different treatments and grouping: The 12 successfully modelled tumor-bearing mice were randomly divided into 4 groups. Among them, 2 groups were injected with ^{177}Lu-DOTA-ibandronic acid with low and high radioactivity (100 μCi, 500 μCi) into the

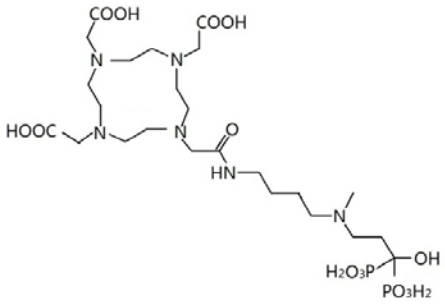
The above results show that when the tumor-bearing mice are treated with the dose of high-activity ^{177}Lu-DOTA-ibandronic acid (500 μCi), their bone pain is relieved to the greatest extent, and the survival rate within 5 weeks of administration is relatively highest, and the therapeutic efficacy of different doses of ^{177}Lu-DOTA-ibandronic acid is higher than that of the corresponding control group, indicating the feasibility and effectiveness of ^{177}Lu-DOTA-ibandronic acid in the treatment of malignant tumor bone metastasis.

Based on the above Examples 1-9 and Experimental Examples 1-8, ^{68}Ga/^{177}Lu/^{225}Ac/^{64}Cu/^{211}At-DOTA-ibandronic acid is provided by a simple labeling method in which the reaction time is short and the labeling yield is high, and has a high water solubility, a good in vitro stability at room temperature, a high plasma protein binding rate, and shows high and long-term bone uptake in both the in vivo distribution in mice and the imaging in New Zealand rabbits, indicating that the preparation invented in the present application is a bone imaging agent with excellent performance and a radioactive drug for the treatment of metastatic bone tumors.

The above-described examples are merely a part, but not all of the examples of the present disclosure. The detailed description of the examples of the present disclosure is not intended to limit the scope of the present disclosure, but rather to represent selected examples of the present disclosure. Based on the examples of the present disclosure, all other examples obtained by those of ordinary skill in the art without making inventive efforts fall within the scope sought to be protected by the present disclosure.

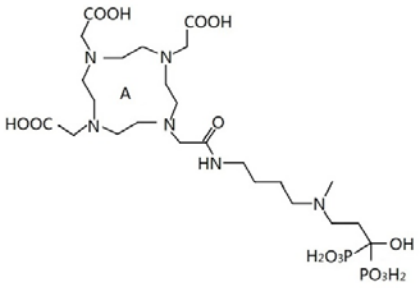
What is claimed is:

1. A precursor compound of a radiolabeled compound with a structure represented by Formula I or pharmaceutically acceptable salt thereof,



Formula I.

2. A radiolabeled compound of a compound represented by Formula I or pharmaceutically acceptable salt thereof, characterized by having a structure represented by Formula II,



Formula II

wherein, A represents a radionuclide, preferably ^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, or ^{211}At.

3. The radiolabeled compound or pharmaceutically acceptable salt thereof according to claim 2, characterized by having a radiochemical purity of greater than or equal to 95%.

4. A preparation method of the precursor compound of the radiolabeled compound according to claim 1, characterized by comprising the following steps:

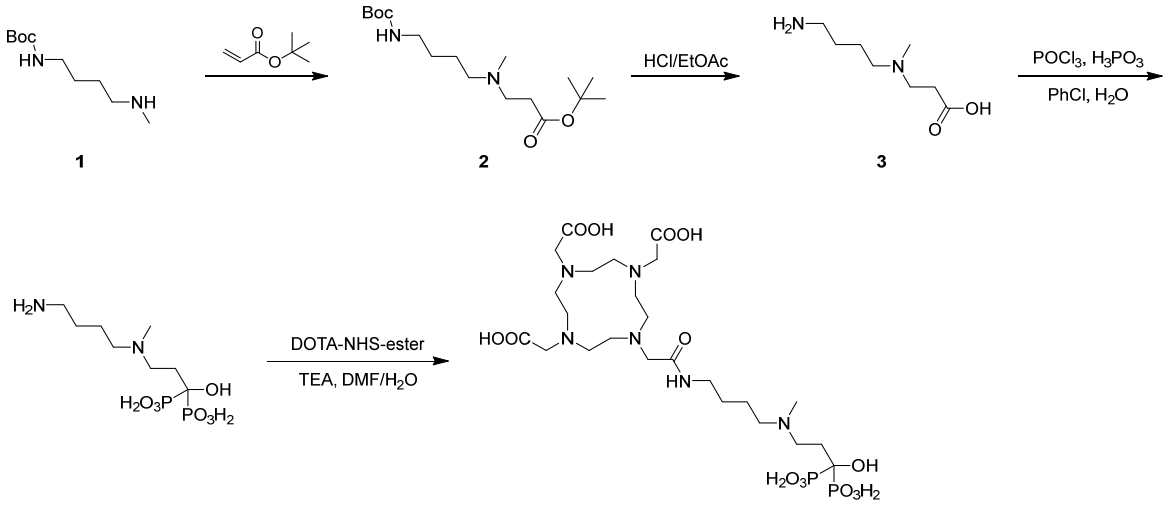
S1, reacting Compound **1** with tert-butyl acrylate to form Compound **2**;

S2, adding HCl/EtOAc dropwise to an EtOAc solution of Compound **2**, reacting to generate Compound **3**;

S3, adding Compound **3** to PhCl, adding $POCl_3$ and H_3PO_3 under nitrogen protection, heating and reacting, cooling and then pouring out chlorobenzene solution, adding H_2O, heating and stirring to generate Compound **4**;

S4, adding a DOTA-NHS-ester solution to an aqueous solution of Compound **4**, then adding triethylamine, and reacting to generate a compound represented by Formula I;

the reaction scheme being as follows:



Formula I

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5. A preparation method of the radiolabeled compound according to claim 2 or 3, characterized by comprising: reacting a compound represented by Formula I with a radionuclide salt solution to obtain a radiolabeled compound represented by Formula II.

6. The preparation method according to claim 5, characterized in, when the radionuclide is ^{68}Ga, ^{177}Lu or ^{64}Cu, mixing a solution of the compound represented by Formula I, a sodium acetate solution, and a radionuclide salt solution evenly, adjusting pH value of the mixed solution, reacting, adjusting pH value again, sterilizing, and filtering to obtain the radiolabeled compound;

when the radionuclide is ^{225}Ac, mixing a solution of the compound represented by Formula I, a sodium citrate solution, a sodium ascorbate solution, and a radionuclide salt solution evenly, adjusting pH value of the mixed solution, reacting, adjusting pH value again, sterilizing, and filtering to obtain the radiolabeled compound;

when the radionuclide is ^{211}At, mixing a solution of the compound represented by Formula I, a sodium borate solution, and a radionuclide salt solution evenly, adjusting pH value of the mixed

solution, reacting, adjusting pH value again, sterilizing, and filtering to obtain the radiolabeled compound.

7. The preparation method according to claim 6, characterized in, when the radionuclide is ^{68}Ga, adding 20-30 μg of the compound represented by Formula I to 0.8-1.4 ml of a sodium acetate solution with a concentration of 0.25M; then adding a ^{68}Ga salt solution with an activity of 20 mCi; mixing evenly, adjusting pH value of the mixed solution to 4-7, preferably 5; reacting at 80-100°C, preferably 95°C; the reaction time being 10-30min, preferably 15min; after the reaction, adjusting the pH value to 5; in which the solution of the compound represented by Formula I has a concentration of 1 mg/ml; and the ^{68}Ga salt solution has a concentration of 5mCi/ml to 10mCi/ml;

when the radionuclide is ^{177}Lu, adding 20-30 μg of the compound represented by Formula I to 0.8-1.4 ml of a sodium acetate solution with a concentration of 0.25M; then adding a ^{177}Lu salt solution with an activity of 2 mCi; mixing evenly, adjusting pH value of the mixed solution to 4-7, preferably 5; reacting at 80-100°C, preferably 95°C; the reaction time being 10-30min, preferably 15min; after the reaction, adjusting the pH value to 4.5; in which the solution of the compound represented by Formula I has a concentration of 1 mg/ml; and the ^{177}Lu salt solution has a concentration of 10mCi/ml to 20mCi/ml;

when the radionuclide is ^{225}Ac, adding 20-30 μg of the compound represented by Formula I to 0.8-1.4 ml of a sodium ascorbate solution with a concentration of 0.1M and 0.8-1.4 ml of a sodium citrate solution with a concentration of 0.1M; then adding a ^{225}Ac salt solution with an activity of 0.01 mCi; mixing evenly, adjusting pH value of the mixed solution to 4-7, preferably 5; reacting at 80-100°C, preferably 95°C; the reaction time being 10-30min, preferably 15min; after the reaction, adjusting the pH value to 4.5; in which the solution of the compound represented by Formula I has a concentration of 1 mg/ml; and the ^{225}Ac salt solution has a concentration of 0.01mCi/ml to 0.02mCi/ml;

when the radionuclide is ^{64}Cu, adding 20-30 μg of the compound represented by Formula I to 0.8-1.4 ml of a sodium acetate solution with a concentration of 0.25M; then adding a ^{64}Cu salt solution with an activity of 5mCi; mixing evenly, adjusting pH value of the mixed solution to 4-7, preferably 5; reacting at 80-100°C, preferably 95°C; the reaction time being 10-30min, preferably 15min; after the reaction, adjusting the pH value to 4; in which the solution of the compound represented by Formula I has a concentration of 1 mg/ml; and the ^{64}Cu salt solution has a concentration of 5mCi/ml to 10mCi/ml;

when the radionuclide is ^{211}At, adding 20-30 μg of the compound represented by Formula I to 0.8-1.4 ml of a sodium borate solution with a concentration of 0.25M; then adding a ^{211}At salt solution with an activity of 1mCi; mixing evenly, adjusting pH value of the mixed solution to 4-7, preferably 5; reacting at 80-100°C, preferably 95°C; the reaction time being 10-30min, preferably 15min; after the reaction, adjusting the pH value to 7; in which the solution of the compound represented by Formula I has a concentration of 1 mg/ml; and the ^{211}At salt solution has a concentration of 1.0mCi/ml to 2.0mCi/ml.

8. Use of the compound represented by Formula I according to claim 1 in the manufacture of a medicament for both imaging and treating a metastatic bone tumor.

9. Use of the compound represented by Formula II according to claim 2 or 3 in the manufacture of a medicament for both imaging and treating a metastatic bone tumor.