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.

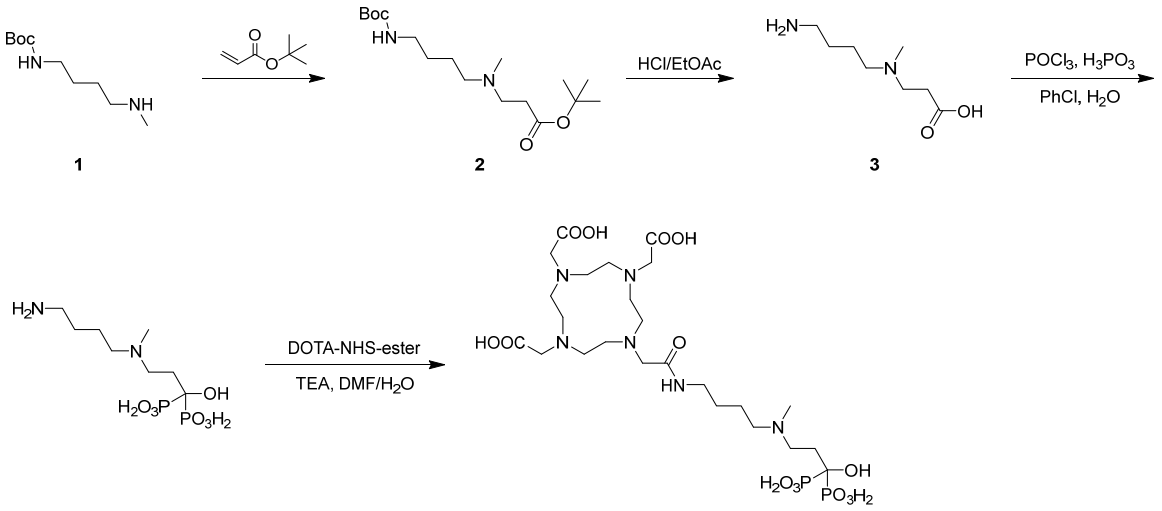
^{68}Ga, ^{177}Lu, ^{225}Ac, ^{64}Cu, and ^{221}At are all medical isotopes with excellent nuclear properties. ^{68}Ga is obtained through a ^{68}Ge/^{68}Ga generator, which is convenient in source and low in cost; it can emit β^+ rays and is used for PET imaging. ^{177}Lu, ^{225}Ac, ^{64}Cu, and ^{221}At 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

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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The present disclosure provides a preparation method of the radiolabeled compound represented by Formula II which comprises: reacting a compound represented by Formula I with a radionuclide salt solution to obtain a radiolabeled compound represented by Formula II.

In some embodiments of the present disclosure, the radiolabeled compound is obtained by, 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;

the radiolabeled compound is obtained by, 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;

the radiolabeled compound is obtained by, 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.