^{68}Ga-Labeled (4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid (BPAMD)

[^{68}Ga]BPAMD

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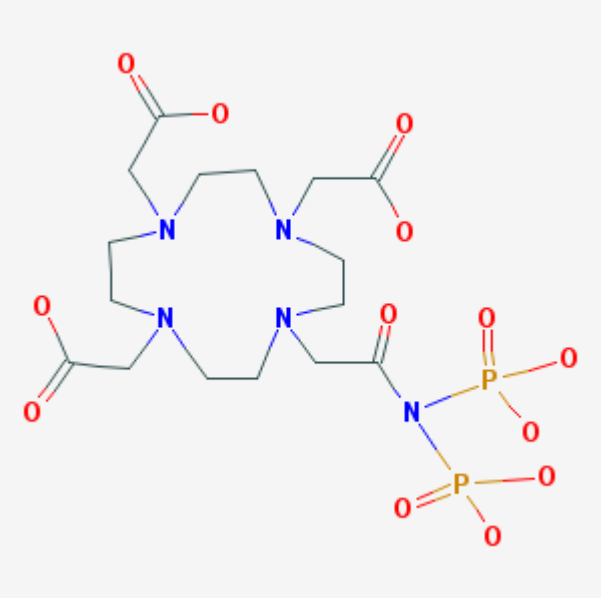
Chemical name:	^{68}Ga-Labeled (4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid (BPAMD)
Abbreviated name:	[^{68}Ga]BPAMD
Synonym:	
Agent Category:	Compound
Target:	Hydroxyapatite; farnesyl diphosphate synthase
Target Category:	Others (bone); enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{68}Ga
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



Click on structure of [^{68}Ga]BPAMD for more information in PubChem.

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Background

[PubMed]

Bisphosphonates (BPs; also known as diphosphonates), such as methylene diphosphonate (MDP) and zoledronic acid, can be labeled with technetium-99m ([^{99m}Tc]-BPs) for bone scintigraphy (gamma planar imaging or single-photon emission computed tomography (SPECT)) to detect osteoporosis and other skeletal-related events (SREs), including bone metastases (1). These chemicals are known to promote osteoclast apoptosis and have a strong affinity for hydroxyapatite, a component of the bone matrix. The exact mechanism of action of these bone-seeking compounds is described in detail elsewhere (2-4). Although the ^{99m}Tc-labeled compounds have high sensitivity, selectivity, and accuracy for the detection of SREs, they are known to generate some false positive and false negative results in the clinic (5). [^{18}F]-Fluoride is another nuclide that is commonly used for bone imaging with positron emission tomography (PET) and is believed to be superior to [^{99m}Tc]-BPs for the diagnosis of SREs (6). However, the main limitations of using ^{18}F are the requirement of a cyclotron to produce it and the high costs that are associated with the production of this radionuclide (5). In an effort to develop an imaging compound that does not have the limitations of tracers that are currently used to detect SREs with scintigraphy or PET, a bisphosphonate labeled with ^{68}Ga was developed and shown to be potentially useful for imaging the mouse skeletal system with PET (5).

The main advantage of using ^{68}Ga (half-life = 68 min; β^+ = 89%; E+β_{max} = 1.9 MeV) for bone imaging over either ^{99m}Tc (half-life = 6 h; γ^+ = 100%; E+γ_{max} = 140 keV) or ^{18}F (half-life = ~110 min; β^+ = 97%; E+β_{max} = 0.635 MeV) as a radiolabel is that ^{68}Ga can be produced economically on-site with a ^{68}Ge/^{68}Ga generator (5, 7). In addition, images obtained with PET have a higher spatial resolution compared with those obtained with SPECT (7). In an ongoing effort to develop a compound that could be used for the targeted imaging of bone metastases, a novel 1,4,7,10-tetraazacyclododecane-*N*,*N*',*N*,*N*'-tetraacetic acid (DOTA) derivative that contained a bisphosphonate within its structure ((4-{[(bis(phosphonomethyl))carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl)acetic acid (BPAMD)) was developed (8, 9), labeled with ^{68}Ga ([^{68}Ga]BPAMD), and shown to be suitable for the imaging of bone metastases in mice (7) and humans (10).

Related Resource Links

Related chapters in MICAD

Protein and mRNA sequence of human farnesyl diphosphate synthase

Gene information regarding human farnesyl diphosphate synthase (GeneID: 2224)

Farnesyl diphosphate synthase in Online Mendelian Inheritance in Man (OMIM) database

Structure of farnesyl diphosphate synthase complexed with a bisphosphonate

Farnesyl diphosphate synthase in Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways

Clinical trials with bisphosphonates (or diphosphonates)

Synthesis

[PubMed]

The synthesis of BPAMD is described elsewhere (8, 9). The labeling of BPAMD with ^{68}Ga was initially optimized for the concentration of the ligand (BPAMD), pH, time, and temperature as detailed by Fellner et al. (7). The radiochemical yield of the labeling reaction was reported to be 90%, and the radiochemical purity of the final product after purification was >98% as determined with high-performance liquid chromatography. The specific activity of [^{68}Ga]BPAMD was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* binding characteristics of [^{68}Ga]BPAMD were studied by exposing the radiochemical to commercially available synthetic hydroxyapatite (Hap) (7). The binding of [^{68}Ga]BPAMD to the matrix was reported as the percent of ^{68}Ga absorbed to Hap and determined to be 81.5 ± 0.5% within 10 min at ambient temperature.

The stability of [^{68}Ga]BPAMD was investigated (n = 5 studies) by incubating the probe in the presence or absence of apo-transferrin (39.2 nmol/mL) in phosphate-buffered saline (PBS; pH 7.4) for 3 h at 37°C (7). Thin-layer chromatographic analysis showed that 4.2 ± 0.8% of ^{68}Ga had transchelated by the end of the incubation when it was incubated with PBS alone, whereas 9.1 ± 0.6% of 68Ga had transchelated in the presence of apo-transferrin during the same time period.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{68}Ga]BPAMD was studied in a healthy rat by administering 15 MBq (555 μCi) of the radiochemical through the tail vein of the animals (7). Dynamic PET scans of the rodent were acquired for 60 min postinjection (p.i.) From the images it was apparent that maximum radioactivity was present in the shoulder joints and certain areas of the vertebral column of the animal that show a relatively high remodeling activity. In the backbone, the accumulation of label in the humerus, sternum, and scapula was 2.49-fold, 2.88-fold, and 2.08-fold higher, respectively, compared with the solid bone. This indicated that the tracer accumulated preferentially in those areas of the skeleton that exhibited a high metabolic activity in the animals. No blocking studies were reported.

In another study, rats were injected with Walker 256 cells to induce bone metastases in the rodents (7). Two weeks later, the animals (n = 7 rats) were injected with 20.5 ± 0.5 MBq (758.5 ± 18.5 μCi) [^{68}Ga]BPAMD to evaluate the use of this tracer for the visualization of metastatic lesions in the skeletal system of the rats. Whole-body PET scans acquired from the animals at 60–70 min p.i. showed that only five animals had developed metastasis in the tibia. The lesions were reported to accumulate 3.97 ± 1.82-fold higher radioactivity (n = 4 rats) compared with a healthy area of the bone that served as an intraindividual control. Presence of osteolytic metastasis in the tibia of the animals was confirmed with histological examination of the tissue.

From these studies, the investigators concluded that [^{68}Ga]BPAMD can be used for the detection of bone metastases in rodents (7).

Other Non-Primate Mammals

[PubMed]

No reference is currently available.

Non-Human Primates

[PubMed]

No reference is currently available.

Human Studies

[PubMed]

A patient known to have extensive bone metastasis of prostate cancer was intravenously injected with 462 MBq (~17 mCi) [^{68}Ga]BPAMD (10). Whole-body PET images of the individual revealed that the radioactivity had accumulated in multiple lesions of the vertebrae, ribs, and the proximal extremities of the patient. For comparison, PET images were also acquired from the patient after injection of 270 MBq (~10 mCi) [^{18}F]-fluoride, and the images showed that the metastatic lesions were present in the entire skeletal system of the patient as observed with [^{68}Ga]BPAMD. With [^{68}Ga]BPAMD, the maximal standardized uptake values (SUV_{max}) of the tenth and twelfth vertebrae were 77.1 and 62.1, respectively, compared with the SUV_{max} values of 39.1 and 39.2, respectively, obtained with ^{18}F. This indicated that [^{68}Ga]BPAMD was probably superior to ^{18}F for the visualization of bone metastasis in humans (10).

Supplemental Information

[Disclaimers]

No information is currently available.

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