^{64}Cu-Labeled 4-((8-amino-3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane-1-ylamino)methyl)benzoic acid (AmBaSar)

[^{64}Cu]-AmBaSar

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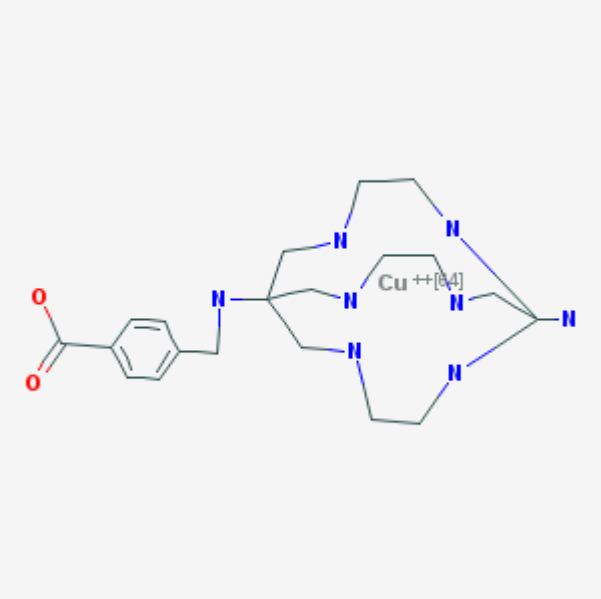
Chemical name:	^{64}Cu-Labeled 4-((8-amino-3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane-1-ylamino)methyl)benzoic acid (AmBaSar)
Abbreviated name:	[^{64}Cu]-AmBaSar
Synonym:	
Agent Category:	Compound
Target:	Non-targeted
Target Category:	
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{64}Cu
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Radionuclides such as ^{18}F, ^{11}C, ^{124}I, ^{64}Cu, etc., are often used to label molecular imaging probes (MIP) for positron emission tomography (PET) of patients to detect and diagnose a variety of diseases, including cancer (1). However, some limitations (to mention a few) for the production and application of these MIPs are a short half-life (e.g., 110 min and 12 min for ^{18}F and ^{11}C, respectively), production of low quality images (e.g., with ^{124}I), high radiation doses (e.g., ^{66}Ga and ^{76}Br), and accumulation in the liver or kidneys due to metabolic degradation (e.g., ^{64}Cu) (1). In addition, MIPs labeled with nuclides that have a short half-life cannot be used in cases where long circulation times are necessary to obtain an optimal target/background signal. The limitations of various nuclides evaluated for the production and application of different PET MIPs are discussed in detail by Nayak and Brechbiel (1). Some investigators are particularly interested in the use of ^{64}Cu to produce PET imaging probes because ^{64}Cu is suitable as a source of the signal, it is relatively easily obtained, and its nuclear properties make it an excellent therapeutic radionuclide ($t_{1/2}$ = 12.7 h; β^+: 17.4%; $E_{\beta+}$max = 656 keV; β: 39%; $E_{\beta-}$max = 573 keV) (2). Linking ^{64}Cu to MIPs requires the use of a bifunctional chelator (BFC) that connects the radionuclide to the targeted probe. Therefore, it is important to have an appropriate BFC to create a ^{64}Cu-labeled radiopharmaceutical that remains stable under *in vivo* conditions and generates suitable results during PET imaging.

Several types of chelating agents have been used for the ^{64}Cu-labeling of imaging probes, but some of the limitations for using these radiochemicals in humans include poor yields due to complicated procedures for the synthesis, harsh conditions used to label the compound that can degrade a probe, *in vivo* instability, lack of sufficient biological data, and accumulation in non-targeted organs that results in the masking of small lesions during PET imaging (3). In an effort to create a BFC that could be synthesized and labeled easily with ^{64}Cu, a sarcophagine-based chelator, 4-((8-amino-3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane-1-ylamino)methyl)benzoic acid (AmBaSar), was produced by Cai et al. (2). A characteristic feature of this BFC is that it can rapidly form a coordination complex with metal ions within a cage-like structure that does not dissociate under physiological conditions. o further simplify the synthesis of AmBaSar, the investigators devised a four-step procedure to label the chelator with ^{64}Cu ([^{64}Cu]-AmBaSar) (3). [^{64}Cu]-AmBaSar was then evaluated for its *in vitro* stability, microPET imaging characteristics, and biodistribution in normal mice (3). In addition, the stability, imaging, and biodistribution properties of [^{64}Cu]-AmBaSar were compared with those of ^{64}Cu-labeled 1,4,7,10-tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetraacetic acid ([^{64}Cu]-DOTA). In an earlier study AmBaSar was linked to Arg-Gly-Asp (RGD), a cyclic peptide that specifically binds to the $\alpha_v\beta_3$ integrin receptor, and labeled it with ^{64}Cu to obtain [^{64}Cu]-AmBaSar-RGD (2). Subsequently the labeled RGD complex was shown to be suitable for the detection of tumors expressing $\alpha_v\beta_3$ integrin receptors in mice. Studies

performed with [^{64}Cu]-AmBaSar-RGD are described in a separate chapter of MICAD (www.micad.nih.gov) (4).

Synthesis

[PubMed]

The simplified synthesis of AmBaSar and its labeling with ^{64}Cu have been described by Cai et al. (3). The radiochemical yield of [^{64}Cu]-AmBaSar was reported to be >95% as determined with radiographic thin-layer chromatography (radio-TLC). During TLC analysis, the R_f value of [^{64}Cu]-AmBaSar was determined to be 0.71 (close to the solvent front), whereas the unbound ^{64}Cu remained at the origin. The radiochemical purity of the tracer was >95% as determined with radiographic high-performance liquid chromatography (radio-HPLC). The specific activity of the labeled compound was not reported.

For comparison purposes, [^{64}Cu]-DOTA was also synthesized and used in some studies (3). This tracer had a radiochemical yield of >98%; however, its radiochemical purity and specific activity were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using a 1-octanol/water system, the partition coefficients of [^{64}Cu]-AmBaSar and [^{64}Cu]-DOTA were reported to be −2.6 and −2.3, respectively, indicating that both radiocompounds had a hydrophilic nature (3).

The *in vitro* stability of [^{64}Cu]-AmBaSar was determined by exposing the labeled compound to phosphate-buffered saline (PBS; pH 7.4), fetal bovine serum (FBS), and mouse blood, respectively (3). The radiochemical had a stability of >97% for up to 26 h in PBS and FBS as determined with radio-HPLC. When incubated with mouse blood, the tracer was reported to have a stability of >98% for up to 4 h.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{64}Cu]-AmBaSar was studied in normal mice (n = 3 animals) and compared with that of [^{64}Cu]-DOTA in the same number of animals (3). The tracers were administered intravenously to the animals, and the mice were euthanized 2 h later to determine the amount of radioactivity accumulated in the major organs. Data obtained from this study were presented as percent of injected dose per gram of tissue (% ID/g). At 2 h after injection of [^{64}Cu]-AmBaSar, the uptake of radioactivity in the liver and kidneys was 0.14 ± 0.01%ID/g and 1.09 ± 0.27% ID/g, respectively, indicating that the label was

cleared from these animals mainly through the urinary route. With [^{64}Cu]-DOTA, the accumulation of radioactivity in the kidneys and the liver was 1.28 ± 0.41% ID/g and 1.25 ± 0.09% ID/g, respectively, during the same period, suggesting that this radiochemical was cleared almost equally through the urinary and hepatobiliary routes in these animals.

MicroPET images were acquired from mice (n = 2 animals/tracer) at 30 min and 2 h after intravenous injection of either [^{64}Cu]-AmBaSar or [^{64}Cu]-DOTA (3). With [^{64}Cu]-AmBaSar, the radioactivity accumulated mainly in the kidneys and the bladder at 30 min after injection; with [^{64}Cu]-DOTA, radioactivity was present primarily in the liver, kidneys, and the bladder at this time point. With both radiochemicals, most of the radioactivity cleared through the bladder by 2 h after injection, but residual radioactivity was still evident in the liver and bowels of animals that received [^{64}Cu]-DOTA. The imaging study confirmed the results obtained from the biodistribution study.

From these studies, the investigators concluded that AmBaSar was suitable for the preparation of ^{64}Cu-labeled radiochemicals and their use as imaging agents in rodents (3).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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