^{99m}Tc-Labeled 1-hydroxy-2-(2-ethyl-4-methyl-1H-imidazol-1-yl)ethane-1,1-diyldiphosphonic acid

[^{99m}Tc]-EMIDP

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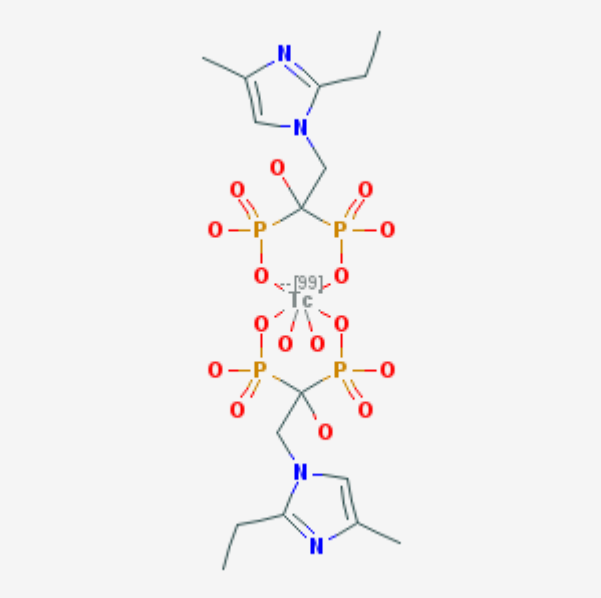
Chemical name:	^{99m}Tc-Labeled 1-hydroxy-2-(2-ethyl-4-methyl-1H-imidazol-1-yl)ethane-1,1-diyldiphosphonic acid
Abbreviated name:	[^{99m}Tc]-EMIDP
Synonym:	
Agent Category:	Compound
Target:	Bone (hydroxyapatite); farnesyl disphosphate (pyrophosphate) synthase (molecular target)
Target Category:	Enzyme
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{99m}Tc
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above proposed structure of [^{99m}Tc]-EMIDP (1) for additional information in PubChem.

Table continues on next page...

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	• Other non-primate mammals	

Background

[PubMed]

Bisphosphonates (BPs) labeled with technetium ([^{99m}Tc]-BP) are often used for bone scintigraphy 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 mechanism of action of these bone-seeking compounds is described in detail elsewhere (2, 3). Bone scintigraphy is usually performed 2–6 h after intravenous injection of a [^{99m}Tc]-BP, resulting in exposure of the patient to radiation for an extended time. To develop BPs that are more efficient and require only a short waiting time before bone scintigraphy, investigators generated various BPs, including zoledronic acid (ZL), which contains an imidazole group in its structure, and evaluated their efficacy for the treatment of various bone-related diseases (4, 5). ZL was determined to be the most potent BP available for treating bone resorption and is approved by the United States Food and Drug Administration (FDA) for the treatment of various tumor-induced SREs (6).

In an effort to further improve the potency of ZL, the imidazole group of the compound was modified to obtain 1-hydroxy-2-(2-ethyl-4-methyl-1H-imidazol-1-yl)ethane-1,1-diyldiphosphonic acid (EMIDP), and the chemical was labeled with ^{99m}Tc to produce [^{99m}Tc]-EMIDP (1). Subsequently, the biodistribution of [^{99m}Tc]-EMIDP was studied in normal mice, and the radiochemical was evaluated as a bone-imaging agent in rabbits.

Other sources of information:

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)

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Structure of farnesyl diphosphate synthase complexed with a bisphosphonate

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

Related chapters in MICAD

Clinical trials with bisphosphonates (or diphosphonates)

Synthesis

[PubMed]

The synthesis and optimization of reaction conditions for labeling EMIDP with ^{99m}Tc have been described by Lin et al. (1). The radiochemical purity of the tracer was reported to be >95% as determined with paper chromatography, and it had an *Rf* value between 0.9 and 1.0. The radiochemical yield of the reaction, specific activity, and final formulation of the labeled compound were not reported.

In another study, ^{99m}Tc-labeled methylene diphosphonate ([^{99m}Tc]-MDP) was compared with [^{99m}Tc]-EMIDP as an imaging agent (1). However, the source, synthesis, radiochemical yield and purity, and specific activity of [^{99m}Tc]-MDP were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

^{99m}Tc-EMIDP was reported to maintain a radiochemical purity of >95% for at least 6 h at room temperature under *in vitro* conditions (1).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{99m}Tc]-EMIDP was studied in normal mice after intravenous injection of the labeled compound through the tail vein (1). The animals (n = 5 mice/time point) were euthanized at various time points ranging from 5 min to 240 min post-injection (p.i.) to harvest the major organs, including bone, and to determine the amount of accumulated radioactivity in the various tissues. The level of radioactivity in the bone was 3.29 ± 0.53% injected dose per gram tissue (% ID/g) at 5 min, increased to 7.07 ± 0.59% ID/g at 60 min, and decreased to 3.76 ± 0.20% ID/g by 240 min p.i. During the same period, radioactivity in the blood decreased from 10.00 ± 0.68% ID/g at 5 min to 0.17 ± 0.08% ID/g at 240 min p.i., and a similar trend was noted with the kidneys (10.58 ± 0.52% ID/g and 1.03 ± 0.07% ID/g at 5 min and 240 min p.i., respectively). All other organs showed an accumulation of the tracer between 0.36 ± 0.04% ID/g (brain) and 4.51 ± 0.12% ID/g (lungs) at 5 min p.i., which decreased to between 0.01 ± 0.00% ID/g (brain)

and 0.22 ± 0.02% ID/g (lungs) at 240 min p.i. From this study it was clear that the radioactivity from [^{99m}Tc]-EMIDP accumulated primarily in the bone and was cleared rapidly from all other soft tissues. No blocking studies were performed and no data was presented to show that the binding of [^{99m}Tc]-EMIDP was saturable.

Pharmacokinetic parameters were derived from the amount of radioactivity cleared from blood of the mice over time (1). The distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) half-lives of [^{99m}Tc]-EMIDP were estimated to be 5.28 min and 59.07 min, respectively.

Other Non-Primate Mammals

[PubMed]

Dynamic and static single-photon emission computed tomography (SPECT) was performed on New Zealand rabbits (anesthetized with ketamine and diazepam) injected with [^{99m}Tc]-EMIDP through the marginal ear vein (1). Dynamic SPECT images of the bones and the soft tissue were obtained every 5 min p.i., and a series of static scans were collected from the animals starting at 90 min p.i. for up to 360 min p.i. Regions of interest were drawn directly on the composite scanning images to calculate the ratios of bone uptake to soft tissue uptake. For comparison, a similar procedure was performed with animals injected with [^{99m}Tc]-MDP, an FDA approved bone-scanning radiochemical. Both tracers were reported to have a similar imaging profile in the rabbits and accumulated mainly in the skeletal tissue, kidneys, and urinary bladder. However, at 1 h p.i., compared to [^{99m}Tc]-MDP the accumulation of [^{99m}Tc]-EMIDP was higher in the bone than in the soft tissues. This indicated that [^{99m}Tc]-EMIDP had a higher selectivity for the bone than [^{99m}Tc]-MDP. In addition, the [^{99m}Tc]-EMIDP uptake ratios of bone to heart, liver, kidney, muscle, and stomach at 10 min p.i. were shown to increase from 1.17, 0.60, 0.53, 3.44, and 2.93, respectively, to 1.76, 1.06, 1.23, 6.70, and 5.93, respectively, at 50 min, suggesting that [^{99m}Tc]-EMIDP was rapidly cleared from the soft tissue but was stable in the bone.

From these studies, the investigators concluded that [^{99m}Tc]-EMIDP had a selectivity for the skeletal tissue in rabbits superior to that of [^{99m}Tc]-MDP. The investigators suggested that more studies with this radiochemical were necessary before it could be used for bone scintigraphy in humans (1).

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.

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