^{99m}Tc-(RR,SS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime

^{99m}Tc-HMPAO

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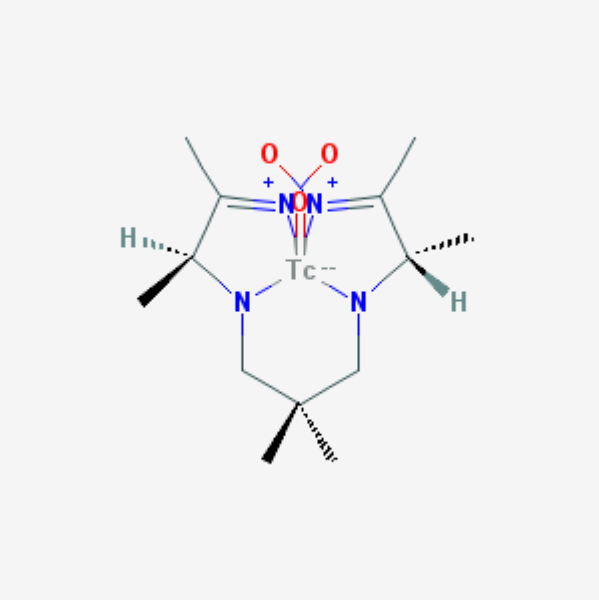
Chemical name:	^{99m}Tc-(RR,SS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime
Abbreviated name:	^{99m}Tc-HMPAO
Synonym:	Ceretec™ Technetium-exametazime; Technetium-99-HMPAO; Technetium-99m-HMPAO; Technetium-99mTc-HMPAO; (99M)Tc-hexamethylpropyleneamine oxime; 99mTc-(RR,SS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime (SP-5-15)-((Rel-(3R,3'R)-3,3'-((2,2-dimethyl-1,3-propanediyl)di(imino-kappaN))bis(2-butanone)di(oximato-kappaN))(3-))oxotechnetium-99Tc; [2,2-dimethyl-3-[(3E)-3-oxidoiminobutan-2-yl]azanidyl-propyl]-[(3E)-3-hydroxyiminobutan-2-yl]azanide; oxotechnetium
Agent Category:	Compound
Target:	Intra-cellular components
Target Category:	Binding



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Method of detection:	Single photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{99m}Tc	
Activation:	Not required	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans	Click on the above structure for additional information in PubChem.

Background

[PubMed]

Timely diagnosis of cerebrovascular diseases (CVD) including stroke, transient ischemic attack, reversible ischemic neurological deficit and multi-infarct dementia etc. is important for the appropriate treatment of patients. Cerebral blood flow (CBF) imaging is a routine technique used for the diagnosis of CVD. Technetium (^{99m}Tc) labeled d,l-hexamethyl propylene-amineoxime (^{99m}Tc-HMPAO) is widely used as a noninvasive cerebral perfusion imaging agent for the diagnosis of CVD (1). ^{99m}Tc-HMPAO is able to cross the blood brain barrier, is highly lipophillic and easily diffuses across the cell membrane. In the cell it is believed to be rapidly hydrolyzed into more polar hydrophilic species that are retained within the cells and can be used for imaging of the brain (1). In addition, ^{99m}Tc-HMPAO has also been used to label leukocytes for the detection of inflammation and infections (2, 3) and bone marrow mononuclear cells to track them under *in vivo* conditions (4).

The synthesis and use of ^{99m}Tc-HMPAO is patented in the US (5) and is available commercially as a kit for intravenous use (6). The kit is approved by the United States

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Food and Drug Administration for the detection of altered regional cerebral perfusion in stroke or for leukocyte labeled scintigraphy as an adjunct for the localization of intra-abdominal infection and inflammatory bowel disease (IBD).

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Synthesis

[PubMed]

The synthesis of ^{99m}Tc-HMPAO has been described in a US patent (5). To start, 2,3-butanedione monoxime was dissolved in benzene containing acetic acid and the solution was refluxed in a nitrogen atmosphere. A solution of 2,2-dimethyl-1,3-propanediamine in benzene was added and the solution refluxed for another 16 h under nitrogen. The solution was then allowed to cool to room temperature. The resulting solid was filtered under suction and washed with cold (-40^{o}C) acetonitrile to obtain a fine white powder. The powder was dried under high vacuum for 2 h to obtain 4,8-diaza-3,6,6,9-tetramethyl-3,8-undecadiene-2,10-dione bisoxime, a diimine, with a 60% yield.

The diimine was slurried in 95% aqueous ethanol at 0^{o}C and sodium borohydrate was added to it over half an hour. The mixture was stirred at 0^{o}C for 2 h followed by addition of water stirring for another 2 h. The ethanol was removed under vacuum and more water was added to the mixture. The pH of the solution was adjusted to 11 to obtain a white solid that was filtered, washed with some water, and dried under *vacuo* to obtain crude HMPAO. Double crystallization from acetonitrile gave the pure product with a yield of 80%.

Labeling of HMPAO should be done carefully, with adherence to all precautions, as described in the product insert by the kit manufacturer (6). The use of methylene blue is recommended by the manufacturer to stabilize ^{99m}Tc-HMPAO only for cerebral scintigraphy with a dose range of 10-20 mCi (370-740 MBq). According to the manufacturer methylene blue should not be used to stabilize ^{99m}Tc-HMPAO for the labeling of leukocytes, as described in the product insert (6). To visualize intra-abdominal infection or inflammation, the recommended dose for a normal adult (70 kg) is 7-25 mCi (0.259-0.925 GBq), as labeled leukocytes.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

A study was performed to compare the *in vitro* labeling efficiency (LE) and cell viability of autologous leukocytes labeled with ^{99m}Tc-stannous (^{99m}Tc-SnF_2) colloid kit and ^{99m}Tc-HMPAO (7). The cells were then used to study IBD. During the study the quantity and quality of spontaneously released ^{99m}Tc (SR) from labeled cells at several time points after labeling was also evaluated. Both radiopharmaceuticals were non-toxic to the leukocytes. Labeling with ^{99m}Tc-SnF_2 was observed to give a higher LE than with ^{99m}Tc-HMPAO;

however, a higher amount of radiolabeled colloids, compared to the radioactivity from ^{99m}Tc-HMPAO labeled cells, was released from the cells over a 4 h period. It was concluded while ^{99m}Tc-HMPAO is physiological excreted into the gastrointestinal tract, ^{99m}Tc-SnF_2 can be re-takenup *in vivo* by the reticulo-endothelial cells of the liver and spleen. These findings suggest that ^{99m}Tc-SnF_2 leukocytes may be better than ^{99m}Tc-HMPAO leukocytes to study IBD.

The contribution of different cell types on ^{99m}Tc-HMPAO retention in the brain was investigated *in vitro* using primary cultures of mouse cortical astrocytes and neurons (8). The data indicated that astrocytes may constitute a prominent site of ^{99m}Tc-HMPAO retention and most likely contributed significantly to the SPECT signal. Data from the study also suggested that specific alterations in glial cell metabolism under some diseased states could explain the flow-independent changes in ^{99m}Tc-HMPAO retention in the brain, as observed by scintigraphy.

Animal Studies

Rodents

PubMed]

Using a scintigraphic method the *in vivo* distribution of naïve and memory CD8+ lymphocytes labeled with ^{99m}Tc-HMPAO was studied in syngenic rats (9). The memory cells were shown to recirculate into the liver and lungs. In the same study total blood lymphocytes were shown to accumulate at the sites of inflammation in inflamed animals.

The possible use of ^{99m}Tc-HMPAO biodistribution to determine the glutathione (GSH) status of tumors in a mouse model has been investigated (10). From this study it was concluded that ^{99m}Tc-HMPAO may be useful to estimate the GSH status of various tumors and this indicator can be used for the development of an appropriate anticancer therapy.

A study was performed to evaluate the use of ^{99m}Tc-HMPAO scintigraphy to assess neutrophil trafficking in a mouse model of dextran sulfate sodium (DSS)-induced colitis (11). The uptake of ^{99m}Tc-HMPAO labeled neutrophils was determined with dedicated animal pinhole SPECT in the DSS-induced colitis animals. It correlated well with the histologic observations ($R = 0.81$) and the wet colon weight ($R = 0.87$) and moderately with clinical weight loss ($R = 0.62$). When neutrophil migration was blocked with a CD97 antibody a significant reduction in the neutrophil uptake ratio ($P < 0.01$) was observed. It was concluded this technique could be used to study inflammation and neutrophil recruitment in an *in vivo* experimental colitis model.

Spermatozoa labeled with ^{99m}Tc-HMPAO were inseminated into female rabbits and dynamic scintigraphic studies were performed on the animals up to 12 hr after the procedure (12). The labeled spermatozoa had a similar *in vivo* behavior as the native spermatozoa. The absolute spermatozoa numbers could be determined noninvasively, and

reliably, within the different parts of the female genital tract at various time points after insemination. According to the investigators ^{99m}Tc-HMPAO can be used to noninvasively follow the dynamic distribution of spermatozoa in the female genital tract.

Other Non-Primate Mammals

[PubMed]

^{99m}Tc-HMPAO radiolabeled leukocytes and scintigraphy were utilized to assess the inflamed feline pancreas (13). The radiolabeled leukocytes were used to visualize pancreatic inflammation that was best visualized at 4 h after administration of the cells. The appearance and contrast enhancement pattern of the inflamed pancreas was observed to be different from normal and scintigraphy allowed a better visualization of the pancreas.

Non-Human Primates

[PubMed]

A baboon (*Papio ursinus*) model was used for the *in vivo* determination of CBF, with a split-dose ^{99m}Tc-HMPAO single photon emission computed tomography (SPECT) method (14). The study showed that the CBF non-human primate model was useful to investigate vasoactive drugs that act through different pharmacological modes.

Using ^{99m}Tc-HMPAO scintigraphy on baboons (*P ursinus*) it was shown a combined treatment of the normal animals with zolpidem and flumazenil, that target the omega receptors of the gamma-aminobutyric acid receptor system, decreased the brain blood flow of the animals (15). Based on these results an involvement of the omega receptors in the brain blood flow of the animals was suggested by Clauss et. al. (15). They hypothesized that an up- or down-regulation of these receptors could contribute to the observed responses in the baboons that are similar to those observed in brain injured patients.

Human Studies

[PubMed]

Clinical trials to compare ^{99m}Tc-HMPAO labeled leukocytes with those labeled with radioactive indium (^{111}In) have been described by the manufacturer in the product kit insert (6). Based on these studies visualization after 2 to 4 h showed the ^{99m}Tc-HMPAO labeled leukocytes had a 95-100% sensitivity and 62-85% specificity for the detection of intra-abdominal infection or inflammation. According to the manufacturer, images obtained after 24 h give inconsistent information and cautions that images obtained with either ^{99m}Tc or ^{111}In labeled leukocytes at this time point should be evaluated carefully for interpretation.

The use of a hybrid SPECT/computed tomography technique with ^{99m}Tc-HMPAO labeled leukocytes to detect bone and joint infections was described by Filippi and

Schillaci (16). The hybrid technique was shown to improve imaging with ^{99m}Tc-HMPAO labeled leukocytes and provide an accurate anatomic localization and precise definition of the infection. In another study the prognostic utility of ^{99m}Tc-HMPAO labeled leukocytes in IBD was evaluated (17). In this study it was shown leukocyte scintigraphy may have a prognostic value for the management of IBD.

Uslu et. al. demonstrated ^{99m}Tc-HMPAO labeled leukocytes could be used accurately and rapidly for the evaluation of acute pancreatitis in patients (2). Scintigraphy has also been used to track ^{99m}Tc-HMPAO labeled bone marrow mononuclear cells in a cardiovascular stem cell study in a man (4).

Using ^{99m}Tc-HMPAO scintigraphy Nishimura et. al. (18) showed that a decreased blood flow in the frontal lobe of Alzheimer's disease (AD) patients correlated with the reduced cognitive functions observed in these individuals. They also showed this technique could be used to follow AD progression in the patients. ^{99m}Tc-HMPAO scintigraphy was shown to be useful for the presurgical evaluation of patients with refractory seizures observed during epilepsy (19). Kemp et. al. reported ^{99m}Tc-HMPAO scintigraphy was of limited value to diagnose of Lewis body dementia (20). An altered regional CBF was demonstrated by ^{99m}Tc-HMPAO scintigraphy in patients with primary hyperparathyroidism (21). It was shown scintigraphy could be used to determine the degree of regional CBF abnormalities in such patients.

Supplemental Information

[Disclaimer]

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