Copper pyruvaldehyde bis(N^4-methylthiosemicarbazone) complex

Cu-PTSM

The MICAD Research Team

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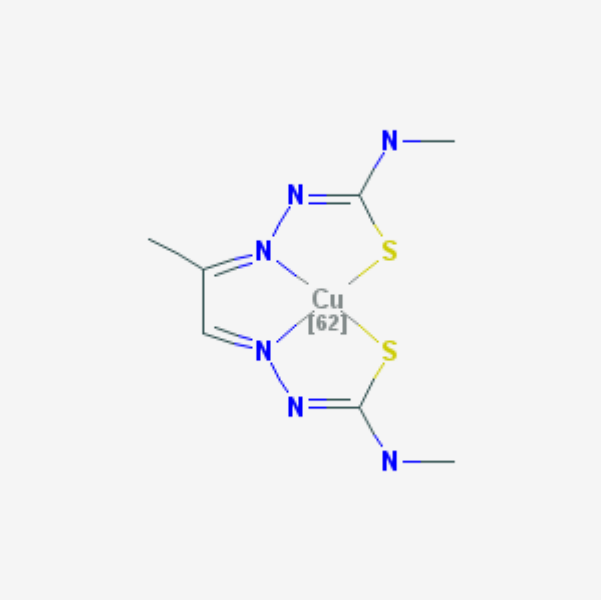
Chemical name:	Copper pyruvaldehyde bis(N^4-methylthiosemicarbazone) complex	
Abbreviated name:	Cu-PTSM, Cu(PTSM)	
Synonym:		
Agent Category:	Compound	
Target:	Cu	
Target Category:	Redox trapping mechanism, reduction of Cu(II) to Cu(I)	
Method of detection:	PET	
Source of signal:	^{62}Cu	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-human primates • Humans	Click on the above structure for additional information in PubChem.

Background

[PubMed]

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Copper pyruvaldehyde bis(N^4-methylthiosemicarbazone) complex, or Cu-PTSM, is a positron emission tomography (PET) radiopharmaceutical that can be used to evaluate blood flow in the heart, brain, and tumors (1, 2). Cu-PTSM belongs to a class of neutral, lipophilic complexes that have demonstrated rapid diffusion into cells. Animal studies have also demonstrated its therapeutic potential to inhibit cancer cell implantation and growth at doses that resulted in no overt signs of toxicity (3).

Synthesis

[PubMed]

Cu-PTSM can be synthesized using the method described by Petering et al. (4). Nevertheless, it can be obtained more efficiently using a $^{62}Zn/^{62}Cu$ PET generator [PubMed]. One system described by Mathias et al. (5) integrates the generator into a device for the preparation and purification of the radiopharmaceutical. This system enables the synthesis of ^{62}Cu-PTSM in <8 min with a radiochemical yield of about 40% and a purity of >98%. Zweit et al. (6) developed and optimized a high-activity $^{62}Zn/^{62}Cu$ PET generator, enabling direct labeling of Cu-PTSM with a 94% radiochemical yield. One system described by Haynes et al. (7) uses purified ^{62}Zn loaded onto a generator column in 2 M HCl, which is then eluted using an internal three-channel peristaltic pump. The pump delivers 2.25 ml of eluant (1.8 M NaCl, 0.2 M HCl) through the generator column to elute the ^{62}Cu in 40 s.

As reported by Fujibayashi et al. (8), ^{62}Cu can be easily eluted as a neutral ^{62}Cu-glycine solution, and PTSM labeling can be complemented by mixing the ^{62}Cu-eluate with a PTSM solution. This simple elution/labeling procedure, coupled with the short half-life of ^{62}Cu, allows clinical studies to be repeated easily (9).

Experimental determinations of dose calibrator settings for generator-produced ^{62}Cu-PTSM were performed by Zimmerman and Cessna (10) using a measurement model developed at National Institute of Standards and Technology (NIST) for short-lived radionuclides.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Several *in vitro* studies have demonstrated the potential therapeutic value of ^{64}Cu-PTSM in various forms of cancer. Using a hamster model of colorectal cancer that mimics the implantation of cancer cells after invasive surgery (11), Lewis et al. (12) showed a rapid uptake of Cu-PTSM in single-cell suspensions, thus demonstrating an inhibition of cancer cell implantation and growth at doses well below the maximum tolerated dose, with no signs of toxicity to the animals.

Electron spin resonance (ESR) spectrometry studies and high-performance liquid chromatography (HPLC) analysis of ^{62}Cu-PTSM in tumor cell lines showed that, in the

brain, a mitochondrial electron transport enzyme reduced Cu-PTSM specifically, but Cu-PTSM was not reduced in tumor mitochondria. The reduction was enzymatic and NADH dependent, possibly similar to the activation mechanism of bioreductive anticancer drugs (8, 13). In murine brain homogenate, ESR and HPLC analysis indicated the reduction and cleavage of Cu(II)-PTSM to Cu(I). This virtually irreversible reduction was specifically initiated by the mitochondrial enzymatic system.

Animal Studies

Rodents

[PubMed]

In rat model systems, Cu-PTSM showed excellent uptake in the brain and heart after intravenous injection, exhibiting a microsphere-like retention in the brain and heart (14, 15). Cu-PTSM was shown to be an effective cell radiolabeling agent in *ex vivo/in vivo* PET studies of cell trafficking in mice, with a labeling procedure of minimal cytotoxicity. Adonai et al. (16) showed maximum cytotoxicity of Cu-PTSM after 180 min, with a labeling efficiency directly proportional to ^{64}Cu-PTSM concentration and influenced negatively by serum. In comparison with FDG, uptake of ^{64}Cu-PTSM was more efficient (3) .

Studies performed on hamsters with colorectal carcinoma cell implants (GW39) showed that ^{64,67}Cu-PTSM could be used to quantify tumor blood flow (17). Because of the relationship between the trapping mechanism of Cu-PTSM (which is thought to result from a reductive decomposition of the copper(II) complex by intracellular sulfhydryls) and glutathione levels in the tissue, and because tumor tissue glutathione levels might vary, the temporal uptake of Cu-PTSM was investigated by PET in both tumor-bearing hamsters and rats bearing R3227 prostate tumors. Results showed that the tumors were clearly visualized, and the retained copper radioactivity in the tumor was constant over the 30-min imaging period. Similarly, Barnhart-Bott and Green (18) investigated the possible effects of glutathione depletion on the biodistribution of ^{67}Cu-PTSM in rats and showed that only very small changes in the biodistribution of copper-labeled Cu-PTSM occurred in the treated rats compared with untreated controls.

Other Non-Primate Mammals

[PubMed]

Studies on dogs with spontaneously occurring soft-tissue neoplasms were performed to evaluate whether [^{62}Cu]Cu-PTSM could serve as a blood flow tracer in PET studies of tumor tissue (19). Results indicate that an excellent linear correlation exists between tumor perfusion calculated from [^{62}Cu]Cu-PTSM data and tumor perfusion measured with ^{85}Sr-microspheres (r = 0.94 for 80 samples), suggesting that [^{62}Cu]Cu-PTSM might be useful as a radiopharmaceutical for PET studies of tumor perfusion. Ultrafiltration and plasma/erythrocyte partitioning studies to assess the protein binding of ^{67}Cu-labeled Cu-

PTSM revealed significant interspecies variability in the strength of Cu-PTSM binding to serum albumin, with ^{67}Cu-PTSM binding much more strongly to human albumin than to dog albumin (20).

Non-Human Primates

[PubMed]

Very few investigations using primate models are reported in the literature. A study by Mathias et al. (21) using baboon single-pass cerebral extraction measurements confirmed the potential of generator-produced ^{62}Cu-PTSM for cerebral perfusion PET imaging. Experiments were carried out with the use of ^{67}Cu ($t_{1/2}$ = 2.6 days), ^{64}Cu ($t_{1/2}$ = 12.7 h), and ^{62}Cu ($t_{1/2}$ = 9.7 min), respectively. All three chelates were extracted into the brain with high efficiency and showed some clearance in the 10-50-second time frame.

Human Studies

[PubMed]

^{62}Cu-PTSM PET was shown to be an effective means of detecting occlusive coronary artery disease in humans and to quantify cerebral and myocardial blood flow [PubMed]. In the study by Wallhaus et al. (22), ^{62}Cu-PTSM myocardial perfusion defects were identified in 100% of patients with three-vessel disease (n = 8), 100% of patients with two-vessel disease (n = 9), and 67% of patients with single-vessel disease (n = 6). In the case of individual vessels, ^{62}Cu-PTSM perfusion defects were seen in 72% of patients with occlusive disease in the left anterior descending artery territory, 67% in the left circumflex artery territory, and 60% in the right coronary artery territory, respectively.

Nevertheless, despite promising results in animals, ^{62}Cu-PTSM myocardial uptake using PET was found to be greatly reduced in humans because of the binding of the tracer to human serum albumin (HSA) (20, 23, 24). A way to counteract the binding to HSA is to add a free acid (e.g., stearic acid). In their study on the release of Cu-PTSM from HSA by fatty acids, Yuan et al. (23) showed that Cu-PTSM was completely released from HSA when the ratio of spin-labeled stearic acid to HSA was 5:1.

^{62}Cu-PTSM appears to be a clinically safe radiopharmaceutical with favorable dosimetry for human studies at injected doses significantly above those projected for use in clinical studies. Human biodistribution studies performed by Wallhaus et al. (25) showed the liver to be the critical organ for radiation absorbed dose estimates (0.0886 rad/mCi), defining the maximum single injected dose at 56 mCi, using the limit of 5 rads to a critical organ per study per year. The whole-body dose was 0.0111 rad/mCi, resulting in a 0.622-rad exposure with a maximum single injection dose. Only trace levels of activity were found in the urine, suggesting low levels of urinary excretion and bladder exposure. No significant clinical, electrocardiographic, or laboratory abnormalities were seen after the injection of ^{62}Cu-PTSM.

Quantitative studies of tracer uptake for investigating angiotensin II-induced changes in blood flow distribution in the liver showed that ^{62}Cu-PTSM-PET was a valuable blood flow assessment method for patients receiving angiotensin II infusions (26).

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