^{44}Sc-Labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–conjugated puromycin

[^{44}Sc]-DOTA-Pur

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Chemical name:	^{44}Sc-Labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–conjugated puromycin	
Abbreviated name:	[^{44}Sc]-DOTA-Pur	
Synonym:		
Agent Category:	Compound	
Target:	Ribosomes (prokaryotic and eukaryotic)	
Target Category:	Other (ribonucleoprotein)	
Method of detection:	Positron emission tomography (PET)	
Source of signal / contrast:	^{44}Sc	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

Puromycin (Pur) is an aminonucleoside antibiotic isolated from the bacteria *Streptomyces alboniger*. This antibiotic is a structural analog of aminoacyl-tRNA, and the insertion of Pur at the C-terminus of the protein inhibits further elongation of the protein chain in the ribosomes (at the translational level) in all organisms (prokaryotic and eukaryotic) (1). This phenomenon leads to accumulation of truncated and mis-folded proteins and

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culminates in cell death. The exact mechanism of action of Pur has been discussed by Starck and Roberts (2). Because cells in cancerous tumors have a very high rate of protein synthesis compared with normal cells, amino acids labeled with radionuclides have often been used to monitor anti-cancer therapy. The amino acids, however, can be utilized in the cells for protein synthesis through several different pathways; as a result, observations made with these tracers may not represent the actual anti-cancer efficacy of a drug (3). Protein synthesis is controlled primarily at the translation level, and it has been suggested that imaging the synthesis of nascent proteins may help researchers understand the relationships between the various normal and abnormal (diseased) physiological pathways *in vivo* (4). In this regard, fluorescence-labeled deoxy-cytidine derivatives of Pur and other fluorescent dyes have been used to investigate the synthesis of proteins in cells (5) and in cell-free systems (6), respectively. However, this approach has limited application under *in vivo* conditions because fluorescence cannot penetrate deep tissues and generates very low signal/noise ratios (4). Investigators have also used anti-Pur antibodies to study protein synthesis in the cell, but these reagents are most suited for use with immunoblots and produce inconsistent results at the cellular level (4).

In an effort to improve the visualization of protein synthesis under *in vivo* conditions, a 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-labeled derivative of Pur was prepared for labeling with radionuclides such as ^{68}Ga or ^{44}Sc, which can be used with positron emission tomography (PET) (7). Although ^{68}Ga is useful in some clinical applications, the short half-life of this radionuclide (half-life = ~68 min) limits its use to the imaging of only those biological processes that occur rapidly (7). Because protein synthesis is a slow process, it requires the use of a tracer that has a longer half-life, such as ^{44}Sc (half-life = ~4 h) (7). Eigner et al. labeled DOTA-Pur with ^{44}Sc ([^{44}Sc]-DOTA-Pur) and evaluated the use of this radiolabeled antibiotic for the visualization of AT1 cell tumors (derived from rat prostate carcinoma) and Walker carcinoma 256 cell tumors (rat breast carcinoma cell line) in rats (7). The biodistribution of [^{44}Sc]-DOTA-Pur was also studied in these animals (7).

Related Resource Links

Clinical trials related to protein synthesis

Ribosomes in Online Mendelian Inheritance in Man database (OMIM)

Ribosome structure in PubMed

Synthesis

[PubMed]

DOTA-Pur was synthesized and labeled with ^{44}Sc as described by Eigner et al. (7). The radiochemical yield of [^{44}Sc]-DOTA-Pur was 59.0 ± 6.0%, with a radiochemical purity of >97% as determined with thin-layer chromatography. The specific activity of purified [^{44}Sc]-DOTA-Pur was 1.5 ± 0.1 GBq/μmol (40.5 ± 2.7 mCi/μmol). Purified [^{44}Sc]-

DOTA-Pur was formulated in 0.9% sodium chloride at a concentration of 30 MBq/ml (810 μCi/ml).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The uptake of [^{44}Sc]-DOTA-Pur was investigated in DU145 cells and BJ cells in the presence or absence of increasing concentrations (10 pmol to ≥200 pmol) of either Pur (irreversible competitive inhibitor) or cyclohexamide (non-competitive inhibitor of Pur), as described elsewhere (7). The uptake of radioactivity by the DU145 cells and BJ cells in the absence of any inhibitor was 2.0 ± 0.1% of the applied dose per 1×10^6 cells and 0.2 ± 0.1% of the applied dose per 1×10^6 cells, respectively. Both cell lines were reported to incorporate 93% of the applied dose of radioactivity into the protein fraction (7).

In another study, unlabeled Pur (≥200 pmol) was shown to decrease the accumulation of label from [^{44}Sc]-DOTA-Pur in the DU145 cells to <8.2 ± 0.2% of the initial uptake value (without Pur). Similarly, unlabeled cyclohexamide (≥200 pmol) decreased the incorporation of radioactivity in these cells to <12.1 ± 0.2% of the initial uptake value (7).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{44}Sc]-DOTA-Pur was investigated in rats bearing either AT1 cell or Walker carcinoma 256 cell tumors (7). The animals (number of animals not mentioned) were injected with a bolus of 20–25 MBq (540–675 μCi) [^{44}Sc]-DOTA-Pur through the tail vein, and microPET dynamic images of the rodents were acquired for up to 120 min postinjection (p.i.). Both types of tumors showed the highest uptake of radioactivity and were clearly visible in the images between 3 min p.i. and 6 min p.i. The tumor/background ratios for both types of lesions were determined to be ≥40. High amounts of label were also detected in the kidneys and the bladder of the animals (exact data not presented), indicating that the tracer was excreted from the body mainly through the renal route (7). No blocking studies were reported.

After completion of the PET scans, the animals were euthanized at 2 h p.i. and 4 h p.i., and all the major organs were retrieved to determine the amount of radioactivity that accumulated in the various tissues (7). Low uptake of label was observed in the normal tissues of the animals (data not presented). The tumor/non-tumor tissue ratios were reported to be 6 and 9 at 2 h p.i. and 4 h p.i., respectively (7).

From these studies, the investigators concluded that [^{44}Sc]-DOTA-Pur can probably be used for the imaging of ribosomal activity or protein synthesis in rodents (7).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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