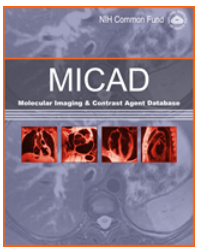
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Leung K. ^{99m}Tc-(Hydrazinonicotinic acid-duramycin)(tricine)(TPPTS). 2008 Oct 25 [Updated 2009 Jan 2]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



^{99m}Tc-(Hydrazinonicotinic acid-duramycin)(tricine)(TPPTS)

^{99m}Tc-Duramycin

Kam Leung, PhD[1]

Created: October 25, 2008; Updated: January 2, 2009.

Chemical name:	^{99m}Tc-(Hydrazinonicotinic acid-duramycin)(tricine)(TPPTS)	
Abbreviated name:	^{99m}Tc-Duramycin	
Synonym:		
Agent category:	Peptide	
Target:	Phosphatidylethanolamine (PE)	
Target category:	Binding	
Method of detection:	SPECT, gamma planar imaging	
Source of signal\contrast:	^{99m}Tc	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available in PubChem.

Background

[PubMed]

Apoptosis (programmed cell death) plays an important role in the pathophysiology of many diseases, such as cancer, neurodegenerative disorders, vascular disorders, and chronic hepatitis, as well as in the biology of normal cells, such as epithelial cells and immune cells (1). During apoptosis, there is rapid redistribution of phosphatidylserine (PS) and phosphatidylethanolamine (PE) from the inner membrane leaflet to the outer membrane leaflet, exposing the anionic head group.

Duramycin (Mw = 2 kDa) is a tetracyclic peptide of 19 amino acids that is produced by *Streptoverticillium cinnamoneus* and is closely related to cinnamycin (2, 3). Both compounds are lantibiotics, which are characterized by the presence of a high proportion of unusual amino acids. Both specifically bind PE, whereas annexin V (Mw = 32–35 kDa) binds to PS (4). PE and PS are present in the inner leaflet of plasma membrane, with little presence in the outer surface of normal viable cells (5). On the other hand, PS and PE are also accessible for binding in necrosis because of disruption of the plasma membrane. Annexin V binds to PS with high affinity (dissociation constant (K_d) = 7 nM) (4), and duramycin binds to PE with a K_d value of 11 nM (6).

Author Affiliation: 1 National Center for Biotechnology Information, NLM, NIH; Email: micad@ncbi.nlm.nih.gov.

Annexin V has been radiolabeled for imaging of apoptosis (7-9). Zhao et al. (10) have used a ternary ligand system (hydrazinonicotinic acid (HYNIC), tricine, and trisodium triphenylphosphine-3,3',3''-trisulfonate (TPPTS)) to label duramycin. HYNIC is a bifunctional coupling agent for ^{99m}Tc labeling, whereas tricine and TPPTS are used as co-ligands to prepare the ternary ligand complex ^{99m}Tc(HYNIC-duramycin)(tricine)(TPPTS) (^{99m}Tc-duramycin) for single-photon emission computed tomography (SPECT) imaging of acute cell death in rats.

Synthesis

[PubMed]

A solution (0.32 ml) of tricine (40 mg), $SnCl_2$ (0.02 mg), TPPTS (1 mg), $Na^{99m}TcO_4$ (37 MBq (1 mCi)), and HYNIC-duramycin (0.015 mg) was incubated for 40 min at room temperature (10). The specific activity at end of synthesis was 58 GBq/mmol (1.57 Ci/mmol) with a radiochemical purity of 78-89% and a radiolabeling efficiency of 80–85%. ^{99m}Tc-duramycin was purified with high-performance liquid chromatography. ^{99m}Tc-duramycin was >97% intact after 2 h in the presence of 100-fold excess of cysteine.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Apoptotic Jurkat T cells incubated with ^{99m}Tc-duramycin exhibited ~32-fold higher binding than normal Jurkat T cells (10). Binding in the apoptotic cells was inhibited by PE-liposomes in a dose-dependent manner with a 50% inhibition concentration value of ~0.1 nM but not by liposomes that consisted of other phospholipid species.

Animal Studies

Rodents

[PubMed]

Zhao et al. (10) performed biodistribution studies of ^{99m}Tc-duramycin in normal rats (n = 4). The level of radioactivity was low in the blood with a half-life of <4 min. The organ with the highest uptake was the kidney (2.32 ± 0.48% injected dose (ID)/g) with little radioactivity in the other organs and tissues at 60 min after injection. Most of the injected radioactivity (22.1 ± 13.3% ID/g) was found in the urine sample at 60 min after injection. ^{99m}Tc-duramycin was intact in the urine and blood samples at 60 min after injection. SPECT imaging in rats with acute myocardial infarction was performed with 7.4 MBq (0.2 mCi, 2.3 nmol) ^{99m}Tc-duramycin. The infarcted area, kidneys, and urinary bladder were clearly visualized at 1 h after injection. Injection of inactivated ^{99m}Tc-duramycin (modification of Asp15) showed an initial accumulation in the infarcted area with a rapid washout. Radioactivity at the infarcted area 1 h after injection was 4.0% ID/g for ^{99m}Tc-duramycin and <1.0% ID/g for inactivated ^{99m}Tc-duramycin. The accumulation of radioactivity in the infarcted tissues was confirmed with autoradiography and histology. No blocking experiment was performed.

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.

References

1. Thompson C.B. Apoptosis in the pathogenesis and treatment of disease. Science. 1995; **267** (5203):1456–62. PubMed PMID: 7878464.
2. Marki F., Hanni E., Fredenhagen A., van Oostrum J. Mode of action of the lanthionine-containing peptide antibiotics duramycin, duramycin B and C, and cinnamycin as indirect inhibitors of phospholipase A2. Biochem Pharmacol. 1991; **42** (10):2027–35. PubMed PMID: 1741778.
3. Hayashi F., Nagashima K., Terui Y., Kawamura Y., Matsumoto K., Itazaki H. The structure of PA48009: the revised structure of duramycin. J Antibiot (Tokyo). 1990; **43** (11):1421–30. PubMed PMID: 2272918.
4. Reutelingsperger C.P., van Heerde W.L. Annexin V, the regulator of phosphatidylserine-catalyzed inflammation and coagulation during apoptosis. Cell Mol Life Sci. 1997; **53** (6):527–32. PubMed PMID: 9230931.
5. Bevers E.M., Comfurius P., Dekkers D.W., Zwaal R.F. Lipid translocation across the plasma membrane of mammalian cells. Biochim Biophys Acta. 1999; **1439** (3):317–30. PubMed PMID: 10446420.
6. Iwamoto K., Hayakawa T., Murate M., Makino A., Ito K., Fujisawa T., Kobayashi T. Curvature-dependent recognition of ethanolamine phospholipids by duramycin and cinnamycin. Biophys J. 2007; **93** (5):1608–19. PubMed PMID: 17483159.
7. Blankenberg F.G. Recent advances in the imaging of programmed cell death. Curr Pharm Des. 2004; **10** (13):1457–67. PubMed PMID: 15134569.
8. Lahorte C., Slegers G., Philippe J., Van de Wiele C., Dierckx R.A. Synthesis and in vitro evaluation of 123I-labelled human recombinant annexin V. Biomol Eng. 2001; **17** (2):51–3. PubMed PMID: 11163751.
9. Keen H.G., Dekker B.A., Disley L., Hastings D., Lyons S., Reader A.J., Ottewell P., Watson A., Zweit J. Imaging apoptosis in vivo using 124I-annexin V and PET. Nucl Med Biol. 2005; **32** (4):395–402. PubMed PMID: 15878509.
10. Zhao M., Li Z., Bugenhagen S. 99mTc-labeled duramycin as a novel phosphatidylethanolamine-binding molecular probe. J Nucl Med. 2008; **49** (8):1345–52. PubMed PMID: 18632826.