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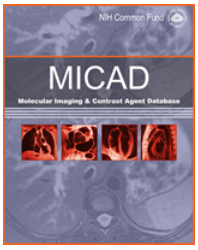

^{99m}Tc-Hydrazinonicotinic acid-Glu-[cyclo(Arg-Gly-Asp-D-Phe-Lys)]$_2$

^{99m}Tc-HYNIC-E-[c(RGDfK)]$_2$

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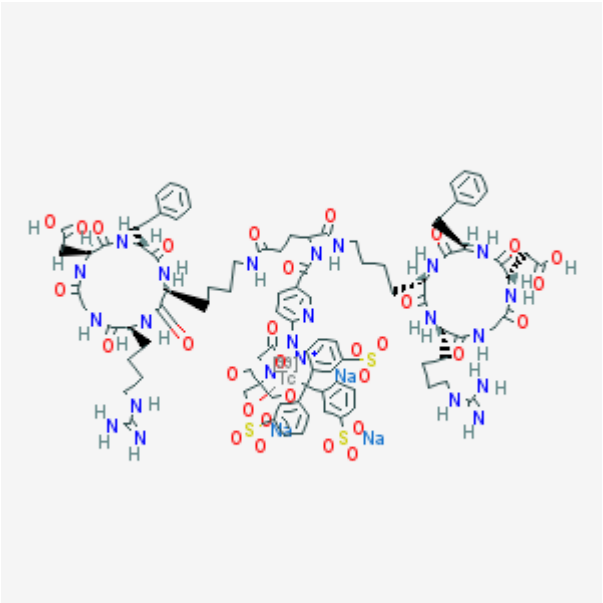
Chemical name:	^{99m}Tc-Hydrazinonicotinic acid-Glu-[cyclo(Arg-Gly-Asp-D-Phe-Lys)]$_2$
Abbreviated name:	^{99m}Tc-HYNIC-E-[c(RGDfK)]$_2$
Synonym:	
Agent Category:	Peptide
Target:	Integrin $\alpha_v\beta_3$
Target Category:	Receptor binding
Method of detection:	SPECT, gamma planar imaging
Source of signal:	^{99m}Tc
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Integrins are a family of heterodimeric glycoproteins on cell surfaces that mediate diverse biological events involving cell–cell and cell–matrix interactions (1). Integrins consist of an α and a β subunit and are important for cell adhesion and signal transduction. The $\alpha_v\beta_3$ integrin is the most prominent receptor affecting tumor growth, tumor invasiveness, metastasis, tumor-induced angiogenesis, inflammation, osteoporosis, and rheumatoid arthritis (2-7). Expression of the $\alpha_v\beta_3$ integrin is strong on tumor cells and activated endothelial cells, whereas expression is weak on resting endothelial cells and most normal tissues. Antagonists of $\alpha_v\beta_3$ are being studied as antitumor and antiangiogenic agents, and the agonists of $\alpha_v\beta_3$ are being studied as angiogenic

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agents for coronary angiogenesis (6, 8, 9). A tripeptide sequence consisting of Arg-Gly-Asp (RGD) has been identified as a recognition motif used by extracellular matrix proteins (vitronectin, fibrinogen, laminin, and collagen) to bind to a variety of integrins, including $\alpha_v\beta_3$. Various radiolabeled antagonists have been introduced for imaging of tumors and tumor angiogenesis (10).

Most cyclic RGD peptides are composed of five amino acids. Haubner et al. (11) reported that various cyclic RGD peptides exhibit selective inhibition of binding to $\alpha_v\beta_3$ (inhibition concentration (IC_{50}), 7–40 nM) but not to integrins $\alpha_v\beta_5$ (IC_{50}, 600–4,000 nM) or $\alpha_{IIb}\beta_3$ (IC_{50}, 700–5,000 nM). Various radiolabeled cyclic RGD peptides have been found to have high accumulation in tumors in nude mice (12). Hydrazinonicotinic acid (HYNIC) is a coupling agent for ^{99m}Tc labeling of peptides that can achieve high specific activities without affecting the receptor-binding ability of the amino acid sequence. ^{99m}Tc is bound to the hydrazine group, and other coordination sites can be occupied by one or more coligands. Liu et al. (13) reported the success of radiolabeling the cyclo(Arg-Gly-Asp-D-Phe-Lys) (c(RGDfK)) dimer linked by glutamic acid that was conjugated with HYNIC. Trisodium triphenylphosphine-3,3',3"-trisulfonate (TPPTS) and tris(hydroxymethyl)-methylglycine (tricine) as coligands. ^{99m}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) showed high tumor accumulation in nude mice bearing human tumor xenografts.

Synthesis

[PubMed]

Liu et al. (13) reported the synthesis of ^{99m}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) by incubation of 20 µg HYNIC-E-$[c(RGDyK)]_2$, 6.5 mg tricine, 5 mg TPPTS, and 1.85 GBq (50 mCi) Na[$^{99m}TcO_4$] for 10 min at 100°C. Radiochemical purity was >90% with a specific activity of ~370 GBq/µmol (10 Ci/µmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Liu et al. (14) performed *in vitro* competition of ^{99}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) with biotinylated vitronectin. ^{99}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) had an IC_{50} value of 1.7 ± 0.5 nM. E-$[c(RGDfK)]_2$ had an IC_{50} value of 0.6 ± 0.4 nM. The *in vitro* solution stability of ^{99}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) was tested by incubating the radiolabeled peptide in phosphate-buffered solution that contained 1.0 mg/ml cysteine at 37°C for up to 6 h. No significant degradation of ^{99}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) was observed under these conditions. Janssen et al. (15) reported that the receptor-binding fraction of ^{99m}Tc-HYNIC-E-$[c(RGDfK)]_2$(tricine)(TPPTS) for conditions representing infinite receptor concentration was >70% using cultured human ovarian carcinoma IGROV-1 cells.

Animal Studies

Rodents

[PubMed]

Janssen et al. (15) performed biodistribution studies of ^{99m}Tc-HYNIC-E-c(RGDfK) and ^{99m}Tc-HYNIC-E-$[c(RGDfK)]_2$ in nude mice bearing human OVCAR-3 ovary carcinoma tumors. Tumor uptake peaked at 5.8 ± 0.7% injected dose (ID)/g (1 h) and 5.2 ± 0.6% ID/g (30 min) for the dimer and the monomer, respectively. At 1, 2, and 4 h after injection, uptake of the dimer in the tumors was significantly higher than that of the monomer. Tumor/blood ratios were similar at all time points, the highest at 24 h with a value of 63 for both compounds. At all time points, kidney accumulation of the dimer was significantly higher than kidney accumulation of the monomer. Both peptides exhibited similar accumulation in the spleen, liver, and lung.

Liu et al. (16) performed biodistribution studies of ^{99m}Tc-HYNIC-E-[c(RGDfK)]$_2$ in nude mice bearing human MDA-MB-435 breast carcinoma tumors. Tumor uptake values were 3.50% ID/g at 5 min, 3.59% ID/g at 30 min, 3.38% ID/g at 60 min, and 3.82% ID/g at 120 min. The organ with the highest uptake was the kidney (14.33% ID/g at 120 min), followed by the intestine (4.95% ID/g at 120 min), lung (2.83% ID/g at 120 min), and liver (3.11% ID/g at 120 min). Blood levels (% ID/g) were 2.70 at 5 min, 1.66 at 30 min, 1.60 at 60 min, and 0.52 at 120 min. Co-injection of E-[c(RGDfK)]$_2$ (30 mg/kg) resulted in a significant reduction of radioactivity in the tumor, lung, liver, spleen, and intestine. The radioactivity in the kidney and muscle was also slightly reduced. Jia et al. (17) performed single-photon emission computed tomography imaging in nude mice bearing U87MG human glioma tumors with 14.8 MBq (0.4 mCi) of ^{99m}Tc-HYNIC-E-[c(RGDfK)]$_2$. The tumors were clearly visualized at 4 h after injection because of fast clearance of the tracer from the liver and lungs.

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.

NIH Support

R01 CA115883-01A2

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