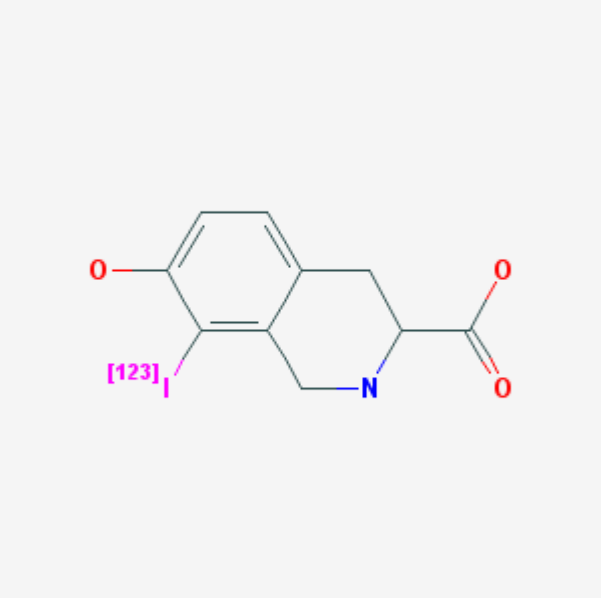
8-[^{123}I]Iodo-L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid

[^{123}I]ITIC

Kam Leung, PhD[1]

Created: February 22, 2007; Updated: May 12, 2008.

Chemical name:	8-[^{123}I]iodo- L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid
Abbreviated name:	[^{123}I]ITIC, [^{123}I]ITIC(OH)
Synonym:	
Agent category:	Compound
Target:	Amino acid transporter T system and membrane potential
Target category:	Transporter
Method of detection:	SPECT, gamma planar
Source of signal:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

NLM Citation: Leung K. 8-[^{123}I]Iodo-L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid. 2007 Feb 22 [Updated 2008 May 12]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[PubMed]

A variety of ^{11}C- and ^{18}F-labeled amino acids have been studied for potential use in positron emission tomography (PET) oncology (1, 2). Most brain tumors show an increased uptake of amino acids as compared with normal brain (3). These amino acids are composed of naturally occurring amino acids, such as L-[^{11}C]leucine, L-[^{11}C]methionine ([^{11}C]MET), and L-[^{11}C]tyrosine, and non-natural amino acids, such as [^{11}C]aminoisobutyric acid, [^{11}C]1-aminocyclopentane-1-carboxylic acid, and [^{11}C]1-aminocyclobutane-1-carboxylic acid. There are also ^{123}I-labeled amino acids, such as L-phenylalanine and L-tyrosine, which are used in imaging in oncology (1, 4, 5).

To date, 20 amino acid transporter systems have been identified (1). Most of the amino acids are taken up by tumor cells not only through the Na^+-independent L, T, and ASC transporter systems but also by the Na^+-dependent A and B^0 transporter systems (6). These amino acids are retained in tumor cells because of their higher metabolic activities than most normal cells (1). Malignant transformation increases the use of amino acids for energy, protein synthesis, and cell division. Tumor cells often overexpress in the transporter systems (7). L-[^{11}C]MET, [^{18}F]fluoro- L-m-tyrosine, L-[^{11}C]leucine, and [^{18}F]fluoro-α-methyl tyrosine have been widely used in the detection of tumors (2, 6) because they are moved into cells by various amino acid transporters and are incorporated into proteins. The fraction of radiolabeled amino acid incorporated into proteins is usually small compared with the total amount taken up into the cell *in vitro*. Recently, it was reported that 75% of L-[^{11}C]leucine was incorporated into proteins of monkey brains at 60 min after injection of the tracer as measured by biochemical analysis and PET imaging (8). These natural amino acid imaging scans are based on amino acid transport and protein incorporation.

No non-natural amino acids are incorporated into proteins (2, 9). These amino acids are rapidly transported into tumor cells. They are retained inside the tumor cells because of their high cellular metabolism and their high activity of the amino acid transporters. Recently, new L-tyrosine analogs, such as *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET), were synthesized and evaluated as amino acid PET tracers for the detection of brain tumors with a higher specificity as compared with [^{18}F]fluoro-2-deoxy-2-D-glucose ([^{18}F]FDG). 8-[^{123}I]Iodo- L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid ([^{123}I]ITIC) is a cyclic analog of L-tyrosine. It accumulated moderately in human pancreatic carcinoma and glioblastoma cells but markedly in human prostate tumor cells, with only a marginal incorporation into proteins (10-13). The cellular uptake into the prostate tumor cells was not dependent on most amino acid transport systems but tentatively dependent on the membrane potential and amino acid transporter T system. [^{123}I]ITIC is being developed as a single-photon emission computed tomography (SPECT) imaging agent of human prostate cancer.

Synthesis

[PubMed]

[^{123}I]ITIC was synthesized by iodide oxidation of L-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (TIC) with sodium ^{123}I-labeled iodide in the presence of 1,3,4,6-tetrachloro-3α,6α-diphenylglycouril (Iodogen) as an oxidant for 5 min at room temperature (12). With a total synthesis time of 30 min, this one-step synthesis produced [^{123}I]ITIC with a radiochemical yield of 80 ± 15% and a radiochemical purity of >98% after high-performance liquid chromatography. The specific activity was >1.5 GBq/μmol (41 mCi/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{123}I]ITIC showed a quickly increasing uptake into human T98 glioma, PaCa44 pancreas, PC-3 prostate, and DU-145 prostate tumor cells in the first 5 min in culture, followed by a plateau of nearly constant radioactivity until 90–120 min of incubation (10, 13). The uptake into the two prostate tumor cells (35–58% of the total loaded radioactivity) was much higher than the T98 and PaCa44 tumor cells (10–33% of the total loaded radioactivity). No significant incorporation of [^{123}I]ITIC into proteins was detected. Testing with various amino acid transporter inhibitors in the two prostate tumor cell lines indicates that [^{123}I]ITIC was not taken up by the common neutral amino acid carrier systems. The cellular uptake was dependent on the membrane potential because high K^+ buffer stimulated the uptake. However, the cellular uptake was inhibited by L-tryptophan but not by L-tyrosine, which indicates a possible involvement of the T transporter system.

Animal Studies

Rodents

[PubMed]

Samnick et al. (13) reported biodistribution studies in rats bearing C6 glioma cells in the brain, which showed a high uptake of radioactivity in the kidneys [8.2% injected dose (ID)/g] at 15 min after injection of [^{123}I]ITIC. Normal brain (0.07% ID/g) and the C6 tumor (0.27% ID/g) showed low uptakes of the tracer. The uptake in the C6 tumor was only 0.1% ID/g at 30–60 min compared with 0.05% ID/g in the normal brain. Therefore, [^{123}I]ITIC was found to be unsuitable for detection of glioma cancer.

The biodistribution of [^{123}I]ITIC was determined in CD-1 nu/nu mice transplanted with human PC-3 and DU-145 prostate cancer cells in the flank or orthotopically in the prostate (11). [^{123}I]ITIC accumulated highly and specifically in the tumors, reaching 13.6 ± 2.1% to 16.2 ± 2.5% ID/g in the heterotopic tumors compared with 14.8 ± 2.6% and 17.6 ± 3.4% ID/g in the orthotopic tumors at 60 and 240 min after injection, respectively. In

contrast, accumulation of radioactivity in the blood, spleen, liver, and intestine was moderate and decreased with time, resulting in marked tumor/background ratios and excellent SPECT visualization of the tumors. Pretreatment of tumor-bearing mice with ITIC (1 mmol) 5 min before [^{123}I]ITIC injection resulted in significant reduction in accumulation of radioactivity in the tumors (up to 70%) and kidneys (40–55%) at 240 min after injection, while the accumulation of [^{123}I]ITIC in the blood, spleen, stomach, intestine, and liver was only marginally affected. Moreover, co-injection of [^{123}I]ITIC with L-tyrosine (1 mmol) did not affect tissue and tumor accumulation. In contrast, co-injection of [^{123}I]ITIC with L-tryptophan (1 mmol) inhibited radioactivity accumulation in the tumor (~40%), which supports possible involvement of the transporter T system. After injection of [^{123}I]ITIC in the mice, 55–65% of the total radioactivity in the urine at 240 min was intact parent compound. Besides iodide (<10%), the main radioactive metabolite was more hydrophilic than [^{123}I]ITIC. In a model of inflamed muscles in mice, the accumulation of [^{123}I]ITIC in the inflamed muscles was similar to that of the healthy muscles. Therefore, [^{123}I]ITIC did not accumulate significantly in the inflamed tissues.

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. Jager P.L., Vaalburg W., Pruim J., de Vries E.G., Langen K.J., Piers D.A. *Radiolabeled amino acids: basic aspects and clinical applications in oncology.* J Nucl Med. 2001;42(3):432–45. PubMed PMID: 11337520.
2. Laverman P., Boerman O.C., Corstens F.H., Oyen W.J. *Fluorinated amino acids for tumour imaging with positron emission tomography.* Eur J Nucl Med Mol Imaging. 2002;29(5):681–90. PubMed PMID: 11976809.
3. Herholz K., Lercher M., Wienhard K., Bauer B., Lenz O., Heiss W.D. *PET measurement of cerebral acetylcholine esterase activity without blood sampling.* Eur J Nucl Med. 2001;28(4):472–7. PubMed PMID: 11357497.

4. Langen K.J., Pauleit D., Coenen H.H. *3-[(123)I]Iodo-alpha-methyl-L-tyrosine: uptake mechanisms and clinical applications.* Nucl Med Biol. 2002;29(6):625–31. PubMed PMID: 12234586.
5. Lahoutte T., Caveliers V., Camargo S.M., Franca R., Ramadan T., Veljkovic E., Mertens J., Bossuyt A., Verrey F. *SPECT and PET amino acid tracer influx via system L (h4F2hc-hLAT1) and its transstimulation.* J Nucl Med. 2004;45(9):1591–6. PubMed PMID: 15347729.
6. Langen K.J., Jarosch M., Muhlensiepen H., Hamacher K., Broer S., Jansen P., Zilles K., Coenen H.H. *Comparison of fluorotyrosines and methionine uptake in F98 rat gliomas.* Nucl Med Biol. 2003;30(5):501–8. PubMed PMID: 12831987.
7. Saier M.H., Daniels G.A., Boerner P., Lin J. *Neutral amino acid transport systems in animal cells: potential targets of oncogene action and regulators of cellular growth.* J Membr Biol. 1988;104(1):1–20. PubMed PMID: 3054116.
8. Smith C.B., Schmidt K.C., Qin M., Burlin T.V., Cook M.P., Kang J., Saunders R.C., Bacher J.D., Carson R.E., Channing M.A., Eckelman W.C., Herscovitch P., Laverman P., Vuong B.K. *Measurement of regional rates of cerebral protein synthesis with L-[1-11C]leucine and PET with correction for recycling of tissue amino acids: II. Validation in rhesus monkeys.* J Cereb Blood Flow Metab. 2005;25(5):629–40. PubMed PMID: 15703697.
9. Wester H.J., Herz M., Weber W., Heiss P., Senekowitsch-Schmidtke R., Schwaiger M., Stocklin G. *Synthesis and radiopharmacology of O-(2-[18F]fluoroethyl)-L-tyrosine for tumor imaging.* J Nucl Med. 1999;40(1):205–12. PubMed PMID: 9935078.
10. Samnick S., Fozing T., Kirsch C.M. *Preparation and tumor affinity testing of the radioiodinated tetrahydroisoquinoline derivative [123I]TIC(OH) for targeting prostate cancer.* Appl Radiat Isot. 2006;64(5):563–9. PubMed PMID: 16426853.
11. Samnick S., Nestle U., Wagner M., Fozing T., Schaefer A., Menger M.D., Kirsch C.M. *Validation of 8-[(123)I]iodo-l-1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid as an imaging agent for prostate cancer in experimental models of human prostate cancer.* Nucl Med Biol. 2007;34(1):99–107. PubMed PMID: 17210466.
12. Samnick S., Richter S., Romeike B.F., Heimann A., Feiden W., Kempski O., Kirsch C.M. *Investigation of iodine-123-labelled amino acid derivatives for imaging cerebral gliomas: uptake in human glioma cells and evaluation in stereotactically implanted C6 glioma rats.* Eur J Nucl Med. 2000;27(10):1543–51. PubMed PMID: 11083545.
13. Samnick S., Schaefer A., Siebert S., Richter S., Vollmar B., Kirsch C.M. *Preparation and investigation of tumor affinity, uptake kinetic and transport mechanism of iodine-123-labelled amino acid derivatives in human pancreatic carcinoma and glioblastoma cells.* Nucl Med Biol. 2001;28(1):13–23. PubMed PMID: 11182560.