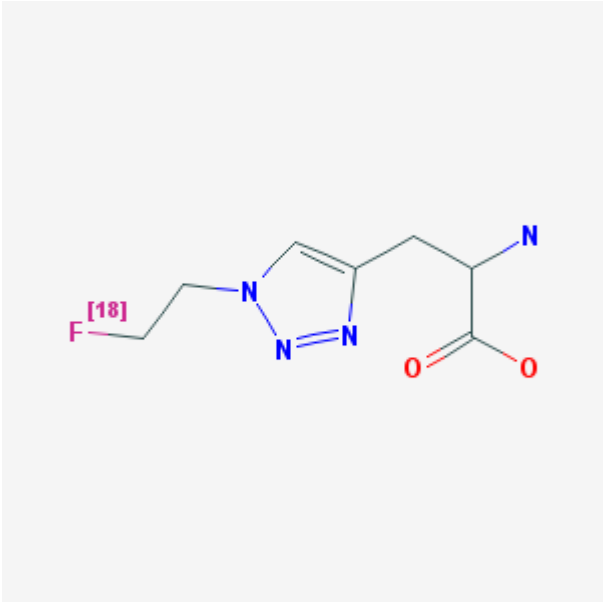
# (*S*)-2-Amino-3-[1-(2-[$^{18}$F]fluoroethyl)-1*H*-[1,2,3]triazol-4-yl]propanoic acid

(*S*)-[$^{18}$F]4

Kam Leung, PhD[1]

Created: July 7, 2011; Updated: October 27, 2011.

| | |
|---|---|
| **Chemical name:** | (*S*)-2-Amino-3-[1-(2-[$^{18}$F]fluoroethyl)-1*H*-[1,2,3]triazol-4-yl]propanoic acid |
| **Abbreviated name:** | (*S*)-[$^{18}$F]4 |
| **Synonym:** | |
| **Agent category:** | Compound |
| **Target:** | Cationic amino acid transporter, L-type amino acid transporter |
| **Target category:** | Transporter |
| **Method of detection:** | Positron emission tomography |
| **Source of signal:** | $^{18}$F |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents |




Click on the above structure for additional information in PubChem.

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

Corresponding author.

NLM Citation: Leung K. (*S*)-2-Amino-3-[1-(2-[$^{18}$F]fluoroethyl)-1*H*-[1,2,3]triazol-4-yl]propanoic acid. 2011 Jul 7 [Updated 2011 Oct 27]. 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 compared with uptake in normal brain tissue (3). These amino acids are composed of naturally occurring amino acids, such as L-[$^{11}$C]leucine, L-[$^{11}$C]methionine, 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. $^{123}$I-Labeled amino acids are also used for imaging in oncology, although no radiolabeled amino acid is approved in the US at present (1, 4, 5).

More than twenty amino acid transporter systems have been identified (1). Most of the amino acids are taken up by tumor cells through an energy-independent L-type amino acid transporter system and the Na-dependent transporter system A, as well as through the $Na^+$-dependent system $B^0$ (6). The amino acids are retained in tumor cells, including incorporation into proteins, due to their high metabolic activities, which are higher than metabolic activities of most normal cells (1). Malignant transformation increases the use of amino acids for energy, protein synthesis, and cell division. Tumor cells were found to have overexpressed transporter systems (7). L-[$^{11}$C]MET, [$^{18}$F]fluorotyrosine, L-[$^{11}$C]leucine, and [$^{18}$F]fluoro-α-methyl tyrosine have been widely used in the detection of tumors (2, 6), but they are not approved by the United States Food and Drug Administration. These radiolabels are moved into cells by various amino acid transporters and are incorporated into proteins, although only L-leucine is quantitatively incorporated into proteins. The fraction of radiolabeled amino acids that is incorporated into proteins is usually small compared to the total amount taken up into the cell. Imaging techniques that use natural amino acids are based on amino acid transport and protein incorporation.

Non-natural amino acids are not incorporated into proteins (2, 8); instead, they are rapidly transported into tumor cells. They are retained inside the tumor cells because of their high cellular metabolism and the high activity of the amino acid transporters. A new L-tyrosine analog, *O*-(2-[$^{18}$F]fluoroethyl)-L-tyrosine ([$^{18}$F]FET), has been synthesized and evaluated as an amino acid PET tracer for the detection of brain tumors. [$^{18}$F]FET has a higher specificity than [$^{18}$F]FDG (8). (*S*)-2-Amino-3-[1-(2-[$^{18}$F]fluoroethyl)-1*H*-[1,2,3]triazol-4-yl]propanoic acid ((*S*)-[$^{18}$F]4) has been found to be a substrate for the cationic amino acid transporter, which transports the naturally occurring amino acids (L-histidine, L-arginine, and L-lysine) (9). (*S*)-[$^{18}$F]4 was synthesized with Click reaction and evaluated as an amino acid PET tracer for the detection of brain tumors.

## Related Resource Links:

- Chapters in MICAD (Amino acid transporters)

- Gene information in NCBI (Cationic amino acid transporter, L-type amino acid transporter)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Amino acid transporters)
- Clinical trials (Amino acid transporters)
- Drug information in FDA (Amino acid transporters)

## Synthesis

[PubMed]

McConathy et al. (9) reported the synthesis of (*S*)-[$^{18}$F]4 in a multi-step reaction. 2-[$^{18}$F]Fluoroethyl azide was prepared using the tosylate (*S*)-precursor in the presence of K[$^{18}$F]F/K2.2.2/$K_2CO_3$ (85°C, 15 min). Cycloaddition reaction of 2-[$^{18}$F]fluoroethyl azide to the alkyne precursor was carried out in *N*,*N*-dimethylformamide for 15 min at room temperature. The purified reaction product was subjected to acid hydrolysis to form (*S*)-[$^{18}$F]4. (*R*)-[$^{18}$F]4 was prepared similarly using the tosylate (*R*)-precursor. (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4 were obtained with radiochemical yields of 51 ± 8% ($n$ = 5) and 57 ± 6% ($n$ = 3), respectively. The radiochemical purity was >98% with a total synthesis time of ~150 min. The specific activities for (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4 were 37 and 11 GBq/μmol (1 and 0.3 Ci/μmol) at the time of biological studies, respectively.

## *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

McConathy et al. (9) showed that (*S*)-[$^{18}$F]4 accumulation in 9L rat gliosarcoma cells was reduced by 50%, 18%, and 89% in the presence of 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH, an L-type transporter inhibitor), *N*-methyl-α-aminoisobutyric acid (an A-type transporter inhibitor), and L-alanine/serine/cysteine (ASC, control), respectively. The further inhibition of uptake by BCH under sodium-free conditions suggests (*S*)-[$^{18}$F]4 is a substrate for system L transport. (*S*)-[$^{18}$F]4 accumulation in cells was inhibited by 50% with L-Arg and by 69% with L-His, suggesting involvement of cationic amino acid transport. In contrast, (*R*)-[$^{18}$F]4 accumulation was not mediated by system L or by cationic amino acid transport. (*R*)-[$^{18}$F]4 accumulation was only partially inhibited (36%) by ASC.

## Animal Studies

### Rodents

[PubMed]

The biodistribution of (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4 (1.1–1.9 MBq (0.03–0.5 mCi)) was studied in rats bearing subcutaneous 9L gliosarcoma tumors ($n$ = 3–4/group) at 15, 30, and 60 min after injection (9). (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4 showed similar accumulation

(percent injected dose/gram (% ID/g)) in most normal tissues with the exception of the pancreas and spleen, where (*S*)-[$^{18}$F]4 showed higher accumulation than (*R*)-[$^{18}$F]4. Tumor accumulation of (*S*)-[$^{18}$F]4 was 0.47%, 0.83%, and 0.72% ID/g at 15, 30, and 60 min, respectively. Tumor accumulation of (*R*)-[$^{18}$F]4 was 0.27%, 0.29%, and 0.17% ID/g at 15, 30, and 60 min, respectively. High accumulation was observed in the pancreas (2.75% ID/g, 0.53% ID/g), lung (0.87% ID/g, 0.74% ID/g), and kidney (11.0% ID/g, 14.0% ID/g) for (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4, respectively, at 15 min after injection. The radioactivity level in the bone declined over the 60-min period, indicating little defluorination. The tumor/blood ratios of (*S*)-[$^{18}$F]4 (1.8, 3.2) at 30 min and 60 min, respectively, were higher than those of (*R*)-[$^{18}$F]4 (1.0, 1.2) at the same time points. Accumulation of both tracers was low in the brain. The tumor/brain ratios at 60 min after injection were 15.2 and 6.9 for (*S*)-[$^{18}$F]4 and (*R*)-[$^{18}$F]4, respectively. No blocking experiment was performed.

PET imaging scans were performed with ~10 MBq (0.27 mCi) (*S*)-[$^{18}$F]4 over 120 min after injection in rats with subcutaneous ($n$ = 2) and intracranial ($n$ = 1) 9L gliosarcoma tumors. Both tumors showed rapid tumor accumulation at 5 min and reached a plateau at ~30 min. High radioactivity levels were observed in the kidneys and urinary bladder. The subcutaneous tumor/muscle ratio was ~6 at 30 min, and the intracranial tumor/brain ratio was ~7 at the same time point. No blocking studies were 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. 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., Heiss W.D. *Positron emission tomography in clinical neurology.* Mol Imaging Biol. 2004;6(4):239–69. PubMed PMID: 15262239.

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. Jr, 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. 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.
9. McConathy J., Zhou D., Shockley S.E., Jones L.A., Griffin E.A., Lee H., Adams S.J., Mach R.H. *Click synthesis and biologic evaluation of (R)- and (S)-2-amino-3-[1-(2-[18F]fluoroethyl)-1H-[1,2,3]triazol-4-yl]propanoic acid for brain tumor imaging with positron emission tomography.* Mol Imaging. 2010;9(6):329–42. PubMed PMID: 21084029.