Methyl 2-(2-[^{18}F]fluoro-4-nitrobenzamido)-3-methylbutanoic acid

[^{18}F]FNBMBA

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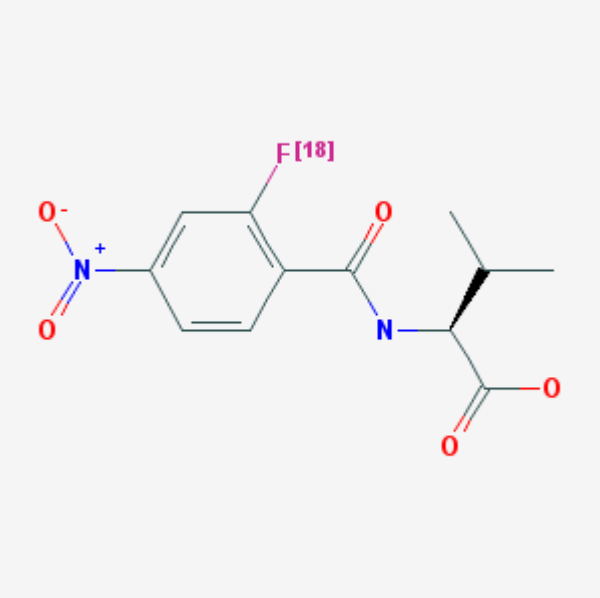
Chemical name:	Methyl 2-(2-[^{18}F]fluoro-4-nitrobenzamido)-3-methylbutanoic acid
Abbreviated name:	[^{18}F]FNBMBA
Synonym:	[^{18}F]1; (2S)-2-[(4-amino-2-fluoranylbenzoyl)amino]-3-methylbutanoic acid
Agent Category:	Compound
Target:	Tumors
Target Category:	Nonspecific tissues
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	[^{18}F]
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure of [^{18}F]FNBMBA for additional information in PubChem.

Background

[PubMed]

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The most commonly used radiochemical for positron emission tomography (PET) imaging of brain or systemic cancerous tumors is 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG), a radiotracer approved by the United States Food and Drug Administration for imaging purposes, but the use of this radiolabel is not without limitations because, among several application drawbacks, it tends to produce a high background in the brain and inflamed tissues during imaging (1, 2). To circumvent problems encountered with [^{18}F]FDG, some investigators developed and evaluated unnatural amino acid (aa) derivatives such as *O*-2-[^{18}F]fluoroethyl-L-tyrosine (L-[^{18}F]FET) for the detection of tumors, particularly of the brain, and it was shown that L-[^{18}F]FET was superior to [^{18}F]FDG in distinguishing tumors from inflammation (3). However, the synthesis of ^{18}F-labeled aa is cumbersome and, because an electrophilic substitution reaction is used to introduce the label into the aa, the final labeled product yields are very low (2). An alternative synthetic method of placing a fluoroalkyl group on the aromatic ring of tyrosine was observed to improve the yield of L-[^{18}F]FET, but it prolonged the synthesis time for the radiochemical (4, 5). In an effort to simplify the synthesis of ^{18}F-radiolabeled aas, ^{18}F-labeled fluoroarylvaline derivatives of L-valine were prepared after modifying the aa with 2,4-dinitrobenzoic acid (2). According to the investigators, introduction of ^{18}F at the *ortho*-position of 2,4-dinitrobenzoic acid is very easy, and the attachment of this moiety to L-valine results in an improved lipophilicity of the molecule. Using this method, two derivatives of L-valine were produced: methyl 2-(2-[^{18}F]fluoro-4-nitrobenzamido)-3-methylbutanoate ([^{18}F]MFNBMB; [^{18}F]1) and methyl 2-(2-[^{18}F]fluoro-4-nitrobenzamido)-3-methylbutanoic acid ([^{18}F]FNBMBA; [^{18}F]2) (2). These radiotracers were evaluated under *in vivo* conditions, and their biological properties were compared with those of [^{18}F]FDG and L-[^{18}F]FET. This chapter describes the characteristics of [^{18}F]FNBMBA and its biodistribution in tumor-bearing mice. The characteristics of [^{18}F]MFNBMB and its biodistribution in tumor-bearing mice is described in a separate chapter of MICAD (6).

Synthesis

[PubMed]

The synthesis of FNBMBA, with a yield of 66%, was detailed by Qiao et al. (2). Radiolabeling of FNBMBA to obtain [^{18}F]FNBMBA was performed using a nucleophilic substitution denitrofluorination reaction as described elsewhere (2). The radiochemical yield of the synthesis was ~30–40% without decay correction, with chemical and radiochemical purity of >99%, respectively. The time required for the synthesis was ~100 min. The specific activity of the labeled compound was not reported.

[^{18}F]FNBMBA was reported to be 100% stable, as determined with thin-layer chromatography and high-performance liquid chromatography (HPLC) in normal saline, phosphate-buffered saline (pH not reported), or 96% ethanol for up to 6 h at room temperature, and in ethanol, dimethylformamide, and acetonitrile for up to 30 min at 60°C (2). HPLC analysis of blood obtained from mice 30 min after treatment with

[^{18}F]FNBMBA showed that the radiolabeled compound was also stable under *in vivo* conditions.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No references are currently available.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{18}F]FNBMBA was investigated in mice bearing mouse sarcoma S180 cell tumors (2). The mice were injected with the radiolabeled compound through the tail vein, and the animals were euthanized at 5, 15, 30, 60, and 120 min (n = 4 animals/time point) after treatment. The tumor and other organs of interest were removed from the animals, and accumulated radioactivity was measured with a gamma counter (represented as percent of injected dose/gram tissue (% ID/g)). A rapid distribution of radioactivity in the various organs and tissue, within 5 min of injection, was observed. In general, by 120 min after the treatment a decrease in accumulated radioactivity was reported in all organs and tissue, including tumors. The tumor/blood ratio increased from 0.56 at 5 min to 2.32 at 30 min, and then decreased to 1.30 at 120 min. The tumor/brain ratio increased from 9.38 at 5 min to 13.30 at 30 min, and then decreased to 6.90 at 120 min. A similar trend was also noticed for the tumor/muscle ratio of the animals. The tumor/blood, tumor/brain, and tumor/muscle ratios with [^{18}F]MFNBMB were lower than those obtained with [^{18}F]FNBMBA (for comparison, see the MICAD chapter regarding [^{18}F]MFNBMB (6)).

For comparison, a similar biodistribution study was also performed with the tumor-bearing mice using [^{18}F]FDG and L-[^{18}F]FET, respectively (2). The blood clearance of both [^{18}F]FNBMBA and [^{18}F]BFNBMB were reported to be slower than that of [^{18}F]FDG, but faster than that of L-[^{18}F]FET. Compared with [^{18}F]FNBMBA, [^{18}F]MFNBMB, or L-[^{18}F]FET, the tumor/blood ratio for [^{18}F]FDG increased from 1.17 at 5 min to 15.85 at 120 min. However, the tumor/brain ratio of [^{18}F]FDG was much lower at all time points (from 0.53 at 5 min to 1.33 at 120 min) than that of the other three labeled compounds (9.38 at 5 min to 6.90 at 120 min for [^{18}F]FNBMBA, 2.79 at 5 min to 2.61 at 120 min for [^{18}F]MFNBMB, and 2.10 at 5 min to 2.95 at 120 min for L-[^{18}F]FET). The tumor/muscle ratios of [^{18}F]FDG and L-[^{18}F]FET (0.81 and 0.72, respectively, at 5 min after injection) increased up to 120 min (2.20 for [^{18}F]FDG and 1.40 for L-[^{18}F]FET). In comparison, the ratios for [^{18}F]MFNBMB and [^{18}F]FNBMBA decreased from 1.94 and 1.38, respectively, at 5 min to 0.54 and 0.66, respectively, at 120 min.

From these studies, the investigators concluded that [^{18}F]FNBMBA was superior to [^{18}F]MFNBMB, [^{18}F]FDG, and L-[^{18}F]FET for the detection of brain tumors in mice (2). However, no studies were reported to investigate if the metabolic pathway followed by [^{18}F]FNBMBA was the same as valine, its parent compound.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimer]

No information is currently available.

References

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