# [$^{18}$F]Fluoroetanidazole

## [$^{18}$F]FETA

The MICAD Research Team

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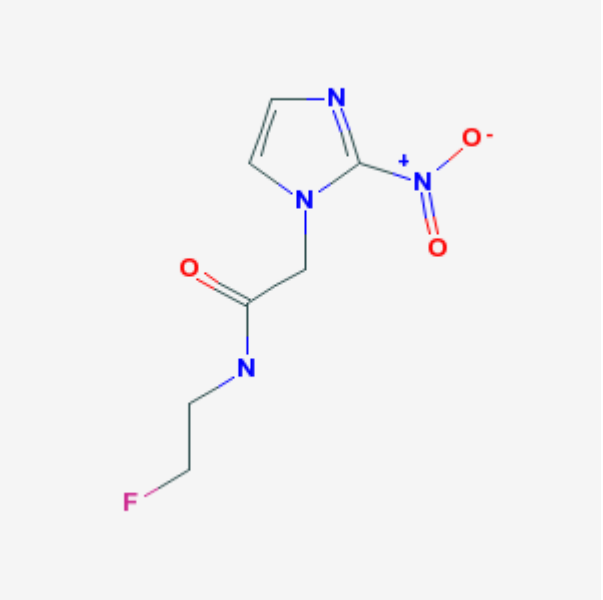
| **Chemical name:** | *N*-(2-([$^{18}$F]Fluoroethyl)-2(2-nitroimidazol-1-yl)-acetamide |
| **Abbreviated name:** | [$^{18}$F]FETA |
| **Synonym:** | [$^{18}$F]Fluoroetanidazole |
| **Agent Category:** | Compound |
| **Target:** | Hypoxic cells (macromolecules) |
| **Target Category:** | Intracellular reduction and binding |
| **Method of detection:** | PET |
| **Source of signal:** | $^{18}$F |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents |

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## Background

[PubMed]

Hypoxia in malignant tumors is thought to be a major factor limiting the efficacy of chemotherapy and radiotherapy, and its accurate diagnosis is considered a very important and urgent problem to address. This has led to the search and development of hypoxia-targeted imaging techniques and non-invasive markers of tumor hypoxia. Among these, [$^{18}$F]-labeled nitroimidazoles, used in conjunction with positron emission tomography

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(PET), offer an alternative to the Eppendorf (oxygen) electrode method because they are less invasive and less prone to sampling errors.

During initial development of nitroimidazoles for *in vivo* imaging, radiohalogenated derivatives of misonidazole, such as fluoromisonidazole ([$^{18}$F]FMISO), were used, some of which have been used in patients. The two main problems with [$^{18}$F]FMISO are: 1) its relatively low concentration within the lesion; and 2) the need to wait several hours to allow clearance of the agent from the normoxic background tissue (contrast between lesion and background is typically <2:1 at about 90 min after injection). This combination of circumstances makes successful evaluation of hypoxic lesions a challenge, even with high-resolution positron emission tomography (PET).

Fluoroetanidazole ([$^{18}$F]FETA), a fluorinated analog of etanidazole, is being investigated as a possible candidate for PET imaging of tumor hypoxia. Thus far, results from comparative studies between [$^{18}$F]FETA and [$^{18}$F]FMISO (1) have shown similar oxygen-dependent binding for both tracers, when compared *in vitro* on the same cell lines. *In vivo*, the two tracers displayed a similar retention in tumors at 4 h after injection, but fewer metabolites were found in plasma and urine for [$^{18}$F]FETA, which might offer some advantages for *in vivo* imaging (2).

The oxygen-dependent metabolism of nitroimidazoles is an intracellular process consisting of a series of one-electron reductions. The nitro-radical anion produced in the first reduction step is very reactive toward oxygen, leaving no substrate for the second step of the reduction process. In contrast, an environment of low oxygen concentration induces further reductive reactions that ultimately lead to the formation of either reactive products that are able to covalently bind to cell components or charged species that diffuse slowly out of the tissues (3). The reactive products observed during this multi-step process include nitroso (2e-), hydroxylamine (4e-), and amine (6e-) derivatives. When the fragmentation of the imidazole ring occurs, reactive portions of the molecule, such as glyoxal, bind to macromolecular components of cells in tissues and tumors (4).

## Synthesis

[PubMed]

[$^{18}$F]FETA can be synthesized by an active ester coupling reaction between the 2,3,5,6-tetrafluorophenyl ester of 2-nitroimidazole acetic acid and [$^{18}$F]fluoroethylamine. [$^{18}$F]Fluoroethylamine is prepared from *N*-[2-(toluene-4-sulfonyloxy)-ethyl]-phthalimide and [$^{18}$F]fluoride. The reaction time of the total procedure is about 90 min, and the radiochemical yield (uncorrected) is about 25% (5).

Attempts have been made to synthesize [$^{18}$F]FETA by fluorination of a sulfonate ester of etanidazole (6) and fluoroethylation of the amide (7), but these attempts were reported to be unsuccessful (5).

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

[PubMed]

*In vitro* studies of [$^{18}$F]FETA uptake in air *versus* nitrogen in RIF-1 cells were reported by Barthel et al. (2). In those experiments, cells were harvested at 0, 15, 30, 45, 60, 90, and 120 min after injection of the radiotracer (80-100 μCi (2.96-3.7 MBq)), and the percentage of bound radioactivity was calculated as bound radioactivity in $10^6$ cells × 100/total radioactivity.

The percentage of bound radioactivity under normoxic conditions remained low (about 2 × 10−$^3$% per $10^6$ cells). In contrast, a rapid time-dependent linear increase was observed under hypoxic conditions (reaching about 13 × 10−$^3$% per $10^6$ cells at 120 min). [$^{18}$F]FETA uptake by hypoxic RIF-1 cells became significant at 60 min and showed 3.0- and 4.3-fold increases as compared with normoxic cells at 60 and 120 min, respectively. Those results appeared consistent with the presence of a 2-nitroimidazole moiety with redox potentials (E1/7) within the range of 380 to −390 mV (8).

In the study reported by Rasey et al. (1), the oxygen dependency of [$^{18}$F]FETA binding to cells was investigated on the four cultured rodent cell lines V79, 36B10, EMT6, and RIF-1. Results showed that $O_2$ levels of 600-1300 ppm inhibited binding by 50%, relative to uptake under anoxic conditions (<10 ppm). Those values were not statistically different from those reported for [$^{18}$F]FMISO on the same cell lines (700-1500 ppm).

# Animal Studies

## Rodents

[PubMed]

In a reported study (2) using mice bearing MCF-7, RIF-1, EMT6, HT1080/26.6, and HT1080/1-3C tumors, the normal tissue retention of [$^{18}$F]FETA at 60 min after injection (1.48-3.7 MBq; 40-100 μCi) was found to be low (<5% injected dose (ID)/g) in lung, heart, brain, and bone. It was intermediate (5-8% ID/ g) in plasma, liver, spleen, small intestines, and muscle; and high (>8% ID/g) in kidney, bile, and urine. Significant accumulation was found in tumors (6-10% ID/g), suggesting the possibility of achieving high tumor-to-background contrast for a variety of tumors such as breast, lung, brain, and head and neck tumors.

[$^{18}$F]FETA was found to be stable in plasma (about 93% as a parent compound at 60 min after injection) and also excreted mainly as the unchanged drug in urine (74% at 60 min after injection). In the liver, it was metabolized to catabolites that appeared to be eliminated predominantly via the hepatobiliary route.

For all of the tumor models used by Barthel et al. (2), the relative [$^{18}$F]FETA retention, expressed as tumor-to-muscle ratio, was found to be positively correlated with the relative

frequency of $pO_2$ values <5 mm Hg; this correlation appeared to be linear ($y = 0.04x - 1.5$; $r = 0.805$) and significant ($P = 0.027$).

The biodistribution of [$^{18}$F]FETA was assessed *ex vivo* and compared with [$^{18}$F]FMISO at 2 and 4 h after intraperitoneal injections of the tracers (300 μCi/ml, 10 μl/g body mass) in C3H mice bearing KHTn tumors (1). Results showed that, at 4 h after injection, the uptakes in the heart, intestine, kidney, and tumor did not show significant differences between the two tracers but were significantly lower in the liver and lung for [$^{18}$F]FETA.

The brain-to-blood ratio of [$^{18}$F]FETA was found to be 1.07 ± 0.31 at 4 h after injection, showing the ability of the tracer to readily cross the normal blood-brain barrier. High-performance liquid chromatography of urine demonstrated that 10% and 15% of [$^{18}$F]FETA -derived activity was in metabolites at 2 and 4 h after injection, respectively. In comparison, 36% and 57% of [$^{18}$F]FMISO activity appeared as metabolites at 2 and 4 h after injection, respectively.

## 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

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