[^{18}F]-2-(2-Nitroimidazol-1*H*-yl)-(3,3,3-trifluoropropyl)acetamide

[^{18}F]EF3

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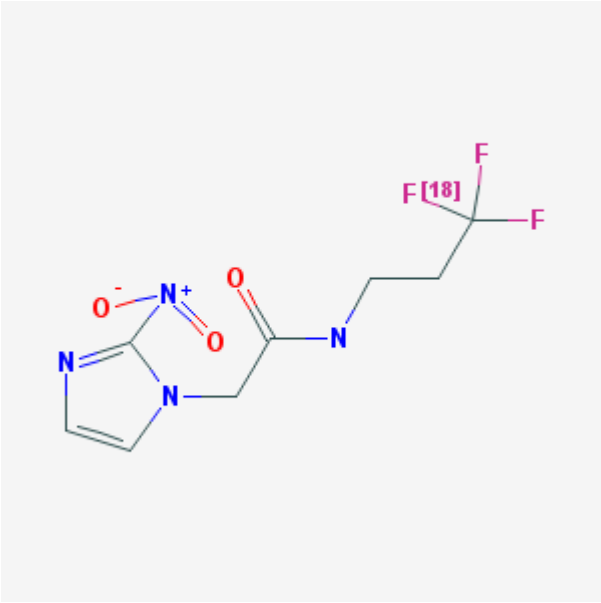
Chemical name:	[^{18}F]-2-(2-Nitroimidazol-1*H*-yl)-*N*-(3,3,3-trifluoropropyl)acetamide
Abbreviated name:	[^{18}F]EF3
Synonym:	
Agent Category:	Compound
Target:	Hypoxic cells
Target Category:	Intracellular reduction and binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• Rodents



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Background

[PubMed]

In a variety of solid tumors, hypoxia was found to lead to tumor progression and the resistance of tumors to chemotherapy and radiotherapy (1-3). Tumor oxygenation is

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heterogeneously distributed within human tumors (4). Hypoxia in malignant tumors is thought to be a major factor limiting the efficacy of chemotherapy and radiotherapy. It would be beneficial to assess tumor oxygenation before and after therapy to provide an evaluation of tumor response to treatment and an insight into new therapeutic treatments (5). Tumor oxygenation is measured invasively using computerized polarographic oxygen-sensitive electrodes, which is regarded as the gold standard (6). Functional and non-invasive imaging of intra-tumoral hypoxia has been demonstrated to be feasible for the measurement of tumor oxygenation (7). This has led to the search and development of hypoxia-targeted, non-invasive markers of tumor hypoxia.

Chapman proposed the use of 2-nitroimidazoles for hypoxia imaging (8). 2-Nitroimidazole compounds are postulated to undergo reduction in hypoxic condition, forming highly reactive oxygen radicals that subsequently bind covalently to macromolecules inside the cells (9). [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is the most widely used positron emission tomography (PET) tracer for imaging tumor hypoxia (7). However, it has slow clearance kinetics and a high lipophilicity, resulting in substantially high background in PET scan. Novel 2-nitroimidazoles, such as [^{18}F]FETA, [^{18}F]FETNIM, 4-Br[^{18}F]FPN, [^{18}F]EF1, and [^{18}F]EF5, are currently being investigated as potential markers of tumor hypoxia [PubMed]. 2-(2-Nitroimidazol-1*H*-yl)-*N*-(3,3,3-trifluoropropyl)acetamide (EF3) is a 3-trifluorinated analog of EF1 (2-(2-nitro-1*H*-imidazol-1-yl)-*N*-(3-fluoropropyl)acetamide). EF3 binding to hypoxic tumor cells was shown to be dependent on oxygen and less dependent on the intracellular level of reductase system (10, 11). [^{18}F]EF3 is being evaluated as a PET probe for detection of tumor hypoxia.

Synthesis

[PubMed]

Josse et al. (12) reported that [^{18}F]EF3 was synthesized by coupling 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl) acetate with [^{18}F]-3,3,3-trifluoropropylamine in 5% radiochemical yield. [^{18}F]-3,3,3-trifluoropropylamine was obtained with 40% overall chemical yield by oxidative [^{18}F]-fluorodesulfurization of ethyl *N*-phthalimido-3-aminopropane dithioate, followed by deprotection with hydrazine. The total synthesis time was <90 min from the [^{18}F]HF production in the cyclotron to the purification of [^{18}F]EF3, which had a specific activity of 2.6 GBq/mmol (71 mCi/mmol) with a radiochemical purity >95%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

Mahy et al. (13) studied the biodistribution of [^{18}F]EF3 in C3H mice bearing NFSA, FSA, FSA II, SCC VII, Sa-NH, or MCa-4 tumors under 10%, 21%, or 95% oxygen until the mice were euthanized 5–770 min after injection. The half-life in blood was 73.9 min. [^{18}F]EF3 was eliminated mainly *via* the kidneys (75% of the injected activity was found in the urine by ~13 h). The biodistribution was fast and homogeneous except in the brain and bone, where it was significantly lower, and in the liver and the kidney, where it was significantly higher. In most organs, the exceptions being the gastrointestinal and urinary tracts, tissue/blood ratios were below or close to unity. There was a relative accumulation of the tracer in tumors with time (tumor/muscle ratios were 1.31–3.52, and tumor/blood ratios were 1.24–2.88 at 220 min after injection). In FSA II tumors, 10% oxygen (P = 0.004) significantly increased the tumor/muscle ratio, whereas 95% oxygen (P = 0.005) decreased it. [^{18}F]EF3 was rapidly metabolized in the tumor, kidney, and liver with 49%, 6%, and 0.04% of the tracer intact at 30 min after injection, respectively. In other experiments, Mahy et al. (14) found a significant correlation (r^2 = 0.57, P < 0.01) between the [^{18}F]EF3 tumor/muscle ratio and the fluorescence intensity of EF5 in the mice bearing tumors.

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.

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