[^{18}F]-3-Fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-ol

[^{18}F]-HX4

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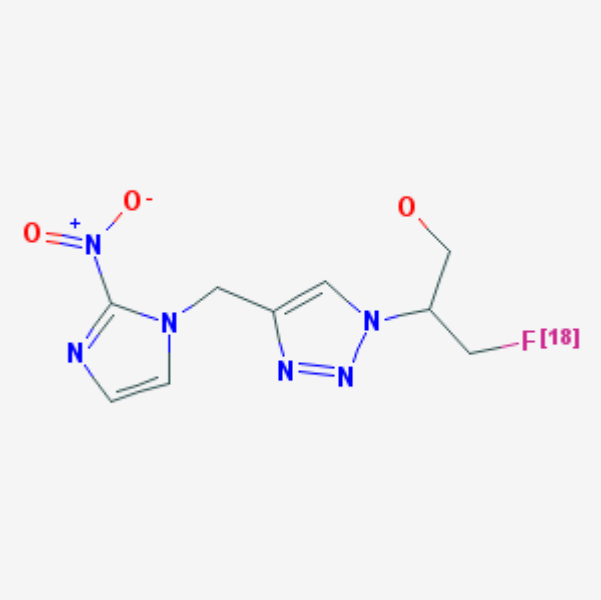
Chemical name:	[^{18}F]-3-Fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-ol
Abbreviated name:	[^{18}F]-HX4
Synonym:	
Agent Category:	Compound
Target:	Hypoxic tissue
Target Category:	Intracellular components
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	Yes
Studies:	• Humans



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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The presence of hypoxia is a characteristic feature of solid neoplastic tumors, and it is believed to be related to the aggressive metastasis nature and the development of chemo- and radiotherapy resistance by the tumor (1, 2). In addition, tumor hypoxia is considered to be an important prognostic factor and indicates a poor outcome for the patient (1). Therefore, the hypoxia characterization of tumors is an important diagnostic method for planning cancer treatment(s). Although several invasive and noninvasive methods are available for the detection of hypoxic tumors, these methods have limitations because of the complex blood supply, tumor structure, and oxygen utilization by the tumor cells (3). The invasive method involves placement of oxygen-sensing electrodes *in situ* and is known to have significant operator variability (1). Among the noninvasive approaches, magnetic resonance imaging with or without contrast agents has been used for the detection of hypoxic tumors, but even this approach does not yield optimal results due to the aberrant blood flow known to exist in different areas of the solid tumors (1). As an alternative, several small molecule tracers or their derivatives (labeled with ^{18}F or various copper isotopes) have been developed for use with positron emission tomography (PET) imaging to screen for tumor hypoxia. However, because of their lypophilic nature, these agents produce either low signal/noise ratios due to low uptake by hypoxic lesions and slow clearance from normal tissues (e.g., ^{18}F-fluoromisonidazole ([^{18}F]FMISO), a 2-nitroimidazole derivative that is frequently used to characterize hypoxic tumors. The mechanisms of activation, biochemistry, and pharmacology of nitroimidazoles are described by Krohn et al. (4)) or do not detect hypoxia in all tumor types (e.g., $^{60/61/62/64}$Cu-labeled diacetyl-bis(N^4-methylthiosemicarbazone) (4).

In an effort to develop a nitroimidazole derivative with superior water solubility and tissue clearance compared to that of [^{18}F]-FMISO, a new ^{18}F-labeled 2-nitroimidazole derivative, [^{18}F]-3-fluoro-2-(4-((2-nitro-1*H*-imidazol-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-ol ([^{18}F]-HX4), was produced and evaluated for PET imaging of hypoxic tumors in a phase I clinical trial involving six cancer patients (5). Preclinical data for this imaging agent have not been published.

Other Sources of Information

Clinical trials with [^{18}F]-HX4

Related chapters in MICAD

Synthesis

[PubMed]

The synthesis and labeling of HX4 with ^{18}F has been described by van Loon et al. (5). The purification, radiochemical yield, and the time required to synthesize the tracer were not reported. The specific activity of [^{18}F]-HX4 was reported to be >14.8 MBq/μmol (>399.9 μCi/μmol), and the final product had a radiochemical purity of >95%. The components of the sterile and pyrogen-free solution used to formulate the imaging agent for human use were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publications are currently available.

Animal Studies

Rodents

[PubMed]

No publications are currently available.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

Six individuals (3 females and 3 males, median age 63 years; all had stage IV carcinoma) enrolled in a phase I clinical trial and were injected with [^{18}F]-HX4 (route of administration not reported). PET images of the largest tumor site were acquired at 30, 60, and 120 min post-injection (p.i.) as described by van Loon et al. (5). The tumor was located on a computed tomographic scan, and the tracer uptake and maximal standardized uptake value (SUV_{max}) were determined within the delineated tumor. Subsequently, the tumor/muscle ratios (TMR) were calculated as described (5). In patients who had PET scans with 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]-FDG) before or after the [^{18}F]-HX4 image, the tumor uptake of [^{18}F]-HX4 was compared to that of [^{18}F]-FDG.

The median TMRs were 1.17 (range, 0.20–1.830), 1.25 (range, 0.25–1.67), and 1.40 (range, 0.63–1.98), respectively, at 30, 60, and 120 min p.i. In two patients, the TMR at 120 min p.i. was considerably higher than at 60 min p.i. (data not presented), suggesting that the optimal TMR in these patients would probably be obtained at a time point later than 120 min. In three patients who had [^{18}F]-FDG PET scans available, a good correlation was observed between the uptake of [^{18}F]-FDG and [^{18}F]-HX4.

From this clinical trial, the investigators concluded that, although [^{18}F]-HX4 appeared to be suitable for the detection of hypoxic tumors in cancer patients, it was necessary to perform more studies involving patients with an early-stage disease and to acquire images at time points beyond 120 min p.i (5).

Supplemental Information

[Disclaimers]

No information is currently available.

References

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