1-(5-[^{18}F]Fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole

[^{18}F]FAZA

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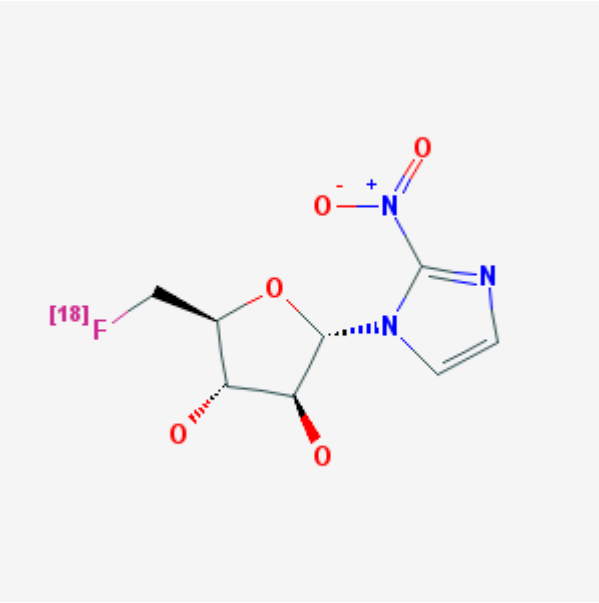
Chemical name:	1-(5-[^{18}F]Fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitroimidazole
Abbreviated name:	[^{18}F]FAZA
Synonym:	[^{18}F]Fluoroazomycinarabinofuranoside, [^{18}F]Fluoroazomycin arabinoside,
Agent Category:	Compound
Target:	Hypoxic tissue
Target Category:	Intracellular reduction and binding to macromolecules
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Humans



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Background

[PubMed]

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Hypoxia was found in a variety of solid tumors, leading to tumor progression and the resistance of tumors to chemotherapy and radiotherapy (1-3). Tumor oxygenation is heterogeneously distributed within human tumors (4). 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 intratumoral hypoxia has been demonstrated to be feasible for the measurement of tumor oxygenation (7).

Chapman proposed the use of 2-nitroimidazoles for hypoxia imaging in 1979 (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 (PE) tracer for imaging tumor hypoxia (7). However, it has slow clearance kinetics and a high lipophilicity, resulting in substantially high background in PET scan. [^{18}F]Fluoroazomycinarabinofuranoside ([^{18}F]FAZA) is a 2-nitroimidazole with a sugar addition (10). [^{18}F]FAZA was studied as hypoxia imaging agent, showing promising results in various tumor models in rats and mice (11, 12). [^{18}F]FAZA PET imaging of tumour hypoxia was evaluated in patients with squamous cell carcinoma of the head and neck (HNSCC), small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC), malignant lymphoma, and high-grade gliomas (13, 14).

Related Resource Links:

- Chapters in MICAD (Hypoxia)
- Gene information in NCBI (Hypoxia)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Hypoxia)
- Clinical trials ([^{18}F]FAZA)

Synthesis

[PubMed]

[^{18}F]FAZA was readily synthesized by standard nucleophilic substitution conditions (Kryptofix 2.2.2 and K_2CO_3), followed by hydrolysis of the protective acetyl groups using 1-(2,3-di-*O*-acetyl-5-*O*-tosyl-α-D-arabinofuranosyl)-2-nitroimidazole and [^{18}F]fluoride (12). Radiochemical yield averaged 20% (decay corrected) based on [^{18}F]fluoride, and the specific activity averaged 2 GBq/μmol (54 mCi/μmol) at the end of synthesis. Radiochemical and chemical purities were 90-95% as determined by high-performance liquid chromatography (HPLC). Reisch et al. (10) used an automated synthesis to provide an overall radiochemical yield of 20.7 ± 3.5% (not decay corrected) and absolute yields up to 9.8 ± 2.3 GBq (260 ± 62 mCi) at the end of synthesis. The synthesis time was 50 min.

In comparison studies, [^{18}F]FMISO was synthesized using 1-(2-nitro-1-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluene-sulfonylpropane-diol by nucleophilic substitution with

[^{18}F]fluoride, followed by hydrolysis (12). This provided [^{18}F]FMISO in 80% (decay corrected) radiochemical yield and 90-95% radiochemical purity at the end of synthesis with a specific activity of 2 GBq/μmol (54 mCi/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies (12) indicated that uptake of both [^{18}F]FAZA and [^{18}F]FMISO in Walker 256 rat tumor cells in hypoxic culture condition (pO_2 < 3 mm Hg) in 20 and 100 min of incubation was of the same magnitude (20 min: 1.24 ± 0.4% ([^{18}F]FAZA); 1.19 ± 0.7% ([^{18}F]FMISO); 100 min: 3.6 ± 1.6% ([^{18}F]FAZA); 3.3 ± 1.7% ([^{18}F]FMISO)). Under normoxic culture condition (pO_2, 70 mm Hg), their uptake was similar but lower than in the hypoxic condition (20 min: 0.9 ± 0.4% ([^{18}F]FAZA); 0.74 ± 0.3% ([^{18}F]FMISO); 100 min: 1.1 ± 0.6% ([^{18}F]FAZA); 1.4 ± 0.6% ([^{18}F]FMISO)).

Animal Studies

Rodents

[PubMed]

Standardized uptake values (SUVs, Bq per cm^3 X body weight in g divided by injected dose) for [^{18}F]FAZA and [^{18}F]FMISO were determined with PET scan in rats bearing Walker 256 carcinosarcoma in their right hind legs (12). Tissue pO_2 values of the normal muscle and tumors were 50-70 and <5 mm Hg, respectively. One h after tracer injection, the SUVs in tumors were 0.68 ± 0.2 for [^{18}F]FAZA and 1.07 ± 0.3 for [^{18}F]FMISO (p < 0.05). Corresponding SUVs in muscle tissue were 0.29 ± 0.09 for [^{18}F]FAZA and 0.40 ± 0.09 for [^{18}F]FMISO (p < 0.05). The concentration of [^{18}F]FAZA in tumor and muscle tissue at 3 h after tracer injection was concordantly decreased to SUVs of 0.35 ± 0.12 (tumor) and 0.13 ± 0.05 (muscle). However, the SUV for [^{18}F]FMISO in the tumor tissue remained unchanged in 3-h PET imaging (1.11 ± 0.7), although it was lower in comparison with early PET scans for the muscle tissue (0.26 ± 0.15). Tumor-to-muscle SUV ratio was not significantly different ([^{18}F]FAZA, 2.4 ± 0.6; [^{18}F]FMISO, 2.7 ± 0.6) when measured 1 h after injection. However, the tumor-to-muscle ratio was significantly higher for [^{18}F]FMISO in comparison with [^{18}F]FAZA (4.4 ± 1.3 *versus* 2.9 ± 0.6, p < 0.05) at 3 h. PET images showed that [^{18}F]FAZA radioactivity was eliminated via the renal system with high radioactivity in the kidneys and urinary bladder and low radioactivity in the liver. In contrast, [^{18}F]FMISO was high in the kidneys and liver. [^{18}F]FAZA showed a faster clearance from the body than [^{18}F]FMISO, providing a lower background than [^{18}F]FMISO.

Biodistribution studies (11) of [^{18}F]FAZA in nude mice bearing AR42J tumors showed a rapid clearance of the tracer from the body over time (10, 60, and 180 min after injection). The highest decrease in radioactivity was found in the blood and the lowest decrease was found in tumor and brain. The tumor-to-muscle ratio increased with time. [^{18}F]FAZA

was eliminated via renal excretion and hepatic metabolism as the radioactivity in the liver and kidneys also decreased from 10 to 180 min. The highest radioactivity was found in the urine (100%ID/g urine) followed by the tumor, intestines, kidneys, and liver at 180 min.

[^{18}F]FAZA and [^{18}F]FMISO biodistribution studies were compared in the three different tumor models (EMT6 BALB/c mice, AR42J and A431 Swiss nude mice) at 3 h after tracer injection (11). [^{18}F]FAZA exhibited a significantly lower uptake in most organs, including the liver and kidneys, and a much faster clearance from the blood compared with [^{18}F]FMISO. In contrast, tumor uptake was not significantly different between both tracers in two of the three tumor models studied. However, [^{18}F]FAZA showed a more favorable tumor-to-blood ratio and tumor-to-organ ratios than [^{18}F]FMISO. Tumor hypoxia was assessed in EMT6 (pO_2, 2.9 ± 2.6) and AR42J (pO_2, 0.4 ± 0.2) by oxygen electrode measurements as compared with normal tissue (pO_2, 25.8-29.0). Therefore, tumor uptake of [^{18}F]FAZA correlates inversely with oxygen concentration.

Serial animal [^{18}F]FAZA PET studies (11) were performed in nude mice bearing A431 tumors and showed that the tumor-to-background ratio was significantly higher in mice breathing room air compared with that of mice breathing pure oxygen (7.3 ± 2.3 *versus*. 4.2 ± 1.2, respectively; $p < 0.001$). Similarly, autoradiography studies in mice bearing EMT6 tumor showed significantly higher tumor-to-muscle ratios in mice breathing room air compared with those of animals breathing carbogen (95% O_2 and 5% CO_2) (5.3 ± 0.8 *versus* 2.2 ± 0.8; respectively; $p < 0.02$). Hence, uptake of [^{18}F]FAZA would be decreased by improving tumor tissue oxygenation through therapy.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Souvatzoglou et al. (13) reported [^{18}F]FAZA PET studies in 11 patients (age 45-75 yr) with squamous cell carcinoma of the head and neck (HNSCC). Dynamic scanning was performed for 2 h after intravenous injection of 315 ± 91 MBq (8.5 ± 2.5 mCi) [^{18}F]FAZA with a whole-body static scan performed at 2 h. Within the first 60 min of the dynamic scanning, the tumor/muscle ratio generally decreased, while generally increasing at later time points. At 2 h , the tumour SUV(max) and SUV(mean) were found to be 2.3 ± 0.5 (range 1.5-3.4) and 1.4 ± 0.3 (range 1.0-2.1), respectively. The mean tumor/muscle ratio at

2 h was 2.0 ± 0.3 (range 1.6-2.4). The tumour volume displaying a tumor/muscle ratio above 1.5 was highly variable. At 2 h, organ radioactivity distribution order was determined as follows: kidney > gallbladder > liver > tumour > muscle > bone > brain > lung.

Postema et al. (14) reported [18F]FAZA PET studies in 50 patients (age 18-90 yr) with HNSCC (*n* = 9), small-cell lung cancer (SCLC) (*n* = 1), non-small-cell lung cancer (NSCLC) (*n* = 12), malignant lymphoma (*n* = 21), or high-grade gliomas (*n* = 7). Dynamic scanning was performed for 2-3 h after intravenous injection of 338-682 MBq (9.1-18.4 mCi) [18F]FAZA. All seven patients with high-grade gliomas showed very high uptake of [18F]FAZA (average tumor/blood ratio, 5.3) in the primary tumour. In six out of nine patients with HNSCC, clear uptake of [18F]FAZA (average tumor/blood ratio, 2.0) was observed in the primary tumour and/or the lymph nodes in the neck. Of the 21 lymphoma patients, 3 demonstrated moderate lymphoma-related [18F]FAZA uptake (average tumor/blood ratio, 2.2). Of the 13 lung cancer patients, 7 patients had increased [18F]FAZA uptake (average tumor/blood ratio, 2.5) in the primary lung tumour. No side effects of the administration of [18F]FAZA were observed. The investigators concluded that [18F]FAZA may be a very useful tracerl for imaging hypoxia in these tumour types.

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