^{18}F-Labeled *N*-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butyl)-2-(2-[^{18}F]-fluoroethoxy)-5-iodo-3-methoxybenzamide

[^{18}F]3f

Arvind Chopra, PhD[1]

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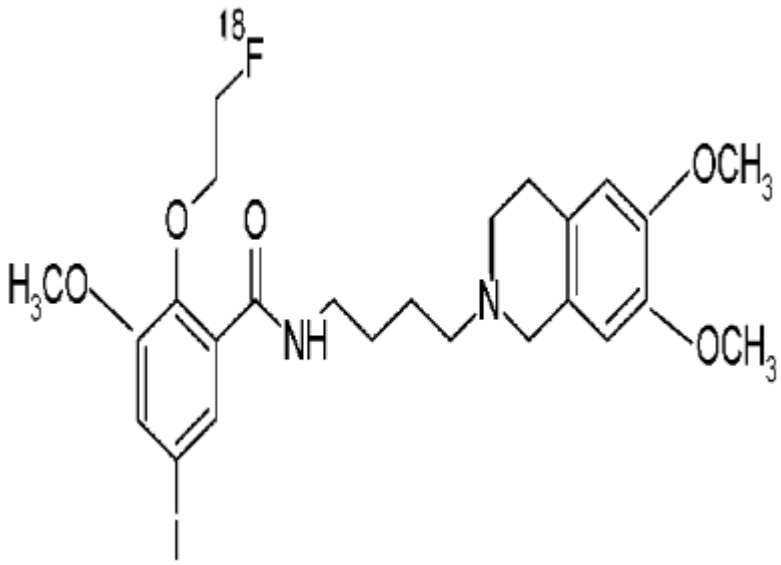
Chemical name:	^{18}F-Labeled *N*-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butyl)-2-(2-[^{18}F]-fluoroethoxy)-5-iodo-3-methoxybenzamide
Abbreviated name:	[^{18}F]3f
Synonym:	
Agent Category:	Compound
Target:	Sigma-2 receptor
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{18}F]3f.

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Background

[PubMed]

Sigma receptor (SR) subtypes 1 (Sig-1R) and 2 (Sig-2R) and are known to be present primarily in the central nervous system and the peripheral tissues. Both receptor subtypes have a different distribution in the two types of tissues, and the exact biological function of these receptors is not known (1). Of the two receptor subtypes, only the Sig-1R has been cloned, expressed, and purified (2). The Sig-2R is known to be overexpressed in various malignant tumors and is believed to promote cell proliferation, indicating that these receptors may play a role in the development of some cancers (3). As a consequence the Sig-2R have been suggested to be biomarkers for tumor cell proliferation (4) and could be targeted for the development of different anti-cancer drugs (5) or imaging agents for tumors that overexpress Sig-2R (3, 5). Several clinical trials have been approved by the United States Food and Drug Administration for the evaluation of drugs that target the Sig-2R for the imaging and treatment of different clinical conditions. In addition, Sig-2R ligands have been used in preclinical studies to chemosensitize tumors to low doses of anti-cancer drugs that are otherwise toxic when given at high doses to animals bearing mammalian cell line tumors (6, 7).

Investigators have developed and characterized several SR ligands, but most of them are either selective only for the Sig-1R or have similar affinity for both the SR subtypes, therefore limiting their use as anti-cancer drugs that target the Sig-2R or as detection and imaging agents for this receptor (3, 7). In an effort to develop a ligand with high specificity for Sig-2R, Tu et al. synthesized a series of ^{18}F-labeled benzamide analogs and evaluated these radiolabeled compounds with positron emission tomography (PET) and computed tomography (CT) imaging of mice bearing allograft tumors expressing the receptor (3). Among the various compounds tested, *N*-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butyl)-2-(2-[^{18}F]-fluoroethoxy)-5-iodo-3-methoxybenzamide (designated [^{18}F]3f) and another analog, *N*-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)butyl)-2-(2-[^{18}F]-fluoroethoxy)-5-methylbenzamide (designated [^{18}F]3c), were determined to be most suitable for the detection of solid tumors expressing Sig-2R with the use of PET and CT imaging. This chapter describes the *in vitro* characterization and *in vivo* biodistribution of [^{18}F]3f and the PET/CT imaging with [^{18}F]3f. The *in vitro* and *in vivo* characterization of [^{18}F]3c are described in a separate chapter in MICAD (www.micad.nih.gov) (8).

Other sources of information regarding SRs

Other SR imaging agents in MICAD.

Sigma receptors in OMIM (Online Mendelian Inheritance in Man).

Protein sequences of human SR1, isoform1 and isoform 2.

Nucleotide (mRNA) sequences of SR1, variant 1 and variant 2.

Synthesis

[PubMed]

The synthesis and ^{18}F-labeling of 3f has been described by Tu et al. (3). The total time of synthesis to obtain [^{18}F]3f was ~2 h with a decay-corrected yield of ~30%. The radiochemical purity of the labeled compound was >99% as determined with analytical high-performance liquid chromatography with a specific activity of >74.07 TBq/mmol (2,000 Ci/mmol). The stability and conditions used to store [^{18}F]3f were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro receptor binding studies with [^{18}F]3c were performed by Tu et al. (3) using membranes isolated from liver homogenates as described elsewhere (9). The affinity of 3c for the two SR subtypes was determined by competition studies using [^{3}H](+)-pentazocine (for Sig-1R) and [^{3}H]1,3-di(2-tolyl)guanidine in the presence of unlabeled (+)-pentazocine (for Sig-2R). The affinity of 3f, as determined with Scatchard plot analysis, was reported to be 2,150 ± 410 and 0.26 ± 0.07 nM for Sig-1R and Sig-2R, respectively, with a Sig-1R/Sig-2R ratio of 8,190. For comparison, the affinity of 3c was reported to be 330 ± 25 and 6.95± 1.63 nM, respectively, for the two receptor subtypes, with a Sig-1R/Sig-2R ratio of 48.

Animal Studies

Rodents

[PubMed]

Tu et al. studied the biodistribution of [^{18}F]3f in BALB/c mice bearing mouse mammary adenocarcinoma EMT-6 cell (these cells express high levels of both SR subtypes (10)) tumors (3). The animals were injected with the labeled compound through the tail vein and euthanized at predetermined time points up to 120 min after the treatment (the number of animals used per time point was not indicated). After euthanasia, tissues from major organs of the animals were removed, weighed, and counted for accumulated radioactivity, and the data were presented as a percentage of injected dose per gram tissue (% ID/g). At 5 min after injection, maximum uptake of radioactivity was noticed in the kidneys (19.98 ± 1.66% ID/g) followed by the liver (15.12 ± 2.21% ID/g) and lungs (18.47 ± 3.07% ID/g). In comparison, the tumor had an uptake of 3.05 ± 0.43% ID/g at this time point. By 2 h after injection, the amount of label in the kidney, liver, lungs, and tumor tissues was reduced to 1.34 ± 0.10, 2.61 ± 0.69, 0.74 ± 0.03, and 1.15 ± 0.23% ID/g, respectively. A similar trend was noticed for the uptake of [^{18}F]3f in all the tissues, including the tumors. The tumor/muscle (T/M) and tumor/fat (T/F) ratios for [^{18}F]3f were ~7 and ~6, respectively, at 2 h after injection. For [^{18}F]3c, the T/M and T/F ratios were ~3 and ~8, respectively. Both [^{18}F]3f and [^{18}F]3c were reported to have rapid

clearance from blood, indicating that both tracers were probably suitable for the detection and imaging of solid tumors expressing Sig-2R.

For blocking studies, mice were injected with [^{18}F]3f in the presence of excess (1 mg/Kg) unlabeled *N*-(4-fluorobenzyl)piperidinyl-4-(3-bromophenyl) acetamide, which has a high affinity for the SR (3), and the mice were euthanized 1 h after the treatment (the number of animals used was not reported) (3). Under these conditions, the T/M and T/F ratios for this labeled compound were reduced by ~50%, indicating that the radiochemical bound selectively to the Sig-2R. Similar results were obtained with [^{18}F]3c under these experimental conditions.

Mice bearing EMT-6 cell tumors were injected with [^{18}F]3f as detailed above, and PET/CT imaging was performed on the animals 1 h later (3). Both detection methods were reported to identify the tumors in the animals easily. Similar results were reported when [^{18}F]3c was used as an imaging agent.

On the basis of results obtained from these studies, the investigators concluded that both [^{18}F]3f and [^{18}F]3c were equally suitable for the detection and imaging of solid tumors expressing Sig-2R using PET (3).

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

[Disclaimers]

No information is currently available.

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