(*R*)-2-(*N*-Benzyl-4-(2-[^{18}F]fluoroethoxy)phenylsulfonamido)-*N*-hydroxy-3-methylbutanamide

[^{18}F]1f

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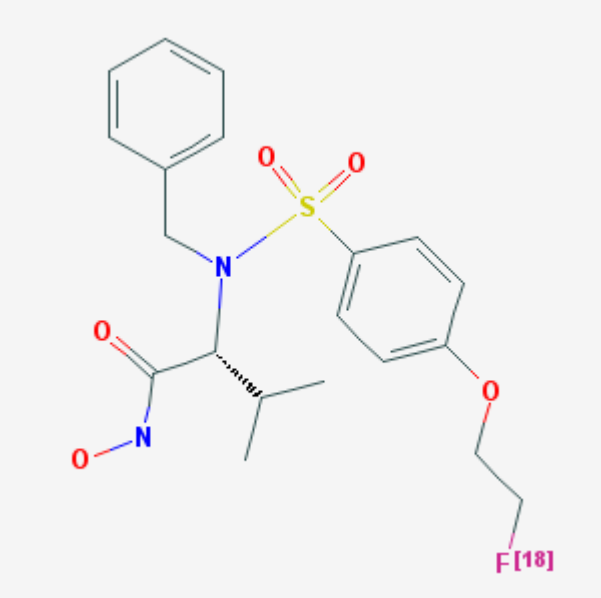
Chemical name:	(*R*)-2-(*N*-Benzyl-4-(2-[^{18}F]fluoroethoxy)phenylsulfonamido)-*N*-hydroxy-3-methylbutanamide
Abbreviated name:	[^{18}F]MMP-1f, [^{18}F]1f
Synonym:	
Agent Category:	Compound
Target:	Gelatinases (MMP-2 and MMP-9)
Target Category:	Enzyme binding
Method of detection:	PET
Source of signal/ contrasat:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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Extracellular matrix (ECM) adhesion molecules consist of a complex network of fibronectins, collagens, chondroitins, laminins, glycoproteins, heparin sulfate, tenascins, and proteoglycans that surround connective tissue cells, and they are mainly secreted by fibroblasts, chondroblasts, and osteoblasts (1). Cell substrate adhesion molecules are considered essential regulators of cell migration, differentiation, and tissue integrity and remodeling. These molecules play a role in inflammation and atherogenesis, but they also participate in the process of invasion and metastasis of malignant cells in the host tissue (2). Invasive tumor cells adhere to the ECM, which provides a matrix environment for permeation of tumor cells through the basal lamina and underlying interstitial stroma of the connective tissue. Overexpression of matrix metalloproteinases (MMPs) and other proteases by tumor cells allows intravasation of tumor cells into the circulatory system after degrading the basement membrane and ECM (3).

Several families of proteases are involved in atherogenesis, inflammation, myocardial infraction, angiogenesis, and tumor invasion and metastasis (4-8). The gelatinase family is a subgroup of MMPs consisting of gelatinase A (MMP-2) and gelatinase B (MMP-9) (9). Gelatinase expression in normal cells, such as trophoblasts, osteoclasts, neutrophils, and macrophages, is highly regulated. Elevated levels of gelatinases have been found in tumors that are associated with a poor prognosis for cancer patients (10). A number of synthetic MMP inhibitors have been developed to block the activated MMPs in pathological conditions (11). (*R*)-2-(*N*-Benzyl-4-(2-fluoroethoxy)phenylsulfonamido)-*N*-hydroxy-3-methylbutanamide (1f) was found to be a potent MMP inhibitor (12). ^{18}F-Labeled 1f ([^{18}F]1f) is being developed for PET imaging of MMP proteolytic activity in tumors, atherosclerosis, myocardial infarction, and other diseases.

Synthesis

[PubMed]

[^{18}F]1f was prepared as described by Wagner et al. (12). [^{18}F]KF/Kryptofix 2.2.2/K_2CO_3 and the tosylate precursor, (*R*)-2-(*N*-benzyl-4-(2-(tosyloxy)ethoxy)phenylsulfonamido)-*N*-hydroxy-3-methylbutanamide, were heated in acetonitrile at 84°C for 4 min, followed by acidic hydrolysis in trifluoroacetic acid and high-performance liquid chromatography (HPLC). Average radiochemical yield was 12.4 ± 3.0% (n = 5) with a total synthesis time of 113 ± 6 min. Radiochemical purity was >97% with specific activities of 44 ± 19 GBq/μmol (1.19 ± 0.51 Ci/μmol) at end of synthesis. [^{18}F]1f has a log $D_{7.4}$ value of 2.02.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Wagner et al. (12) performed *in vitro* fluorogenic inhibition assays for MMP-2, MMP-8, MMP-9, and MMP-13. The MMP inhibitor 1f exhibited IC_{50} values of 4 ± 3 nM for MMP-2, 2 ± 1 nM for MMP-8, 50 ± 27 nM for MMP-9, and 11 ± 0.3 nM for MMP-13.

Animal Studies

Rodents

[PubMed]

Wagner et al. (12) performed biodistribution studies of [^{18}F]1f in normal mice. [^{18}F]1f accumulated mainly in the duodenum (uptake index (UI) = 10), kidney (UI = 5), and liver (UI = 2), with low blood, lung, heart, muscle, and brain radioactivity (UI < 0.3) at 20 min after injection. The UI for the tibia was about half that of the heart, indicating little defluorination of [^{18}F]1f. Radioactivity levels in all tissues were very low by 60 min after injection with the exception of the bile (UI = 89 at 60 min). Approximately 53% of radioactivity in the plasma was intact [^{18}F]1f at 20 min after injection with one polar metabolite as measured by HPLC. Pretreatment of 1f had little effect on the biodistribution and clearance of [^{18}F]1f, indicating that there was little or no specific [^{18}F]1f binding to MMPs in any of the normal tissues studied. The authors suggested that low accumulation of [^{18}F]1f in normal tissues may be an advantage for future studies of activated MMPs in experimental animal models.

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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