2-(3-{1-Carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid

[^{18}F]DCFPyL

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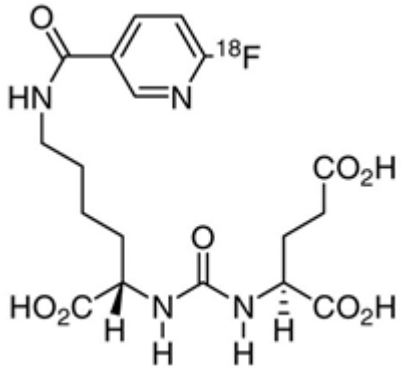
Chemical name:	2-(3-{1-Carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid
Abbreviated name:	[^{18}F]DCFPyL
Synonym:	[^{18}F]**3**
Agent Category:	Compounds
Target:	Prostate-specific membrane antigen (PSMA)
Target Category:	Antigens
Method of detection:	Positron emission tomography
Source of signal / contrast:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of [^{18}F]DCFPyL (1).

Background

[PubMed]

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2-(3-{1-Carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, abbreviated as [^{18}F]DCFPyL, was synthesized by Chen et al. for use in positron emission tomography of tumors expressing prostate-specific membrane antigen (PSMA) (1).

PSMA is a type II transmembrane glycoprotein with three structural domains, including a 19-amino-acid intracellular domain, a 24-amino-acid transmembrane domain, and a large 707-amino-acid extracellular domain (2, 3). Two site-specific carboxypeptidase activities have been assigned to PSMA: *N*-acetylated α-linked acidic dipeptidase, which hydrolyzes the neuropeptide *N*-acetyl-aspartyl-glutamate (NAAG) in the brain to regulate release of neurotransmitters, and folate hydrolase activity, which is characterized by the cleavage of terminal glutamates from poly- and gamma-glutamated folates, which play a role in the cellular uptake of dietary folate (2). PSMA has been found to be expressed in the prostate at a level 1,000-fold greater than in other tissues, and many folds higher in prostate cancer tumors than in normal and benign prostate tissues (4, 5). High-grade hormone-sensitive and hormone-insensitive tumors have the greatest PSMA expression. PSMA is also consistently and abundantly expressed on the neovascular endothelium in a wide variety of human solid tumors, but not in blood vessels in normal tissues. These features of PSMA make it an optimal target for developing imaging and therapy strategies for prostate cancer (6).

Besides antibodies and antibody fragments, low molecular weight compounds have also been intensively tested as PSMA inhibitors and as PSMA-targeted imaging agents (1, 6). These compounds can be largely classified into two types: ureas and phosphoramidates (1). Both types of compounds possess a terminal glutamate at the P1' position, which enables productive binding with PSMA. They are also amenable to modification with bulky substituents that interact with the arginine patch or tunnel region on PSMA. Investigators have synthesized a series of ureas, including [^{18}F]DCFBC, [^{18}F]DCFPyL, and [^{111}In]**3** (1, 7, 8). [^{111}In]**3** is a bivalent compound that was synthesized by incorporating a PSMA-binding Lys-Glu urea motif for exploiting click chemistry and a second lysine residue for subsequent modification with an imaging or therapeutic moiety (8). Studies have shown that these radiolabeled PSMA inhibitors have desirable properties as imaging agents for prostate cancer imaging in animal models (1, 7, 8). This chapter summarizes the data obtained with [^{18}F]DCFPyL. In another chapter, the data obtained with [^{111}In]**3** are summarized. The data obtained with [^{18}F]DCFBC can be reviewed in the chapter on [^{18}F]DCFBC in MICAD.

Related Resource Links:

- PSMA-targeted imaging agents in MICAD
- Gene information in NCBI (PSMA)
- Articles in Online Mendelian Inheritance in Man (OMIM) (PSMA)
- PSMA-related clinical trials in ClinicalTrials.gov

Synthesis

[PubMed]

Chen et al. described the synthesis of [^{18}F]DCFPyL in detail (1). The tosylate salt of 2-{3-[1-p-methoxybenzylcarboxylate-(5-aminopentyl)]-ureido}-di-p-methoxybenzyl pentanedioate (compound **1**) was synthesized, and then compound **1** was reacted with 6-fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester to generate fluoropyridyl urea (65% yield, compound **2**). Deprotection produced 2-(3-{1-carboxy-5-[(6-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (compound **3**, DCFPyL), with 81% yield. The ^{18}F-labeled prosthetic group 6-fluoro-nicotinic acid 2,3,5,6-tetrafluoro-phenyl ester was used to generate [^{18}F]DCFPyL.

The radiochemical yields of [^{18}F]DCFPyL were 36%–53% based on starting [^{18}F]F– (n = 3), with absolute yields of 285–385 MBq (7.7–10.4 mCi) after purification. The mean synthesis time was 128 min from the time of addition of [^{18}F]F–. With the addition of 1,628–2,257 MBq (44–61 mCi) [^{18}F]F–, the specific radioactivity of [^{18}F]DCFPyL was 12.6–17.8 GBq/μmol (340–480 Ci/mmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The PSMA enzyme inhibition potency of compound **3** was determined with a modified Amplex Red glutamic acid assay after incubation with the cell lysates of LNCaP cell extracts in the presence of NAAG for 2 h at 37°C (1, 6). The enzyme inhibitory constant (K_i) for compound **3** was 1.1 ± 0.1 nmol/L, comparable with that of ZJ-43, which was 1.4 ± 0.2 nmol/L under same measurement conditions. ZJ-43 is a urea-based potent inhibitor of NAAG and is used as an internal reference in the assay.

Animal Studies

Rodents

[PubMed]

Biodistribution of [^{18}F]DCFPyL was determined at 30, 60, 120, and 240 min after tail vein injection of 3.7 MBq (0.1 mCi) [^{18}F]DCFPyL to nonobese diabetic severe-combined immunodeficient (NOD-SCID) mice that carried both PSMA-positive PC3-PIP and PSMA-negative PC3-flu xenografts (n = 4 mice/group) (1). The percentage of injected dose per gram tissue (% ID/g) was measured *ex vivo* in selected organs (Table 1). [^{18}F]DCFPyL showed a PSMA-dependent uptake, reaching a value of 46.7 ± 5.8% ID/g at 30 min in PC3-PIP xenografts, which decreased by only ~10% over the 4-h period of study. The uptake ratio of PC3-PIP/PC3-flu tumors ranged from 40:1 to >1,000:1. An explanation for the increased tumor uptake of [^{18}F]DCFPyL over time could be due to PSMA-mediated internalization within tumor cells. At 60 min after injection, the kidney,

liver, and spleen displayed the highest uptake among organs. Rapid clearance from the kidneys was observed, decreasing from 74.1 ± 6.6% ID/g at 30 min to 7.4 ± 0.9% ID/g at 4 h after injection. Relatively low bone uptake (<1% ID/g at all time points) suggests little metabolic defluorination of the [^{18}F]DCFPyL.

Table 1: Biodistribution of [^{18}F]DCFPyL in selected organs (percent of ID/g) in tumor-bearing mice.

Organ	30 min	60 min	120 min	240 min
Blood	1.53 ± 0.19	0.24 ± 0.05	0.43 ± 0.37	0.03 ± 0.01
Liver	3.88 ± 0.74	2.87 ± 0.92	2.14 ± 0.11	1.80 ± 0.39
Kidney	74.1 ± 6.6	42.3 ± 19.0	15.7 ± 3.3	7.42 ± 0.89
Bone	0.82 ± 0.16	0.42 ± 0.15	0.33 ± 0.08	0.43 ± 0.06
Bladder (empty)	18.6 ± 18.1	9.88 ± 4.92	6.44 ± 4.42	1.54 ± 1.79
PC3-PIP	46.7 ± 5.8	44.2 ± 9.7	39.4 ± 5.4	36.6 ± 4.3
PC3-Luc	1.17 ± 0.41	0.36 ± 0.14	0.11 ± 0.02	0.03 ± 0.01
PC3-PIP/PC3-Luc	40	123	358	1,220

PET/computed tomography was performed after tail vein injection of 14.1 MBq (0.38 mCi) [^{18}F]DCFPyL into one NOD-SCID mouse that carried both PSMA-positive PC3-PIP and PSMA-negative PC3-flu xenografts (1). Successive whole-body images were acquired in two bed positions. The dwell time at each position was 1 min, such that a given bed position (or mouse organ) was revisited every 3 min. Imaging showed intense radiochemical uptake only in the kidneys and PC3-PIP tumor after administration of [^{18}F]DCFPyL. By 3.5 h after injection, only the PC3-PIP tumor was visible with no radiochemical background in liver or the gastrointestinal tract to obscure potential metastases. No blocking studies were performed in either experiments, but the tumors with and without PSMA support specific tumor binding.

The human dosimetry values were obtained based on the mouse biodistribution data (1). The mouse organ activity concentrations in % ID/g were converted to the human % ID/organ by setting the ratio of organ % ID/g to whole-body % ID/g in the mouse equal to that in humans. The conversion showed that the organ with the highest mean absorbed dose per unit administered activity was the urinary bladder wall (0.15 mGy/MBq), followed by the kidneys (0.05 mGy/MBq). The effective dose based on the International Commission on Radiological Protection 60 (ICRP 60) tissue weighting factors was 13.6 μSv/MBq. A maximum of 331 MBq (9 mCi) could be administered without exceeding the 50-mGy critical organ dose limit (urinary bladder wall in this case) for a single administration of radioactive material for research use as specified in Code of Federal Regulations 21, part 361.

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.

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