N-(4-[^{18}F]Fluoro-benzoyl)-*N*'-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine

[^{18}F]PC-10

Kam Leung, PhD[1]

Created: June 29, 2011; Updated: August 25, 2011.

Chemical name:	*N*-(4-[^{18}F]Fluorobenzoyl)-*N*'-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine
Abbreviated name:	[^{18}F]PC-10
Synonym:	
Agent category:	Compound
Target:	Prokineticin receptor 1 (PKR1, PROKR1)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No

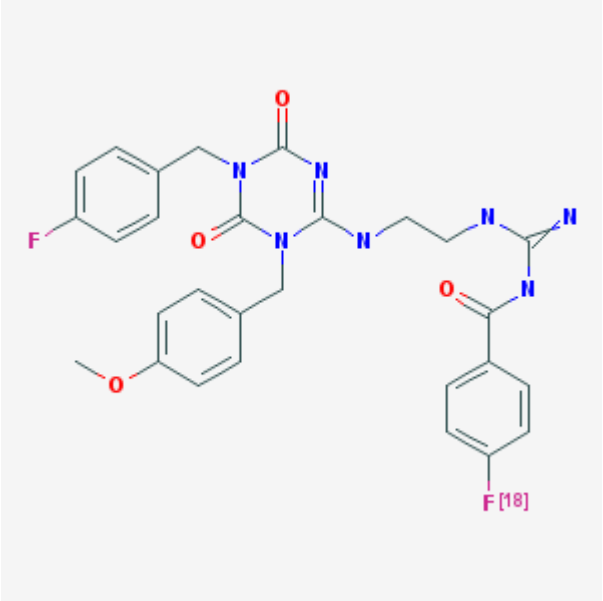

Table continues on next page...

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Table continued from previous page.

Studies:	• *In vitro* • Rodents	Click on the above structure for additional information in PubChem.

Background

[PubMed]

Bv8 is a small protein secreted by frog skin (1). The prokineticins PK1 and PK2, which are mammalian homologs of Bv8, and their G-protein–coupled receptors prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2) have been identified and linked to several biological functions such as gut motility, neurogenesis, angiogenesis, circadian rhythms, hematopoiesis, and nociception (2-4). Prokineticins are also associated with pathologies of the reproductive and nervous systems, myocardial infarction, and tumorigenesis. PKR1 shares 33% identity with human neuropeptide Y receptor-2, and PKR1 is expressed in the brain, spleen, prostate, testis, leukocytes, pancreas, adrenal gland, thyroid, salivary gland, pituitary, stomach, small intestine, colon, and rectum. On the other hand, PKR2 is expressed mainly in the ileocecum and discrete nuclei of the central nervous system. PK1 is secreted by endocrine glands, whereas PK2 is highly expressed in the bone marrow, lymphoid organs, and leukocytes, which suggests a role for PK2 in inflammation, immunomodulation, and hematopoiesis. Binding of PK2 to PKR1 has been shown to reduce the pain threshold in sensory neurons and can contribute to inflammatory pain. PK2 is highly expressed by neutrophils and other inflammatory cells as a pronociceptive mediator in inflamed tissues.

Several nonpeptidic PK antagonists have been developed for pain reduction and cancer therapy (5). However, noninvasive quantification of PKR1 levels *in vivo* is not available for drug development. A nonpeptidic PKR1 antagonist, *N*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine (PC-7), which contains a free guanidine group, was labeled with ^{18}F by reacting the guanidine moiety with *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]FBA) to form *N*-(4-[^{18}F]fluoro-benzoyl)-*N'*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine ([^{18}F]PC-10). Jacobson et al. (6) evaluated [^{18}F]PC-10 binding in mice injected with complete Freund adjuvant (CFA) to induce inflammatory pain by upregulation of PK2 and PKR1.

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NLM Citation: Leung K. *N*-(4-[^{18}F]Fluoro-benzoyl)-*N'*-{2-[5-(4-fluoro-benzyl)-1-(4-methoxy-benzyl)-4,6-dioxo-1,4,5,6-tetrahydro-[1,3,5]triazin-2-ylamino]-ethyl}-guanidine. 2011 Jun 29 [Updated 2011 Aug 25]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Related Resource Links:

- Chapters in MICAD (Prokineticin receptor 1)
- Gene information in NCBI (Prokineticin receptor 1, prokineticin 1)
- Articles in Online Mendelian Inheritance in Man (OMIM) (Prokineticin receptor 1, prokineticin 1)

Synthesis

[PubMed]

Jacobson et al. (6) prepared [^{18}F]PC-10 with a two-step synthesis in a modular system. [^{18}F]FBA was synthesized using a standard nucleophilic radiofluorination ([^{18}F]KF/Kryptofix 2.2.2) reaction, with 50%–60% yield and >99% radiochemical purity. [^{18}F]FBA and PC-7 were incubated in dimethylformamide for 10 min at 60°C. [^{18}F]PC-10 was purified with high-performance liquid chromatography, with a radiochemical purity of >99% and a specific activity of 70.2 ± 7.4 GBq/μmol (1.9 ± 0.2 Ci/μmol) at the end of synthesis. The overall decay-corrected yield was 16 ± 3% (n = 4). The total synthesis time was ~160 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Chinese hamster ovary (CHO) cells were transfected with human PKR1 or human PKR2 (6). A receptor-binding assay was performed with ^{125}I-Mamba intestinal toxin-1, a Bv8 homolog. [^{18}F]PC-10 exhibited 50% inhibition concentration (IC_{50}) values of 109.7 ± 4.9 nM and 1,200 ± 69 nM for PKR1 and PKR2, respectively. [^{18}F]PC-10 accumulated rapidly in CHO-PKR1 cells with 30 min of incubation at 37°C, and ~50% of radioactivity was internalized with up to 2 h of incubation. Retention studies showed a rapid release of radioactivity by CHO-PKR1 cells in fresh medium; 50% of radioactivity was unbound at 15 min, and radioactivity levels reached a plateau after 1 h.

Animal Studies

Rodents

[PubMed]

Jacobson et al. (6) performed static positron emission tomography scans in a CFA-induced inflammatory pain model in mice (n = 3–5/group) at 0.5, 1, and 2 h after injection of 1.85 MBq (0.05 mCi) [^{18}F]PC-10. Accumulation of [^{18}F]PC-10 in the inflamed paws was determined to be 0.95 ± 0.20% injected dose/gram (ID/g), 1.21 ± 0.32% ID/g, and 0.78 ± 0.04% ID/g at 0.5, 1, and 2 h, respectively. Accumulation in the control paws was 0.13–0.25% ID/g at these time points. [^{18}F]PC-10 accumulation in the inflamed paws was significantly higher than in the control paws at these three time points

($P < 0.01$), with inflamed paw/control paw ratios of 4.2–5.7. In comparison, 2-[^{18}F]fluoro-2-deoxy-2-D-glucose ([^{18}F]FDG) provided inflamed paw/control paw ratios of ~2 at these time points. [^{18}F]PC-10 accumulation was high in the PKR1-expressing organs, such as the gastrointestinal tract (54.3% ID/g) and salivary gland (3.05% ID/g), at 2 h after injection. The liver (3.80% ID/g) and kidneys (5.26% ID/g) exhibited moderate accumulation, and blood (0.22% ID/g) and bone (0.69% ID/g) had low radioactivity levels. Coinjection with excess PC-7 (0.3 mg) reduced the radioactivity level in the inflamed paws by 70% at 1 h after injection. Effect of PC-7 on [^{18}F]PC-10 accumulation in other tissues was not reported.

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.

NIH Support

Intramural Research Program

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