4-[^{18}F]Fluoropaclitaxel

[^{18}F]FPAC

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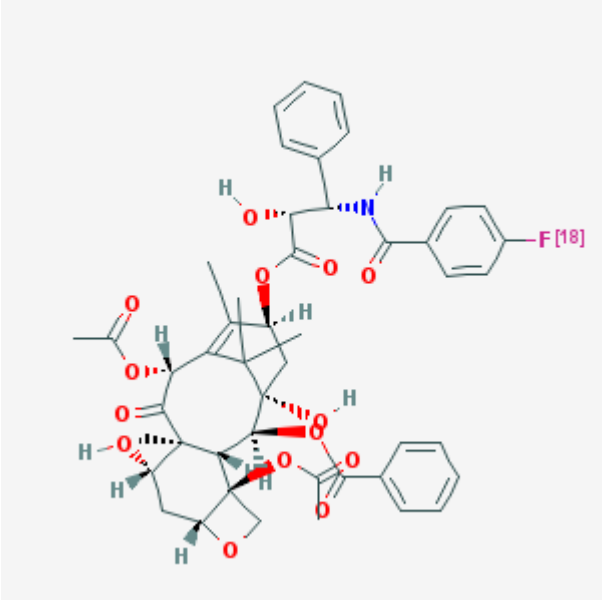
Chemical name:	4-[^{18}F]Fluoropaclitaxel
Abbreviated name:	[^{18}F]FPAC
Synonym:	[^{18}F]Taxol®
Agent category:	Compound
Target:	P-glycoprotein (P-gp) multidrug transporter, MDR-1
Target category:	Transporter
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-Human Primates • Humans



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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One of the mechanisms that tumor cells use to escape the cytotoxic effects of chemotherapeutic agents, such as Adriamycin, Vinca alkaloids, epipodophyllotoxins, actinomycin D, and paclitaxel (PAC), is to limit their presence inside the cells through the actions of P-glycoprotein (P-gp), a protein encoded by the multidrug resistance (MDR-1) gene (1, 2). P-gp is an ATP-dependent transmembrane multidrug transporter that is capable of actively pumping a variety of agents out of cells. Injection of unlabeled efflux pump substrates increases the retention of radioactivity in tumors rather than lessening the retention, as seen with receptor-binding radiotracers. Overexpression of P-gp in tumor cells (such as renal carcinoma, hepatoma, pheochromocytoma, and colon carcinoma) leads to resistance to anticancer drugs (3). P-gp is also present in a variety of normal cells, such as intestinal mucosal cells, hepatocytes, renal proximal tubule epithelial cells, and endothelial cells of the blood-brain barrier (4, 5). Calcium channel blockers, cyclosporin A, and its non-immunosuppressive analog PSC 833 are MDR modulators that inhibit transport of P-gp substrates out of cells (6, 7).

Sestamibi (MIBI) is a substrate for P-gp. ^{99m}Tc-MIBI has been approved by the United States Food and Drug Administration (FDA) as a myocardial perfusion imaging agent for use with single-photon emission computed tomography (SPECT) to assess the risk of future cardiac events. It is also approved as a tumor-imaging agent in breast, lung, thyroid, and brain cancers. PAC is an FDA-approved chemotherapeutic agent exerting its antitumor activity by binding to β-tubulin to inhibit cell division (8). It is also a transport substrate for P-gp in tumor cells, leading to drug-related resistance to chemotherapy (8, 9). Therefore, [^{18}F]fluoropaclitaxel ([^{18}F]FPAC) is being developed as a positron emission tomography (PET) agent to noninvasively study P-gp function and multidrug resistance in tumors and normal tissues.

Related Resource Links:

- Chapters in MICAD (P-glycoprotein)
- Gene information in NCBI (P-glycoprotein)
- Articles in OMIM (P-glycoprotein)
- Clinical trials (P-glycoprotein, ^{99m}Tc-MIBI, Paclitaxel)
- Drug information in FDA (^{99m}Tc-MIBI, Paclitaxel)

Synthesis

[PubMed]

Kiesewetter et al. (10) prepared [^{18}F]FPAC by incorporating [^{18}F]fluoride (Kryptofix 2.2.2 and K_2CO_3) into [^{18}F]fluorobenzoate ester via nucleophilic displacement of a trimethylammonium moiety. The ester group was removed, and the resulting [^{18}F]fluorobenzoic acid was coupled to 3′-debenzoylpaclitaxel (10).The final product was purified by high-performance liquid chromatography. The radiochemical yield for the syntheses was 18.3 ± 5.5% (not corrected for decay). The specific activity at the end of

bombardment was 169-453 GBq/mmol (4.58-12.25 Ci/mmol) for 14 syntheses. The total synthesis time was 80 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In an *in vitro* study using human hepatocytes, 50% [^{18}F]FPAC was metabolized to produce one major metabolite, 6α-hydroxy-FPAC, after 4 h of incubation (10). In rat hepatocytes, 3 metabolites were produced from [^{18}F]FPAC with a half-life of 194 min.

Animal Studies

Rodents

[PubMed]

Biodistribution studies in normal rats showed high accumulation of radioactivity, as measured by differential uptake ratio, in the liver (1.64), followed by the kidney (1.59), heart (1.28), and lung (0.99) at 60 min after injection of [^{18}F]FPAC (10). Levels of the tracer were low in the brain (0.018) and blood (0.08). Pretreatment (20 min) with PAC (200 nmol) increased [^{18}F]FPAC accumulation in the blood (33%), heart (32%), lung (38%), liver (30%), kidney (142%), and brain (5%). Increased accumulation is consistent with saturation of the efflux pump, P-gp. There was a significantly greater accumulation of [^{18}F]FPAC in the heart (79% increase), lung (143%), muscle (38%), and brain (1300%) in mdr1a/1b(-/-) mice than in wild-type mice. Furthermore, biodistribution studies in both types of mice with pre-injection of PAC or XR9576, an MDR modulator, showed little effect on the accumulation of [^{18}F]FPAC in the knockout mice compared with the wild-type mice, which showed significant increases only in the lung and kidney. The kidney contained 42-71% intact [^{18}F]FPAC, whereas the liver contained 59-86% at 30 min after injection in both types of mice.

Biodistributions of [^{18}F]FPAC and [^{3}H]PAC were very similar in nude mice bearing MCF-7 human breast tumors, with the highest accumulations in the small intestine, the lowest accumulations in the brain, and intermediate accumulations in the tumor (11). Uptake in these and other tissues was not significantly inhibited or enhanced by the presence of unlabeled PAC (20 mg/kg). Administration of cyclosporin A (10 mg/kg) increased uptake of both [^{18}F]FPAC and [^{3}H]PAC into the tumor by 1-fold.

Other Non-Primate Mammals

[PubMed]

No publications are currently available.

Non-Human Primates

[PubMed]

Kurdziel et al. (12) performed PET imaging in 3 rhesus monkeys after injection of 222-444 MBq (6-12 mCi) of [^{18}F]FPAC. Pretreatment with XR9576 (a P-gp blocker) changed the Logan plot slope (distribution volume) for the liver by +104% (P = 0.02), the lung by +87% (P = 0.01), and the kidney by -14% (P = 0.08) (12). Changes in the mean area under time-activity curve (AUC; plasma metabolite-corrected) were +54% (P = 0.08), +97% (P = 0.04), and -12% (P = 0.02), respectively, for the liver, lung, and kidney. This indicates that accumulation of [^{18}F]FPAC in the liver and lung is modulated by the MDR P-gp efflux pump. No significant difference was found in the AUC between the baseline and XR9576 studies.

Kurdziel et al. (12) estimated the human dosimetry of [^{18}F]FPAC in 3 rhesus monkeys after injection of 222-444 MBq (6-12 mCi) of [^{18}F]FPAC. The organs that received the highest absorbed doses were the gallbladder (0.19 mGy/MBq, or 0.69 rad/mCi), the liver (0.14 mGy/MBq, or 0.52 rad/mCi), upper intestine (0.094 mGy/MBq, or 35 rad/mCi), and the kidneys (0.044 mGy/MBq, or 0.163 rad/mCi). The effective dose was 0.022 mSv/MBq (0.083 rem/mCi).

Human Studies

[PubMed]

Kurdziel et al. (13) estimated the human dosimetry of [^{18}F]FPAC in 3 healthy subjects after injection of 192.4 MBq (5.2 mCi) of [^{18}F]FPAC. The organs receiving the highest radiation dose were the gallbladder, large intestine and small intestine at 0.23 mGy/MBq (0.85 rad/mCi), 0.19 mGy/MBq (0.68 rad/mCi), and 0.16 mGy/MBq (0.60 rad/mCi), respectively. The effective dose was 28.79 μSv/MBq (0.107 rem/mCi). [^{18}F]FPAC PET studies were performed with dynamic scans for 60 min and static scans for 120 min in 3 breast cancer patients. The tumor uptake was low with an average maximum standard uptake value (SUV_{max}) of 1.8 at 80 s after injection decreased slightly over time. When compared with background tissue (contralateral breast), the tumors were visible with an average maximum tumor/background ratio of 7.7 at 20 min. Tumor/blood ratios increased slightly over time to an average maximum of 1.9.

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