[^{18}F]Fluoropropyl-Tanaproget

[^{18}F]FPTP

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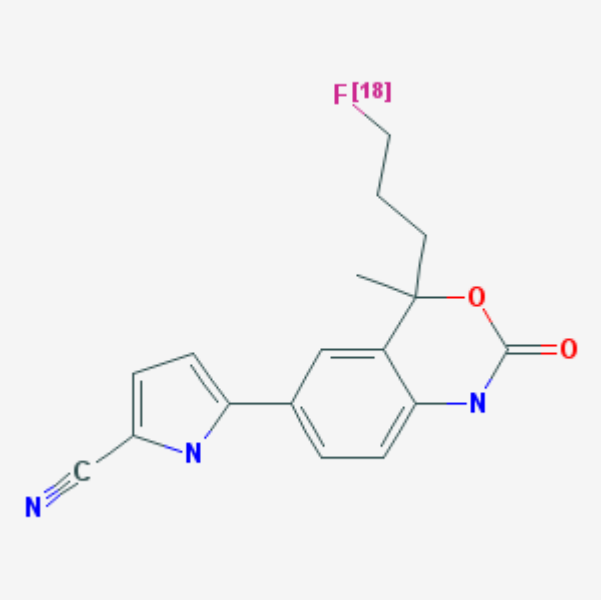
Chemical name:	[^{18}F]Fluoropropyl-Tanaproget
Abbreviated name:	[^{18}F]FPTP
Synonym:	
Agent category:	Compound
Target:	Progesterone receptor (PR)
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Estrogens and progesterones are endogenous hormones that produce many physiological effects (1). Estrogens act primarily by regulating gene expression. Estrogen receptors (ERs) are found in the cytoplasm and nucleus of cells in the female reproductive tract,

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breast, pituitary, hypothalamus, bone, liver, and other tissues, as well as in various tissues in men. Estrogens are lipophilic in that they enter the cell passively by diffusion through the cellular membrane. They bind to ERs in the cytoplasm and are transported to the nucleus.

Breast cancer is the most common malignancy in women. Approximately 33% of women who have this disease will die of disseminated breast cancer. The growth of breast epithelial cells is dependent on estrogen stimulation to induce progesterone receptor (PR) expression. Two-thirds of breast carcinomas express ERs. It has also been established that the ER status of the tumor is an important prognostic indicator in breast cancer (2). Women with ER-positive breast tumors have a better prognosis than women with ER-negative tumors in terms of responsiveness to anti-estrogen treatment. ER content in breast cancer was assessed *in vitro* with receptor binding assays, which suffer from inter-assay variability and are also limited by intrinsic receptor heterogeneity of the primary and metastatic tumors. 16α-[^{18}F]Fluoro-17β-estradiol ([^{18}F]FES) has been proven to be a valuable tracer for studies of the ER status of primary and metastatic breast cancer (3). However, [^{18}F]FES is cleared from the blood and metabolized in 20 min with only 20% of [^{18}F]FES intact in a study with 15 breast cancer patients (4). A newly developed nonsteroidal progestin analog, Tanaproget, exhibits a potent agonist activity for PR with a high binding affinity (K_d = 0.2 nM) (5). Lee et al. (6) reported the synthesis of [^{18}F]fluoropropyl-Tanaproget ([^{18}F]FPTP) and its tissue distribution in immature, estrogen-primed, female rats with a high uterus/blood ratio.

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (Estrogen receptor, progesterone receptor)
- Articles in OMIM (Estrogen receptor, progesterone receptor)

Synthesis

[PubMed]

A mixture of the methanesulfonate precursor and *n*-Bu$_4$N[^{18}F]F in *tert*-amyl alcohol was heated for 20 min at 130°C (6). After removal of the solvent, the mixture was heated for 10 min at 160°C to undergo deprotection. The mixture was heated with Lawesson's reagent in toluene for 30 min at 130°C to convert the carbamate group to the thiocarbamate group. [^{18}F]FPTP was isolated to provide a radiochemical yield of 5% (decay-corrected) with a specific activity of ~20 GBq/μmol (550 mCi/μmol) and a chemical purity of >95% after purification with high-performance liquid chromatography. The total synthesis time was ~140 min from the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In an alkaline phosphatase assay in T47D cells, Tanaproget had an effective dose (EC_{50}) of 0.15 nM, comparable to steroidal PR agonists (e.g., medroxyprogesterone acetate (MPA, EC_{50} = 0.12 nM)) (7). Tanaproget showed high affinity for the human PR with an IC_{50} of 1.6 nM in a T47D cell cytosol competition-binding assay (IC_{50} = 10.8 nM). Tanaproget did not show any ER, androgen receptor, or glucocorticoid receptor agonist activity when tested at concentrations up to 10 μM in appropriate cell-based reporter assays. A competition binding assay was used to determine whether Tanaproget competes with [^{3}H]dihydrotestosterone for sex hormone–binding globulin (SHBG) binding (8). Tanaproget did not significantly compete for the SHBG binding at a concentration up to 10 μM.

Relative binding affinities for PR were determined with a competitive binding assay using 10 nM [^{3}H]R5020 ([17R-methyl-^{3}H]-promegestone) as a tracer and purified full length progesterone receptor B (5). FPTP exhibited a binding affinity to PR similar to that of the parent compound Tanaproget (K_d = 0.2 nM).

Animal Studies

Rodents

[PubMed]

It was demonstrated that [^{18}F]FPTP uptake by target tissues (the uterus and ovaries) in immature, estrogen-primed, female rats (n = 5/group) is highly specific (6). The rats were injected with 1.0 MBq (0.026 mCi) [^{18}F]FPTP. The initial tracer accumulation in the uterus was 4.6 ± 1.1% injected dose per gram (ID/g) and 5.3 ± 0.4% ID/g at 1 h and 3 h after injection, respectively. Tracer accumulation in the ovaries was 2.3 ± 0.2% ID/g and 2.2 ± 0.4% ID/g at 1 h and 3 h after injection, respectively. There was also a significant reduction (~80%) of [^{18}F]FPTP accumulation in the uterus and ovaries at the two time points with co-injection of excess FPTP. The accumulation in the liver, spleen, muscle, and kidneys was lower than uptake in the uterus and ovaries at 3 h after injection. The accumulation of radioactivity in the bone was 0.9% ID/g and 0.6% ID/g at 1 h and 3 h after injection, respectively. Co-injection of FPTP had little inhibitory effect in these non-targeted tissues. The uterus/blood ratios were 9 and 32 at 1 h and 3 h after injection, respectively. The ovary/blood ratios were 5 and 13 at 1 h and 3 h after injection, respectively.

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

R01 CA025836, R24 CA086307

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