4-[^{18}F]Fluorobenzyl-triphenylphosphonium

[^{18}F]FBnTP

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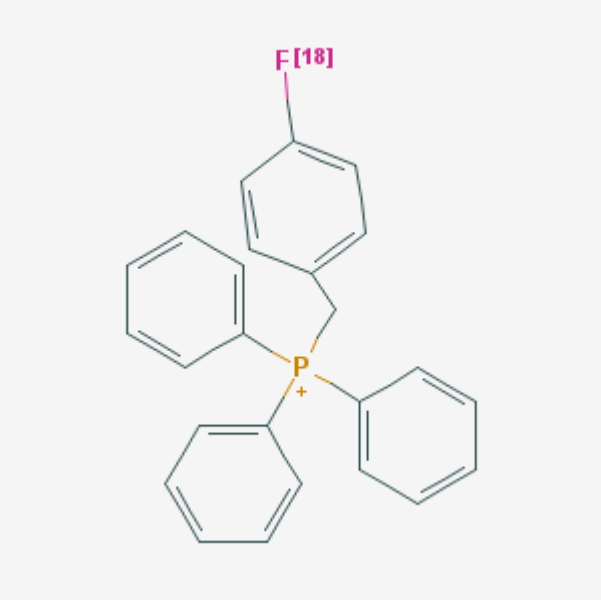
Chemical name:	4-[^{18}F]Fluorobenzyl-triphenylphosphonium
Abbreviated name:	[^{18}F]FBnTP
Synonym:	
Agent Category:	Compound
Target:	Mitochondria
Target Category:	Lipophilic cation, mitochondrial membrane potential
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals



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Background

[PubMed]

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Lipophilic cations are capable of passing through biological membranes by passive diffusion into the cytoplasm and mitochondria of cells in response to large negative plasma and mitochondrial membrane potentials. ^{99m}Tc-2-Methoxyisobutylisonitrile (^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin are delocalized lipophilic cations, which are rapidly taken up into cells driven by metabolic demand and membrane potential (1-4). They are used as myocardial-perfusion single-photon emission computed tomography as well as tumor imaging agents. However, the high accumulation of technetium tracers in the lung and liver may interfere with the detection of flow abnormalities in the myocardium.

Triphenylmethylphosphonium is a lipophilic cation and has been used to measure membrane potentials of cells *in vitro* (5). ^{11}C-Labeled triphenylmethylphosphonium ([^{11}C]TPMP) has been investigated as a positron emission tomography (PET) agent for myocardial and tumor imaging. [^{11}C]TPMP demonstrated rapid clearance from the blood, fast accumulation and prolonged retention in the myocardium, and low lung accumulation in dogs (6). However, the short physical half-life of ^{11}C (20 min) may make [^{11}C]TPMP unsuitable for routine myocardial perfusion imaging in patients. Therefore, 4-[^{18}F]fluorobenzyl-triphenylphosphonium ([^{18}F]FBnTP) (^{18}F has a physical half-life of 110 min) has been investigated as a PET agent for myocardial imaging to provide a better assessment of flow abnormalities in the myocardium. [^{18}F]FBnTP may also be a tool for detection of physiological and pathological processes associated with mitochondrial dysfunction.

Synthesis

[PubMed]

[^{18}F]FBnTP was prepared as described by Madar et al. (7). [^{18}F]Fluoride/Kryptofix 2.2.2/K_2CO_3 and 4-trimethylammoniumbenzaldehyde trifluoromethanesulfonate were heated and then eluted through a reverse solid-phase extraction cartridge and a column containing sodium borohydride and potassium carbonate. This procedure yielded 4-[^{18}F]-fluorobenzyl alcohol, which was reacted with triphenylphosphine dibromide to produce [^{18}F]FBnTP-bromide. Average radiochemical yield (n = 20) was 6% with a total synthesis time of 82 min. Radiochemical purity was >99% with an average specific activity of 16.7 GBq/μmol (451 mCi/μmol) at the end of synthesis.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Isolated canine heart cells (i.e., myocytes) accumulated [^{18}F]FBnTP rapidly, with 30% of total radioactivity at 5 min and 40% at 15 min reaching a plateau (~45%) at 30–120 min (7). Resuspension of the myocytes in isotope-free incubation medium showed that cell-bound radioactivity was 88% and 85% of control radioactivity at 60 and 120 min, respectively. Hence, [^{18}F]FBnTP was mostly retained by the myocytes with slight washout.

Madar et al. (8) demonstrated that [^{18}F]FBnTP and ^{3}H-labeled tetraphenylphosphonium ([^{3}H]TPP) exhibited similar uptake kinetics and plateau concentrations in H345 human lung carcinoma cells. Stepwise membrane depolarization induced by increasing potassium ion concentrations resulted in a linear decrease in [^{18}F]FBnTP cellular uptake similar to those measured for [^{3}H]TPP. Selective collapse of mitochondrial membrane potential by carbonyl cyanide *m*-chlorophenylhydrazone (uncoupler) and proapoptotic staurosporine (known to decrease membrane potential) caused a marked decrease (69–85%) in cellular uptake for [^{18}F]FBnTP and [^{3}H]TPP compared with control. [^{18}F]FBnTP is a mitochondria-targeting PET radiopharmaceutical responsive to alterations in membrane potential with voltage-dependent performance similar to that of [^{3}H]TPP.

Animal Studies

Rodents

[PubMed]

Madar et al. (7) determined accumulation of [^{18}F]FBnTP in the femur bone of CD1 mice to be 1.38% injected dose (ID) as compared with free [^{18}F]fluoride (15.3% ID). The extent of defluorination of [^{18}F]FBnTP was relatively low. Further biodistribution studies in CD1 mice showed that [^{18}F]FBnTP accumulated mainly in the kidney (24.7% ID/g), heart (12.2% ID/g), and liver (8.1% ID/g) with low blood radioactivity (0.05% ID/g) at 60 min after injection (8). PET imaging showed that [^{18}F]FBnTP accumulated mainly in the kidney, followed by the heart and liver, with low accumulation in the lung.

Other Non-Primate Mammals

[PubMed]

Madar et al. (7) performed quantitative PET imaging measurements of [^{18}F]FBnTP binding in the heart of four mongrel dogs injected intravenously with 126–240 MBq (3.4–6.5 mCi) of [^{18}F]FBnTP. PET scans showed distinct accumulation of [^{18}F]FBnTP in the myocardium, which reached a plateau within 5 min and was retained up to 90 min. In contrast, the radioactivity of the blood pool in the left ventricular (LV) chamber was only 26.2% of the LV wall at 5 min and 13.4% of the LV wall at 10 min. [^{18}F]FBnTP was uniformly distributed throughout the myocardium with 6–8% distribution covariance. The LV wall/blood, LV wall/lung, and LV wall/liver ratios were 16.6, 12.2, and 1.2 at 60 min, respectively. [^{18}F]FBnTP whole-body distribution showed the highest accumulation in the kidney cortex, followed by the gall bladder, LV wall, and liver. Low accumulation was observed in the bone, spleen, and lung. The fraction of unchanged [^{18}F]FBnTP in plasma samples as determined by high-performance liquid chromatography was 95% at 5 min and 75% at 30 min after injection.

Madar et al. (9) performed dynamic PET imaging and *ex vivo* biodistribution studies of [^{18}F]FBnTP myocardial uptake in dogs (n = 17) with various degrees of stenosis of the left anterior descending or circumflex coronary arteries during adenosine vasodilation. The

quantitative assessment of the perfusion defect was significantly ($P < 0.03$) more accurate with [^{18}F]FBnTP than with ^{99m}Tc-tetrofosmin in mild and severe stenosis compared with microsphere flow assessments. The ischemic/nonischemic (IS/NIS) ratio of both tracers correlated linearly with microsphere flow disparity with a similar slope. Flow defect contrast was 2.7 times greater for [^{18}F]FBnTP than for ^{99m}Tc-tetrofosmin. The [^{18}F]FBnTP PET IS/NIS ratio (mild, 0.70 ± 0.04; severe, 0.46 ± 0.02) did not differ significantly ($P > 0.33$) from that measured *ex vivo*.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

U54 HL081028, R21 HL-72185, RO1 HL65455, RO1 AG25017, R24 CA92871

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