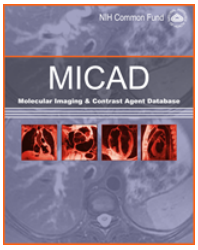
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Leung K. 2-{4-[-Pyridin-4-yl-1-(2-[^{18}F]fluoro-ethyl)-1*H*-pyrazol-3-yl]-phenoxymethyl}-quinoline. 2010 Dec 20 [Updated 2011 Mar 2]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



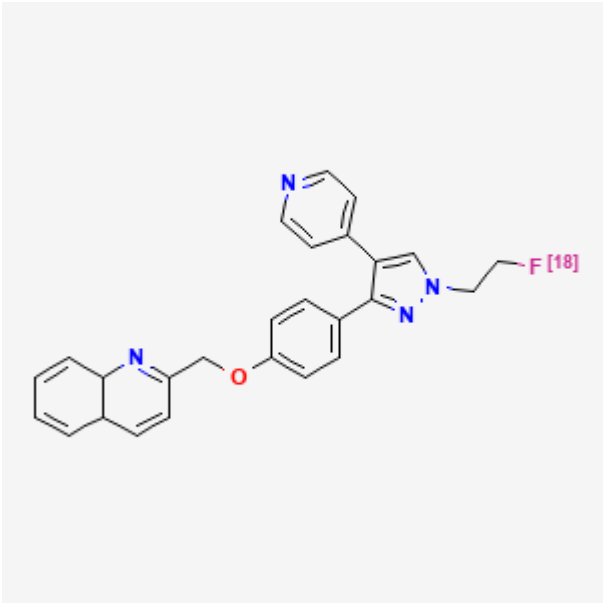
2-{4-[-Pyridin-4-yl-1-(2-[^{18}F]fluoro-ethyl)-1*H*-pyrazol-3-yl]-phenoxymethyl}-quinoline

[^{18}F]JNJ41510417

Kam Leung, PhD[1]

Created: December 20, 2010; Updated: March 2, 2011.

Chemical name:	2-{4-[-Pyridin-4-yl-1-(2-[^{18}F]fluoro-ethyl)-1*H*-pyrazol-3-yl]-phenoxymethyl}-quinoline
Abbreviated name:	[^{18}F]JNJ41510417
Synonym:	
Agent category:	Compound
Target:	Phosphodiesterase type 10A
Target category:	Enzyme binding
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

Phosphodiesterases (PDEs) are composed of at least 11 families of enzymes that hydrolyze cyclic 3′,5′-adenosine monophosphate (cAMP) and/or cyclic 3′,5′-guanosine monophosphate (cGMP) to the corresponding inactive 5′-AMP and 5′-GMP, respectively (1, 2). These second-messenger cyclic nucleotides are formed in response to stimuli (such as hormones, neurotransmitters, and cytokines) to regulate cellular functions. PDEs are essential in the termination of cellular responses *via* their degradation of cyclic nucleotides. PDE type-10A (PDE10A) is a dual-specificity PDE that can act on both cAMP and cGMP (3). PDE10A is found

Author Affiliation: 1 National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

Corresponding author.

mainly in the brain (striatum) and testes, with low concentrations in other tissues (4). PDE10A may play a role in the regulation of glutamatergic and dopaminergic functions in neurons (5, 6). PDE10A inhibitors have been studied in the treatment of neuropsychiatric disorders such as schizophrenia, Huntington's disease, Parkinson's disease, obsessive-compulsive disorder, and addiction (7-11).

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisoquinoline (papaverine) has been found to be a specific inhibitor of PDE10A with 50% inhibition concentration (IC_{50}) values of 36 nM for PDE10A, 1,300 nM for PDE3A, and 320 nM for PDE4D (9). 1-(3-[^{11}C]Methoxy-4-methoxybenzyl)-6,7-dimethoxyisoquinoline ([^{11}C]Papaverine)has been evaluated as a positron emission tomography (12) agent for the non-invasive study of PDE10A in the brain in rats and monkeys (13). However, the results of these studies indicated that the rapid brain clearance of the tracer limits its utility as a PET agent for *in vivo* measurements of PDE10A. In this chapter, 2-{4-[-pyridin-4-yl-1-(2-[^{18}F]fluoro-ethyl)-1*H*-pyrazol-3-yl]-phenoxymethyl}-quinoline ([^{18}F]JNJ4151047) was found to be a selective inhibitor of PED10A (>1,000-fold better selectivity than the other nine PDE subtypes) with an IC_{50} value of 0.5 nM for PDE10A (14). [^{18}F]JNJ4151047 has been evaluated in rats and PED10A-knockout mice for *in vivo* brain imaging of PED10A activity.

Related Resource Links:

- Chapters in MICAD (PDE)
- Gene information in NCBI (PDE10A)
- Articles in Online Mendelian Inheritance in Man (OMIM) (PDE10A)

Synthesis

[PubMed]

The synthesis of [^{18}F]JNJ4151047 was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{nat}F]JNJ4151047 was found to be a selective inhibitor of PED10A (>1,000-fold greater inhibition than PDE1B1, PDE2A, PDE3A, PDE4D3, PDE5A3, PDE6, PDE7A, PDE8A1, and PDE9A) with an IC_{50} value of 0.5 nM for rat PDE10A (14). [^{nat}F]JNJ4151047 exhibited a measured log $D_{7.4}$ lipophilicity value of 4.7.

Animal Studies

Rodents

[PubMed]

Ex vivo biodistribution studies in normal rats (n = 3/group) showed high initial accumulation of radioactivity in the liver at 2 min after injection of [^{18}F]JNJ4151047 (41.1% injected dose (ID)/g), followed by the intestines (9.4% ID/g), kidney (6.9% ID/g), and lung (2.4% ID/g) (14). [^{18}F]JNJ4151047 accumulation in the brain was 0.447% ID/g at 5 min, 0.266% ID/g at 30 min, and 0.257% ID/g at 60 min after injection. Radioactivity in the liver, stomach, and intestines increased in the later time points, whereas other tissues showed rapid washout. The regional brain accumulation at 60 min after injection was highest in the striatum (2.6% ID/g) and lowest in the cerebellum (0.4% ID/g), as predicted by the density of PDE10A enzymes. The blood concentration was 0.3% ID/g. There was ~73% of intact [^{18}F]JNJ4151047 in the plasma at 60 min after injection, with one major radioactive hydrophilic metabolite. In the brain, 95% of [^{18}F]JNJ4151047 was intact at 30 min after injection. No blocking studies were performed.

Celen et al. (14) performed dynamic PET studies of the brain in normal rats with high radioactivity in the striatum and only background radioactivity in the cortex and cerebellum at 20–60 min after injection of [^{18}F]JNJ4151047. A maximum striatum/cerebellum ratio of 2.9 was observed at 32 min after injection. Pretreatment (60 min) with PED10A inhibitors (TP-10 and MP-10, 5 mg/kg) or JNJ4151047 (2.5 mg/kg) reduced the striatum/cerebellum ratio to <1.4. A displacement study with MP-10 (3 mg/kg) at 32 min after [^{18}F]JNJ4151047 injection reduced the striatum/cerebellum ratio to 1.0 at 60 min after injection. Imaging studies in PDE10A-knockout and wild-type mice exhibited a high uptake in the striatum of the wild-type mice but not in the knockout mice. *Ex vivo* autoradiography of brain sections showed that the radioactivity in the striatum of the wild-type mice at 75 min after injection was 22.5-fold higher than that in the striatum of the knockout mice at the same time point. Hence, there was specific accumulation of [^{18}F]JNJ4151047 in the striatum.

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.

References

1. Sutherland E.W., Rall T.W. *Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles.* . J Biol Chem. 1958;232(2):1077–91. PubMed PMID: 13549488.
2. Essayan D.M. *Cyclic nucleotide phosphodiesterases.* . J Allergy Clin Immunol. 2001;108(5):671–80. PubMed PMID: 11692087.
3. Fujishige K., Kotera J., Michibata H., Yuasa K., Takebayashi S., Okumura K., Omori K. *Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A).* . J Biol Chem. 1999;274(26):18438–45. PubMed PMID: 10373451.
4. Fujishige K., Kotera J., Omori K. *Striatum- and testis-specific phosphodiesterase PDE10A isolation and characterization of a rat PDE10A.* . Eur J Biochem. 1999;266(3):1118–27. PubMed PMID: 10583409.
5. Nishi A., Kuroiwa M., Shuto T. *Role of phosphodiesterases in dopamine signal transduction.* . Nippon Yakurigaku Zasshi. 2010;135(1):8–13. PubMed PMID: 20075564.
6. Xie Z., Adamowicz W.O., Eldred W.D., Jakowski A.B., Kleiman R.J., Morton D.G., Stephenson D.T., Strick C.A., Williams R.D., Menniti F.S. *Cellular and subcellular localization of PDE10A, a striatum-enriched phosphodiesterase.* . Neuroscience. 2006;139(2):597–607. PubMed PMID: 16483723.
7. Kehler J., Kilburn J.P. *Patented PDE10A inhibitors: novel compounds since 2007.* . Expert Opin Ther Pat. 2009;19(12):1715–25. PubMed PMID: 19939189.
8. Chappie T., Humphrey J., Menniti F., Schmidt C. *PDE10A inhibitors: an assessment of the current CNS drug discovery landscape.* . Curr Opin Drug Discov Devel. 2009;12(4):458–67. PubMed PMID: 19562642.
9. Siuciak J.A. *The role of phosphodiesterases in schizophrenia : therapeutic implications.* . CNS Drugs. 2008;22(12):983–93. PubMed PMID: 18998737.

10. Menniti F.S., Chappie T.A., Humphrey J.M., Schmidt C.J. *Phosphodiesterase 10A inhibitors: a novel approach to the treatment of the symptoms of schizophrenia.* . Curr Opin Investig Drugs. 2007;8(1):54–9. PubMed PMID: 17263185.
11. Hebb A.L., Robertson H.A. *Role of phosphodiesterases in neurological and psychiatric disease.* . Curr Opin Pharmacol. 2007;7(1):86–92. PubMed PMID: 17113826.
12. Akerman M.E., Pilch J., Peters D., Ruoslahti E. *Angiostatic peptides use plasma fibronectin to home to angiogenic vasculature.* . Proc Natl Acad Sci U S A. 2005;102(6):2040–5. PubMed PMID: 15687502.
13. Tu Z., Xu J., Jones L.A., Li S., Mach R.H. *Carbon-11 labeled papaverine as a PET tracer for imaging PDE10A: radiosynthesis, in vitro and in vivo evaluation.* . Nucl Med Biol. 2010;37(4):509–16. PubMed PMID: 20447563.
14. Celen S., Koole M., De Angelis M., Sannen I., Chitneni S.K., Alcazar J., Dedeurwaerdere S., Moechars D., Schmidt M., Verbruggen A., Langlois X., Van Laere K., Andres J.I., Bormans G. *Preclinical evaluation of 18F-JNJ41510417 as a radioligand for PET imaging of phosphodiesterase-10A in the brain.* . J Nucl Med. 2010;51(10):1584–91. PubMed PMID: 20847170.