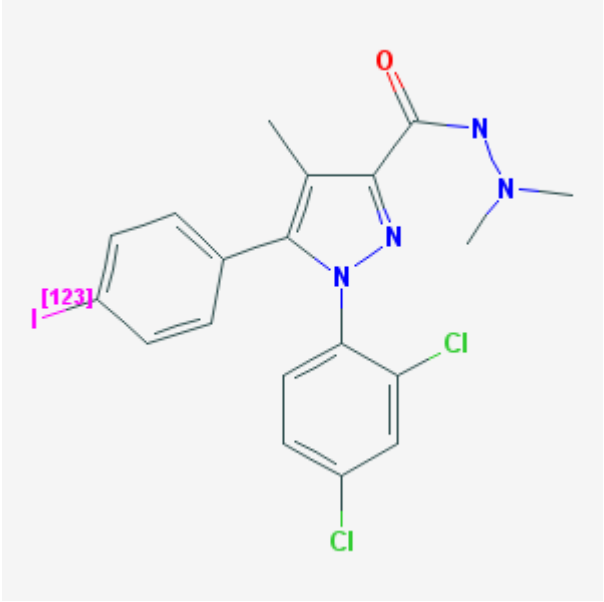
1-(2,4-Dichlorophenyl)-5-(4-[^{123}I]iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *N*',*N*'-dimethyl-hydrazide

[^{123}I]Me$_2$Pyr

Kam Leung, PhD[1]

Created: March 5, 2007; Updated: March 13, 2007.

Chemical name:	1-(2,4-Dichlorophenyl)-5-(4-[^{123}I]iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *N*',*N*'-dimethyl-hydrazide
Abbreviated name:	[^{123}I]Me$_2$Pyr
Synonym:	
Agent category:	Compound
Target:	Cannabinoid CB1 receptors
Target category:	Receptor
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging
Source of signal:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

[1] National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

Background

[PubMed]

There are two subtypes of cannabinoid receptors in mammalian tissues: CB1 and CB2 (1, 2). CB1 receptors are expressed abundantly in neuronal terminals in the central nervous system (CNS) and some peripheral tissues to inhibit neurotransmitter release. CB1 receptors are found predominantly in the striatum, hippocampus, substantia nigra, globus pallidus, and cerebellum. The CB2 receptors are present mainly on immune cells to modulate cytokine release. Both receptor subtypes are coupled through $G_{i/o}$ proteins to inhibit adenylate cyclase and to modulate potassium and calcium channels. CB1 receptors have been demonstrated to be involved in analgesia, regulation of food intake, and control of movement in normal subjects (3). Alteration of CB1 receptor function has been implicated in a number of human diseases such as depression, schizophrenia, and obesity (4-6).

Δ9-Tetrahydrocannabinol (THC) is a major active cannabinoid that is found in marijuana and activates CB1 receptors (7). THC has a very high lipophilicity (log $D_{7.4}$ value of 7), which causes imaging studies using radiolabeled THC to be unsuccessful because of slow entry into the brain and high nonspecific binding in the brain. However, a high lipophilicity is essential for binding to CB1 receptors, and an optimal lipophilicity (log $D_{7.4}$ 1–4) is required for crossing the blood–brain barrier (BBB). Existing radiolabeled ligands are mainly analogs of the antagonist rimonabant (SR141716A) and the agonist WIN 55,212-2, which also exhibit high nonspecific binding and lipophilicity, limiting their application in imaging (8). Therefore, there is a need to lower the lipophilicity of the CB1 radioligands with little effect on binding affinity and ability to cross the BBB. 1-(2,4-Dichlorophenyl)-5-(4-[^{123}I]iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *N*',*N*'-dimethyl-hydrazide ([^{123}I]Me_2Pyr) is a CB1 analog of *N*-(morpholin-4-yl)-5-(4-[^{123}I]iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide ([^{123}I]AM281) with the *N*-heterocyclic residue substituted by a dimethylamino group (9). [^{123}I]Me_2Pyr is being developed as a single-photon emission computed tomography (SPECT) agent for the non-invasive study of CB1 receptors in the brain.

Related Resource Links:

- Chapters in MICAD (CB1 receptors)
- Gene information in NCBI (CB1 receptors)
- Articles in Online Mendelian Inheritance in Man (OMIM) (CB1 receptors)

NLM Citation: Leung K. 1-(2,4-Dichlorophenyl)-5-(4-[^{123}I]iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid *N*',*N*'-dimethyl-hydrazide. 2007 Mar 5 [Updated 2007 Mar 13]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

- Clinical trials (CB1 receptors)

Synthesis

[PubMed]

Gielow et al. (9) reported synthesis of [^{123}I]Me_2Pyr by radioiododestannylation reaction of the tributyltin precursor with [^{123}I]iodide in the presence of HCl and chloramine-T. Radiochemical yields were 48% after high-performance liquid chromatography purification. Specific activities were >75 GBq/μmol (>2 Ci/μmol) with a radiochemical purity of >92%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Gielow et al. (9) reported that the lipophilicity values were 3.7 for AM281, 4.5 for Me_2Pyr, and 4.8 for SR141716A.

Animal Studies

Rodents

[PubMed]

Ex vivo autoradiography of rat brain showed the highest radioactivity in the substantia nigra, globus pallidus, and cerebellum at 120 min after injection of [^{125}I]AM281 (n = 3) or [^{125}I]Me_2Pyr (n = 2), which is consistent with the CB1 distribution in the brain (9). Ratios of [^{125}I]AM281 in the substantia nigra/frontal cortex, globus pallidus/frontal cortex, and cerebellum/frontal cortex were 1.72, 1.68, and 1.30, respectively; ratios of [^{125}I]Me_2Pyr in the substantia nigra/frontal cortex, globus pallidus/frontal cortex, and cerebellum/frontal cortex were 1.89, 1.67, and 1.46, respectively. However, these ratios were not different between the two compounds.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Human Studies

[PubMed]

References

1. Howlett A.C., Barth F., Bonner T.I., Cabral G., Casellas P., Devane W.A., Felder C.C., Herkenham M., Mackie K., Martin B.R., Mechoulam R., Pertwee R.G. *International Union of Pharmacology. XXVII. Classification of cannabinoid receptors.* Pharmacol Rev. 2002;54(2):161–202. PubMed PMID: 12037135.
2. Pertwee R.G. *Pharmacology of cannabinoid CB1 and CB2 receptors.* Pharmacol Ther. 1997;74(2):129–80. PubMed PMID: 9336020.
3. Pertwee, R.G., *Pharmacological actions of cannabinoids.* Handb Exp Pharmacol, 2005(168): p. 1-51.
4. Gambi F., De Berardis D., Sepede G., Quartesan R., Calcagni E., Salerno R.M., Conti C.M., Ferro F.M. *Cannabinoid receptors and their relationships with neuropsychiatric disorders.* Int J Immunopathol Pharmacol. 2005;18(1):15–9. PubMed PMID: 15698507.
5. De Vries T.J., Schoffelmeer A.N. *Cannabinoid CB1 receptors control conditioned drug seeking.* Trends Pharmacol Sci. 2005;26(8):420–6. PubMed PMID: 15992935.
6. Guzman M., Sanchez C. *Effects of cannabinoids on energy metabolism.* Life Sci. 1999;65(6-7):657–64. PubMed PMID: 10462066.
7. Martin B.R. *Cellular effects of cannabinoids.* Pharmacol Rev. 1986;38(1):45–74. PubMed PMID: 2872689.
8. Gifford A.N., Makriyannis A., Volkow N.D., Gatley S.J. *In vivo imaging of the brain cannabinoid receptor.* Chem Phys Lipids. 2002;121(1-2):65–72. PubMed PMID: 12505691.
9. Gielow P., Klinge P., Knapp W.H., Berding G. *Synthesis and preliminary biological evaluation of [123I]Me2Pyr, a new potential ligand for imaging of central cannabinoid CB1 receptors.* Appl Radiat Isot. 2006;64(7):763–8. PubMed PMID: 16554168.