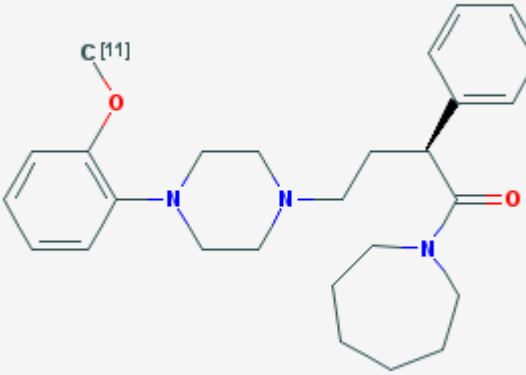
(R)-2,3,4,5,6,7-Hexahydro-1-[4-[1-[4-(2-[^{11}C]methoxyphenyl)piperazinyl]]-2-phenylbutyryl]-1*H*-azepine

(*R*)-[^{11}C]RWAY

Kam Leung, PhD[1]

Created: September 2, 2007; Updated: October 22, 2007.

Chemical name:	*(R)*-2,3,4,5,6,7-Hexahydro-1-[4-[1-[4-(2-[^{11}C]methoxyphenyl)piperazinyl]]-2-phenylbutyryl]-1*H*-azepine
Abbreviated name:	(*R*)-[^{11}C]RWAY, [^{11}C]RWAY
Synonym:	
Agent category:	Compound
Target:	5-HT$_{1A}$ serotonin receptor
Target category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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.

NLM Citation: Leung K. *(R)*-2,3,4,5,6,7-Hexahydro-1-[4-[1-[4-(2-[^{11}C]methoxyphenyl)piperazinyl]]-2-phenylbutyryl]-1*H*-azepine. 2007 Sep 2 [Updated 2007 Oct 22]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

Background

[P ubMed]

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiologic roles as a neurotransmitter in the central nervous system (1). 5-HT is involved in regulation and modulation of sleep, affective and personality behaviors, and pain. It also is a regulator of smooth muscle function and platelet aggregation. The brain cortical 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, schizophrenia, and obsessive-compulsive disorder (2, 3). The effects of 5-HT are mediated by as many as seven classes of receptor populations (5-HT_1 to 5-HT_7), many of which include several subtypes (4). There are five receptor subtypes within the G protein–coupled 5-HT_1 receptor family: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}.

5-HT_{1A} receptors are abundantly present in the hippocampus, entorhinal cortex, frontal cortex, raphe nucleus, and septum, and the lowest densities are observed in the basal ganglia, substantia nigra, and cerebellum (5). Some thalamic and hypothalamic nuclei have intermediate densities. 5-HT_{1A} receptors are involved in the mediation of emotion and the function of the hypothalamus. 5-HT_{1A} receptors are implicated in anxiety, depression, hallucinogenic behavior, motion sickness, and eating disorders (6). Thus, there is a need for selective ligands to investigate the pharmacologic role of 5-HT_{1A} receptors.

There have been several studies to develop specific 5-HT_{1A} radioligands [PubMed] for positron emission tomography (PET) imaging, such as [*carbonyl*-^{11}C]WAY 100635, [^{18}F]FPWAY, and [^{18}F]MPPF. However, some of these compounds lack resistance to *in vivo* metabolism (7), which may cause difficulties in using the reference region method for determination of 5-HT_{1A} receptor densities in the brain. *(R)*-2,3,4,5,6,7-Hexahydro-1-[4-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylbutyryl]-1*H*-azepine (RWAY) is structurally similar to WAY100635 with the direction of its amide group reversed, which might be less susceptible to amide hydrolysis in vivo. RWAY was reported to be a potent antagonist of 5-HT_{1A} receptors (K_i = 0.6 nM) (8). This led to the development of *(R)*-2,3,4,5,6,7-Hexahydro-1-[4-[1-[4-(2-[^{11}C]methoxyphenyl)piperazinyl]]-2-phenylbutyryl]-1*H*-azepine ([^{11}C]RWAY) as a useful tool for in vivo PET imaging of the 5-HT_{1A} receptor. However, a relatively slow washout of radioactivity from the human brain likely reflects the accumulation of radiometabolite(s) in human brain (9). Therefore, the use of [^{11}C]RWAY has been discontinued in humans.

Related Resource Links:

- Chapters in MICAD (5-HT_{1A})
- Gene information in NCBI (5-HT_{1A})
- Articles in Online Mendelian Inheritance in Man (OMIM) (5-HT_{1A})
- Clinical trials (5-HT_{1A})
- Drug information in Food and Drug Administration (5-HT_{1A})

Synthesis

[PubMed]

The radiosynthesis of [^{11}C]RWAY reported by McCarron et al. (8) involved standard ^{11}C-methylation of the corresponding desmethyl precursor (R)-2,3,4,5,6,7-hexahydro-1{4-[1[4-(2-hydroxyphenyl)-piperazinyl]]-2-phenylbutyryl}-1*H*-azepine with [^{11}C]CH_3I in DMF in the presence of tetrabutylammonium hydroxide at room temperature for 5 min. The reported overall radiochemical yield of the radiosynthesis from [^{11}C]CO_2 production was 33% at the end of synthesis (EOS), the specific radioactivity was 118 TBq/mmol (3,180 Ci/mmol), and the radiochemical purity was >99%. The total synthesis time was 35 min at EOS.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro competition binding studies in cloned human 5-HT_{1A} receptors. (R)-RWAY had a binding affinity value (K_i) of 0.60-1.88 nM (8). The Ki values were 7.2 nM for 5-HT2B, 9.5 nM for 5-HT1D and >65 nM for the remaining 5-HT subtypes. The affinity of RWAY for various biogenic amines, brain receptors, and transporters was determined to be 9-16 times lower than that of (R)-RWAY. There was a measurable free fraction of [^{11}C]RWAY (2.9 ± 0.8%) in monkey plasma after 5 min incubation and 20 min centrifugation at room temperature.

Animal Studies

Rodents

[PubMed]

Using small animal positron emission tomography (PET), Liow et al. (10) investigated rodent brain uptake of [^{11}C]RWAY in control and cyclosporine A (CsA)-treated rats as well as P-glycoprotein (P-gp) knockout and wild type mice. [^{11}C]RWAY and its radiometabolite in plasma and brain samples were determined at 30 min after injection. Regional brain binding potential (BP) values were calculated with a reference tissue (cerebellum) model. P-gp knockout mice had 2.5- and 2.8-fold greater brain accumulation of [^{11}C]RWAY than wild type ones as measured by in vivo PET and *ex vivo* tissue sampling, respectively. Similarly, CsA increased rat brain accumulation 4.9- and 5.3-fold, *in vivo* PET and *ex vivo*. In addition, CsA increased the plasma free fraction of [^{11}C]RWAY in rats by 2.7-fold. Although CsA increased brain accumulation in wild type mice by 2.5-fold, it had no effect on plasma free fraction in knockout animals. Three radiometabolites [^{11}C]RWAY were uniformly distributed in rat brain, suggesting they were inactive. CsA treatment increased brain accumulation of [^{11}C]RWAY and only one of its radiometabolites. Regional rat brain BP increased 27-70% in the CsA-treated rats and the P-gp knockout mice. [^{11}C]RWAY is a P-gp substrate in rat and mouse. The effects

of CsA in rats are mediated by both P-gp blockade and displacement of the radiotracer from plasma proteins.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET imaging was studied by McCarron et al. (8) in the brain of rhesus monkeys after intravenous injection of 196-218 MBq (5.29-5.90 mCi) of [^{11}C]RWAY. Various brain regions exhibited rapid accumulation in 5-18 min with gradual decreases thereafter. [^{11}C]RWAY PET images (up to 120 min after injection) displayed radioactivity concentrations that followed a rank order (tissue/cerebellum ratio): cingulate gyrus (6.4), frontal cortex (4.1), temporal cortex (3.8), raphe nucleus (2.1), and cerebellum (1.0) at 87.5 min. Pretreatment with WAY-100635 (antagonist, 0.5 mg/kg) 15 min prior to the injection of [^{11}C]RWAY markedly reduced the radioactivity in the regions of interest to homogeneity at 15 min after tracer injection. Injection of WAY-100635 at 40 min after injection of [^{11}C]RWAY immediately decreased the radioactivity levels in 5-HT1A receptor-rich regions. After injection of [^{11}C]RWAY, 81.0 ± 4.3% and 14.0 ± 1.5% of the total plasma radioactivity was intact at 5 and 60 min, respectively. Three more hydrophilic metabolites were detected. Yasuno et al. (11) used mathematical modeling to show that the estimated values of regional BP were correlated strongly (r = 0.93-0.97) between two-tissue compartment model and multilinear reference tissue model with cerebellum as a reference region. The BP values of dorsal raphe nucleus, prefrontal cortex, and medial temporal region were 0.77-0.87, 1.45-1.57, and 1.68-1.79, respectively.

Human Studies

[PubMed]

Zhang et al. (9) studied [^{11}C]RWAY PET in six healthy human subjects, using kinetic brain imaging and serial arterial measurements of plasma parent radiotracer. Brain receptor-rich regions/cerebellum ratios were ~3 at 80 min after injection. However, the washout from brain was unexpectedly slow relative to plasma clearance of the parent radiotracer. In both receptor-rich regions and cerebellum, distribution volumes were unstable and increased continuously from 90 to 150 min by about 30%. When the metabolites of [^{11}C]RWAY in human and monkey were compared, a moderate lipophilic radiometabolite was present at a significantly higher percentage of total plasma radioactivity in humans (20.6%) than in monkeys (3.2%). The relatively slow washout of activity from brain and the temporal instability of distribution volume likely reflect the

accumulation of radiometabolite(s) in human brain. Therefore, the use of [^{11}C]RWAY has been discontinued in humans.

Supplemental Information

[Disclaimers]

Synthesis Protocol

Toxicology

Preclinical Pharmacology

Animal Dosimetry

NIH Support

Intramural Research Program

References

1. Lucki I. *The spectrum of behaviors influenced by serotonin.* Biol Psychiatry. 1998;44(3): 151–62. PubMed PMID: 9693387.
2. Fletcher A., Cliffe I.A., Dourish C.T. *Silent 5-HT1A receptor antagonists: utility as research tools and therapeutic agents.* Trends Pharmacol Sci. 1993;14(12):41–8. PubMed PMID: 8122313.
3. Hoyer D., Clarke D.E., Fozard J.R., Hartig P.R., Martin G.R., Mylecharane E.J., Saxena P.R., Humphrey P.P. *International Union of Pharmacology classification of receptors for 5-hydroxytryptamine (Serotonin).* Pharmacol Rev. 1994;46(2):157–203. PubMed PMID: 7938165.
4. Lanfumey L., Hamon M. *5-HT1 receptors.* Curr Drug Targets CNS Neurol Disord. 2004;3(1):1–10. PubMed PMID: 14965240.
5. Pazos A., Probst A., Palacios J.M. *Serotonin receptors in the human brain--III. Autoradiographic mapping of serotonin-1 receptors.* Neuroscience. 1987;21(1):97–122. PubMed PMID: 2955249.
6. Cowen P.J. *Psychopharmacology of 5-HT(1A) receptors.* Nucl Med Biol. 2000;27(5): 437–9. PubMed PMID: 10962247.
7. Slifstein M., Parsey R.V., Laruelle M. *Derivation of [(11)C]WAY-100635 binding parameters with reference tissue models: effect of violations of model assumptions.* Nucl Med Biol. 2000;27(5):487–92. PubMed PMID: 10962256.
8. McCarron, J.A., S.S. Zoghbi, H.U. Shetty, E.S. Vermeulen, H.V. Wikstrom, M. Ichise, F. Yasuno, C. Halldin, R.B. Innis, and V.W. Pike, *Synthesis and initial evaluation of [(11)C](R)-RWAY in monkey-a new, simply labeled antagonist radioligand for imaging brain 5-HT(1A) receptors with PET.* Eur J Nucl Med Mol Imaging, 2007
9. Zhang X.Y., Yasuno F., Zoghbi S.S., Liow J.S., Hong J., McCarron J.A., Pike V.W., Innis R.B. *Quantification of serotonin 5-HT1A receptors in humans with [11C](R)-(-)-*

RWAY: radiometabolite(s) likely confound brain measurements. Synapse. 2007;61(7): 469–77. PubMed PMID: 17415792.

10. Liow J.S., Lu S., McCarron J.A., Hong J., Musachio J.L., Pike V.W., Innis R.B., Zoghbi S.S. *Effect of a P-glycoprotein inhibitor, Cyclosporin A, on the disposition in rodent brain and blood of the 5-HT1A receptor radioligand, [11C](R)-(-)-RWAY.* Synapse. 2007;61(2):96–105. PubMed PMID: 17117422.
11. Yasuno F., Zoghbi S.S., McCarron J.A., Hong J., Ichise M., Brown A.K., Gladding R.L., Bacher J.D., Pike V.W., Innis R.B. *Quantification of serotonin 5-HT1A receptors in monkey brain with [11C](R)-(-)-RWAY.* Synapse. 2006;60(7):510–20. PubMed PMID: 16952161.