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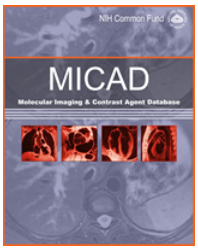

[*carbonyl*-^{11}C](*R,S*)-(*N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)(2-methylethyl)))-*N*-pyridinyl)cyclohexanecarboxamide

[*carbonyl*-^{11}C](*R,S*)-JWAY

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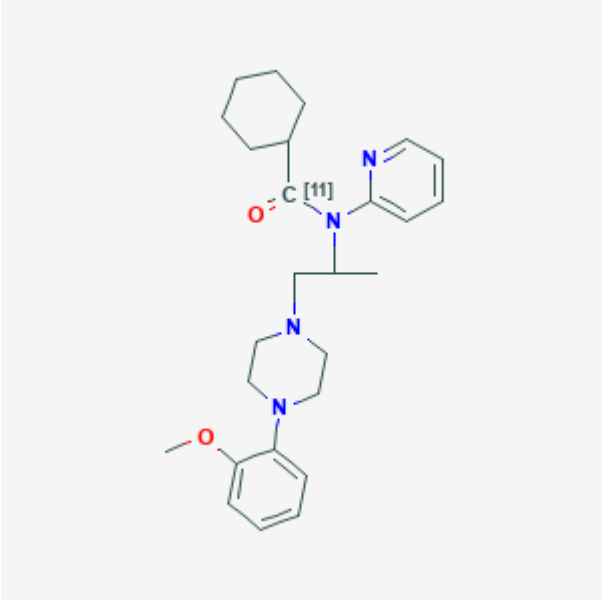
Chemical name:	[*carbonyl*-^{11}C](*R,S*)-(*N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)(2-methylethyl)))-*N*-pyridinyl)cyclohexane-carboxamide
Abbreviated name:	[*carbonyl*-^{11}C](*R,S*)-JWAY
Synonym:	[^{11}C]JWAY, {^{11}C](*R,S*)-JWAY
Agent Category:	Compound
Target:	5-HT$_{1A}$ receptors
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



Click on the above structure for additional information in PubChem.

Background

[PubMed]

[*carbonyl*-^{11}C](*R,S*)-(*N*-(2-(1-(4-(2-Methoxyphenyl)piperazinyl)(2-methylethyl)))-*N*-pyridinyl)cyclohexanecarboxamide ([*carbonyl*-^{11}C](*R,S*)-JWAY) is a radioligand developed for positron emission tomography (PET) imaging of serotonin-1A (5-HT$_{1A}$) receptors in the central nervous system (1). It is a selective 5-HT$_{1A}$ antagonist labeled with ^{11}C, a positron emitter with a physical $t_{½}$ of 20.4 min (2).

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The serotonin (5-hydroxytryptamine (5-HT)) neurotransmission system comprises mainly neurons in the brainstem, with nerve tracts extending from these neurons to many areas of the brain and spinal cord (3). When neurons fire, they release 5-HT, a neurotransmitter that is involved in the modulation of various important physiologic functions and behavior, such as thermoregulation, cardiovascular function, aggressive and sexual behavior, mood, appetite, and the sleep–wake cycle (4). 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 also contain several subtypes (5). There are five receptor subtypes within the G protein-coupled 5-HT_1 receptor family, with the 5-HT_{1A} subtype located primarily in the limbic forebrain (the hippocampus, entorhinal cortex ,septum, and raphe) (4, 5). 5-HT_{1A} receptors appear to function both as presynaptic (somatodendritic) autoreceptors in the raphe nuclei and as postsynaptic receptors in the terminal fields. This receptor subtype is involved in the modulation of emotion and the function of the hypothalamus, and is implicated in the pathogenesis of anxiety, depression, hallucinogenic behavior, motion sickness, dementia, schizophrenia, and eating disorders (6). A radioligand that can be used to assess the *in vivo* densities of 5-HT_{1A} receptors and their changes may facilitate investigation of the relationship of these receptors to various neuropsychiatric diseases and aid in the design of novel drugs for their treatment.

Many psychiatric drugs modulate serotonergic transmission or specifically target the 5-HT_{1A} receptors (2). Various compounds have been radiolabeled for visualization and quantification of these receptors (7). WAY 100635 was developed as a highly selective, silent antagonist (possessing no intrinsic agonist activity) of 5HT_{1A} receptors at both pre- and postsynaptic sites. WAY 100635 radiolabeled with ^{11}C at the carbonyl position is an effective radioligand but it is rapidly cleared and metabolized. Analogs of WAY100635 bearing bulkier cycloalkylcarbonyl groups appear to be more resistant to amide hydrolysis. However, the added lipophilicity also reduces receptor affinity (8). McCarron et al. (1) proposed adding a smaller group to WAY-100635 for less impact on lipophilicity and receptor affinity. They synthesized (*R*,*S*)-JWAY by adding a methyl group (α-carbon position to the carbonyl group) on the ethyl side chain of WAY100635. This WAY-100635 analog was radiolabeled with ^{11}C and evaluated with PET in a monkey. The radioligand gave a high 5-HT_{1A} receptor-selective PET signal, but the added methyl group did not appear to have the desired influence on the rate of metabolism.

Synthesis

[PubMed]

.McCarron et al. (1) reported the synthesis of (*R*,*S*)-JWAY from commercially available 2-methoxyphenyl piperazine in four steps. 2-Methoxyphenyl piperazine was first reacted with α-chloro-propionyl chloride in anhydrous tetrahydrofuran (THF) and triethylamine at room temperature overnight to give 1-(2-chloro-propionyl)-4-(2-methoxyphenyl)piperazine with a yield of 83%. In the second step, this amide was added to 2-aminopyridine in potassium-t-butoxide and anhydrous N,N-dimethylformamide at room temperature overnight to produce an intermediate compound with a yield of 89%. In the third step, this compound was reacted with lithium aluminum hydride in diethyl ether at room temperature overnight to produce 1-(2-methoxyphenyl)-4-((2-methyl)-2-(2-aminopyridinyl)ethyl)piperazine with a yield of 79%. The final step involved reacting this compound with cyclohexanecarbonyl chloride in THF at room temperature overnight. (*R*,*S*)-JWAY was produced from this final step with a yield of 60%. This compound was used as a precursor for the radiosynthesis of [*carbonyl*-^{11}C](*R*,*S*)-JWAY.

The radiosynthesis method involved acylation of the precursor with [^{11}C]cyclohexanecarbonyl chloride (1). The procedure used immobilized cyclohexylmagnesium chloride as a Grignard reagent in a long polypropylene tube to trap $^{11}CO_2$ and to obtain the desired [*carbonyl*-^{11}C]cyclohexanecarbonyl chloride (by passing thionyl chloride through the tube) (9). The radioligand was separated by high-performance liquid chromatography (HPLC) with 98% decay-corrected radiochemical yields. Radiochemical purity of [*carbonyl*-^{11}C](*R*,*S*)-JWAY

was >99%. The specific activity at the time of injection was 6.99 GBq/μmol (189 Ci/mmol) in the baseline experiments and 8.51 GBq/μmol (230 Ci/mmol) in the pretreatment experiments.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

McCarron et al. (1) computed the *n*-octanol-water partition (logP) and distribution coefficients for all charged and neutral species between octanol and buffer at pH 7.4 (log D) values of (*R*,*S*)-JWAY from drawn molecular structures using a software program. These values were 3.81 and 3.08 for logP and LogD, respectively. In comparison, the calculated values for WAY-100635 were 3.28 and 2.88, respectively. The binding affinity (K_i) value of (*R*,*S*)-JWAY was 0.91 nM based on the inhibition of binding of [^{3}H]5-carboxamidotryptamine to cloned human 5-HT$_{1A}$ receptors *in vitro*. WAY-100635 had a K_i value of 0.37 nM.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

[*carbonyl*-^{11}C](*R*,*S*)-JWAY was evaluated by PET imaging in a male cynomolgus monkey (1). The animal received 54 MBq (1.46 mCi) of (*carbonyl*-^{11}C](*R*,*S*)-JWAY (7.72 nmol, 3.36 μg) by i.v. administration. In the baseline study, in which only the radioligand was injected, radioactivity uptake in the whole brain reached a maximum of 4.8% of the injected dose at 2.5 min and decreased to 1.2% at 90 min. Clearance was more rapid from the cerebellum than from 5-HT$_{1A}$ receptor–rich regions. At 90 min, the ratios of 5-HT$_{1A}$ receptor–rich regions to cerebellum were 2.60 (cingulated cortex), 2.58 (hippocampus), 2.20 (frontal cortex), and 2.15 (temporal cortex), and these ratios were still increasing. When the animal was pretreated with WAY-100635 (0.5 mg/kg), the retention of [*carbonyl*-^{11}C](*R*,*S*)-JWAY radioactivity in 5-HT$_{1A}$ receptor–rich regions was reduced to the same level as in the receptor-devoid cerebellum. The 90-min ratios were reduced to 1.42 (cingulated cortex), 1.27 (hippocampus), 1.22 (frontal cortex), and 1.07 (temporal cortex).

In the metabolite analysis, (*carbonyl*-^{11}C](*R*,*S*)-JWAY radioactivity cleared rapidly from the monkey blood with a $t_{½}$ of 7.8 min, and the radioligand appeared to be rapidly metabolized (1). In both the baseline and pretreatment studies, about 64% and 12% of (*carbonyl*-^{11}C](*R*,*S*)-JWAY remained in the plasma at 4 min and 45 min, respectively. The HPLC analysis of the plasma showed two radioactive metabolites were present, and both of them were more polar than (*carbonyl*-^{11}C](*R*,*S*)-JWAY. This was consistent with amide hydrolysis of (*carbonyl*-^{11}C](*R*,*S*)-JWAY as the primary route of metabolism. In comparison, (*carbonyl*-^{11}C]WAY-100635 was reported to have 69% and 19% of the injected dose in monkey plasma at the same time points (1, 10).

Human Studies

[PubMed]

No publication is currently available.

NIH Support

NIH intramural support.

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