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NLM Citation: Cheng KT. (2*S*,3*S*)-*N*-[[2-[^{11}C]Methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine. 2006 Jul 19 [Updated 2008 Apr 3]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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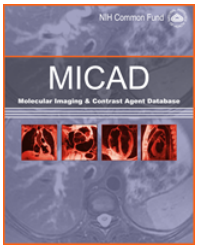

(2*S*,3*S*)-*N*-[[2-[^{11}C]Methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine

[^{11}C]GR205171

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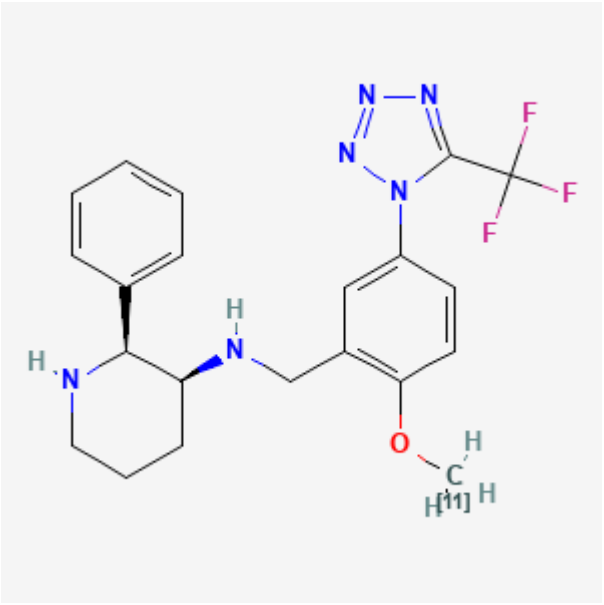
Created: July 19, 2006; Updated: April 3, 2008.

Chemical name:	(2*S*,3*S*)-*N*-[[2-[^{11}C]Methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine
Abbreviated name:	[^{11}C]GR205171
Synonym:	
Agent Category:	Compound
Target:	NK_1 receptor
Target Category:	Receptor binding
Method of detection:	PET
Source of signal/ contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Non-human primates



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Background

[PubMed]

(2*S*,3*S*)-*N*-[[2-[^{11}C]Methoxy-5-[5-(trifluoromethyl)tetrazol-1-yl]phenyl]methyl]-2-phenyl-piperidin-3-amine ([^{11}C]GR205171) is a radioligand developed for positron emission tomography (PET) imaging of NK_1 receptors (substance P (SP) receptors) in the central nervous system (CNS) (1).

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Tachykinins are peptides comprising 10 to12 amino acids that share a common carboxy-terminal sequence "Phe-X-Gly-Leu-Met-amide" where "X" is different but always a hydrophobic residue that is either an aromatic or a beta-branched aliphatic (2-4). This peptide family consists of SP, neurokinin A (NK_A), and neurokinin B (NK_B). The tachykinin peptides mediate their effects by specific G protein-coupled receptors. These receptors are divided into three subtypes: neurokinin 1 (NK_1, formerly the SP receptor), neurokinin 2 (NK_2, formerly the substance K/substance E receptor/NK_A receptor), and neurokinin 3 (NK_3, formerly the NK_B receptor). The effects of SP are mediated primarily *via* the NK_1 receptor subtypes. There is evidence that SP behaves like a neurotransmitter involved in regulation of emotional and behavioral responses to a range of noxious and stressful stimuli (5). SP may also play a role in neurogenic inflammation, vasomotor control, and many gastrointestinal functions. Studies in the brain have shown that in the brain SP is found in the neocortex, in limbic areas, habenula, periaqueductal gray matter, midbrain nuclei, and is especially enriched in the basal ganglia. There is little SP in the cerebellum. The distribution of the NK_1 receptors in the brain generally corresponds to that of SP.

SP-NK_1 receptor pathways are found in both the CNS and the peripheral nervous system. The CNS pathways have been implicated in the pathophysiology of pain, nausea/emesis, and depression disorders (6). PET and single-photon emission tomography of radioligands targeting NK_1 receptors can visualize and allow the study of CNS NK_1 receptors in normal and pathologic states. These studies can identify the degree of receptor occupancy in patients with depression and the change in response to therapy (6). A number of NK_1 selective agonists and antagonists have been successfully labeled, but they failed to provide a specific signal *in vivo* (6, 7). Solin et al. (7) developed a selective NK_1 receptor antagonist, SPA-RQ, with a high affinity for NK_1 receptor. Gardner et al. (8) reported the discovery of a trifluoromethyl compound, GR205171, as a potent NK_1 receptor antagonist. This compound has a high affinity for the human NK1 receptor and has a high degree of selectivity and specificity. ^{11}C-labeled GR205171 shows promising potential to be used as a PET ligand to characterize NK_1-receptor binding (1).

Synthesis

[PubMed]

Ward et al. (9) reported the synthesis of GR203040, a tetrazolyl-substituted analogue of CP-99,994 (10). Gardner et al. (8) prepared GR205171 by trifluoromethyl substitution at the C-1 position of the GR203040 tetrazole moiety. Radiosynthesis of [^{11}C]GR205141 was conducted by dissolving GR205141 in dichloromethane (1). Tetrabutylammonium hydroxide was added, and the mixture was heated and shaken for 2 min. After the solvent was evaporated, the residue was redissolved in *N*,*N*-dimethylformamide. [^{11}C]methyl iodide was trapped in this solution at room temperature. The mixture was then heated at 80°C for 5 min. [^{11}C]GR205141 was obtained and purified by high performance liquid chromatography. The radiochemical yield was 45% based on [^{11}C]methyl iodide with a total synthesis time of 45 min. The radiochemical purity was >98%, and the specific activity was 20-120 GBq/ μmol. (0.54-3.24 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Gardner et al. (8) studied the *in vitro* NK_1 receptor binding affinity of GR205171 in the rat cortex membrane, ferret cortex membrane, and human Chinese hamster ovary (CHO) cells (expressing human recombinant NK_1 receptors). Based on inhibition of ^{3}H labeled SP binding, the pK_i values (n = 4–5) were calculated to be 9.5 ± 0.15, 9.8 ± 0.13, and 10.6 ± 0.22 for the rat cortex membrane, ferret cortex membrane, and human CHO cells, respectively. In comparison, the pK_i values of CP-99,994 and GR203040 for the human NK_1 receptors were 9.6 ± 0.1 (n = 20) and 10.3 ± 0.1 (n = 4–5), respectively.

Animal Studies

Rodents

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

Bergstrom et al. (1) conducted PET imaging of [^{11}C]GR205171 in rhesus monkeys. The monkeys were given either a low i.v. dose (10 MBq (0.27 mCi); $n = 3$) or a high I.v. dose (50 MBq (1.35 mCi); $n = 6$) of [^{11}C]GR205171. The striatum had the highest level of radioactivity in all studies. The standardized uptake value (SUV) of the striatum increased from 2 at 10 min after injection to 2.8 at 50 min. The SUVs of other grey matter regions remained constant at 2. The SUV of cerebellum decreased with time. With pretreatment of the monkeys with unlabeled GR205171 (0.05 mg/kg – 1 mg/kg; $n = 8$) 5 min before [^{11}C]GR205171 administration, the striatum could not be visually identified, and the SUV decreased from the initial 2.3 to approximately1.7 at 50 min. For the linear graphs generated from the Patlak graphical method using the cerebellum as the reference tissue without GR205171 treatment, the highest slope values were found for the striatum and the lowest slope values were in the white matter. The absence of a plateau in these graphs indicated that there was a very slow dissociation of the ligand from the receptor. There was a significant decrease in the slope values of all regions after pretreatment with GR205171. The decrease in the slope values was >80% at all doses of GR205171. The plasma radioactivity level decreased rapidly and reached a plateau at SUV 0.5 after 10 min without GR205171 pretreatment. With GR20517 pretreatment, the plasma radioactivity level increased by 50%.

Human Studies

[PubMed]

No publication is currently available.

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