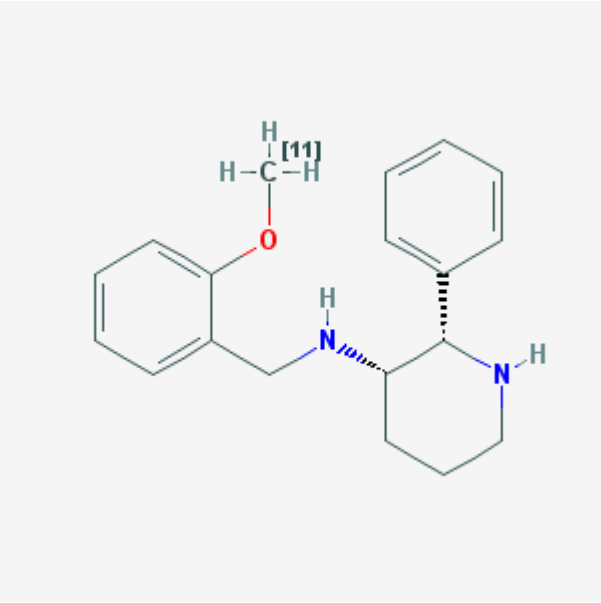
(+)-(2*S*,3*S*)-3-(2-[^{11}C]Methoxybenzylamino)-2-phenylpiperidine

[^{11}C]CP-99,994

Kenneth T. Cheng, PhD[1]

Created: November 14, 2006; Updated: January 23, 2008.

Chemical name:	(+)-(2*S*,3*S*)-3-(2-[^{11}C]Methoxybenzylamino)-2-phenylpiperidine
Abbreviated name:	[^{11}C]CP-99,994
Synonym:	
Agent Category:	Compound
Target:	Neurokinin 1 (NK_1) receptor (substance P or SP receptor)
Target Category:	Receptor binding
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents



Click on the above structure for additional information in PubChem.

Background

[PubMed]

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

NLM Citation: Cheng KT. (+)-(2*S*,3*S*)-3-(2-[^{11}C]Methoxybenzylamino)-2-phenylpiperidine . 2006 Nov 14 [Updated 2008 Jan 23]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

(+)-(2*S*,3*S*)-3-(2-[^{11}C}Methoxybenzylamino)-2-phenylpiperidine ([^{11}C]CP-99,994) is a radioligand developed for positron emission tomography (PET) imaging of neurokinin 1 (NK_1) receptors [substance P (SP) receptors) in the central nervous system (CNS) (1)

Tachykinins are peptides comprising 10–12 amino acids that share a common carboxy-terminal sequence "Phe-X-Gly-Leu-Met-amide" where "X" may vary but is always a hydrophobic residue that is either an aromatic or a β-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: NK_1 (formerly the SP receptor), NK_2 (formerly the substance K/substance E receptor/NK-A receptor), and NK_3 (formerly the NK-B receptor) receptors. 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 SP is found in the neocortex, 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 computed tomography of radioligands that target NK_1 receptors can visualize and allow the study of the 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).

Snider et al. (7) developed CP-96,345, a potent nonpeptide antagonist of the NK_1 receptor, and showed that ^{3}H-labeled CP-96,345 distributed in a similar CNS pattern similar to ^{3}H-labeled SP in guinea pigs. Desai et al. (8) proposed that the position of the inner phenyl ring of the benzhydryl group relative to the C-3 benzylamino group in CP-96,345 was important for activity. On the basis of this observation, they synthesized CP-99,994, a similar nonpeptide compound with better CNS penetration. Livni et al. (1) first described the CP-99,994 radiolabeled with ^{11}C as a potential PET imaging agent and evaluated its *in vivo* biodistribution in hamsters.

Synthesis

[PubMed]

Desai et al. (8) reported the synthesis of CP-99,994. The enantiospecific synthesis of CP-99,994 started with the N-protection of (−)-(4*R*)-4-phenyl-2-azetidinone. The resulting compound was reacted with 1-bromo-3-chloropropane in a highly stereoselective alkylation to produce a β-lactam product. This was followed by simultaneous removal of the N-protection group and the hydrolysis of the β-lactam to produce an aminomethyl ester compound. Cyclization of this compound was carried out

in the presence of sodium iodide and sodium bicarbonate at 100°C for 15 min. The stereospecific conversion of the carbomethoxy group in this compound to an amino group was conducted in a four-step sequence to yield an intermediate product. Reductive amination of this intermediate product with *o*-methoxybenzaldehyde followed by cleavage of the Cbz group yielded CP-99,994 in the form of (+)–(2*S*,3*S*) dihydrochloric salt.

Livni et al. (1) used the CP-99,994 dihydrochloric salt to prepare the precursor for radiosynthesis of [^{11}C]CP-99,994. Briefly, the hydrochloric salt was combined with concentrated hydrochloric acid, 10% palladium, methanol, and ethanol in a pressure bottle and shaken under hydrogen overnight. The resulting product was mixed and stirred in acetic acid, sodium triacetoxyborohydride and *o*-salicylaldehyde at room temperature for 16 h to produce (2S, 3S)-3-(2-hydroxybenzylamino)-2-phenylpiperidine. This compound was reacted with triethylamine and di-*tert*-butyldicarbonate in tetrahydrofuran at room temperature for 15 h to yield the precursor, (−)-(2*S*,3*S*)-1-*tert*-butyloxycarbonyl-3-(2-hydroxybenzylamino)-2-phenylpiperidine. In the radiosynthesis, this precursor was dissolved in dimethyl sulfoxide and then reacted with ^{11}C-labeled methyl iodide in potassium hydroxide. The reaction mixture was heated at 85°C for 8 min. After methylation of the precursor, deprotection was performed by addition of 1 N hydrochloric acid and heating at 110°C for 2.5 min. The final product was purified by high-performance liquid chromatography. Radiochemical yield was 10% at the end of synthesis (EOS), and chemical and radiochemical purities were >95%. Specific activity at EOS was 34.7 ± 16.2 GBq/μmol (937 ± 439 mCi/μmol; n = 10), and the synthesis time was 40 min from the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Desai et al. (8) determined the *in vitro* binding affinity of CP-99,994 for the human NK_1 receptor in human IM-9 cells by using [^{125}I]-BH-SP, an SP antagonist. The inhibition constant (K_i) of CP-99,994 was 0.17 ± 0.04 nM. In comparison, the K_i of CP-96,3435 was 0.66 ± 0.26 nM. McLean et al. (9) reported that CP-99,994 exhibited affinity that was >10,000-fold more selective for the NK_1 receptors relative to the NK_2 and NK_3 receptors.

Animal Studies

Rodents

[PubMed]

Livni et al. (1) studied the biodistribution of [^{11}C]CP-99,994 in Syrian hamsters. Each animal received a dose of 370 kBq (10 μCi) by i.v. administration. There were significant levels of accumulation in most organs. The highest concentrations were found in the lung and the gastrointestinal tract. The distribution pattern was consistent with the known distribution pattern of NK_1 receptors in these tissues. The cerebral concentration was 1.35

± 0.16% ID/g (percentage of injected dose per gram) at 30 min after injection (n = 5–6). In comparison, the cerebral concentration of CP-96,345 was ≈0.04% ID/g.

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. Livni E., Babich J.W., Desai M.C., Godek D.M., Wilkinson R.A., Rubin R.H., Fischman A.J. Synthesis of a 11C-labeled NK1 receptor ligand for PET studies. Nucl Med Biol. 1995;**22**(1):31–6. PubMed PMID: 7735167.
2. Hietala J., Nyman M.J., Eskola O., Laakso A., Gronroos T., Oikonen V., Bergman J., Haaparanta M., Forsback S., Marjamaki P., Lehikoinen P., Goldberg M., Burns D., Hamill T., Eng W.S., Coimbra A., Hargreaves R., Solin O. Visualization and quantification of neurokinin-1 (NK1) receptors in the human brain. Mol Imaging Biol. 2005;**7**(4):262–72. PubMed PMID: 16155744.
3. Severini C., Improta G., Falconieri-Erspamer G., Salvadori S., Erspamer V. The tachykinin peptide family. Pharmacol Rev. 2002;**54**(2):285–322. PubMed PMID: 12037144.
4. Datar P., Srivastava S., Coutinho E., Govil G. Substance P: structure, function, and therapeutics. Curr Top Med Chem. 2004;**4**(1):75–103. PubMed PMID: 14754378.
5. Mantyh P.W. Neurobiology of substance P and the NK1 receptor. J Clin Psychiatry. 2002;**63Suppl 11**6–10. PubMed PMID: 12562137.
6. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. J Clin Psychiatry. 2002;**63Suppl 11**18–24. PubMed PMID: 12562139.
7. Snider R.M., Constantine J.W., Lowe J.A., Longo K.P., Lebel W.S., Woody H.A., Drozda S.E., Desai M.C., Vinick F.J., Spencer R.W., Hess H.-J. A potent nonpeptide antagonist of the substance P (NK1) receptor. Science. 1991;**251**(4992):435–7. PubMed PMID: 1703323.

8. Desai M.C., Lefkowitz S.L., Thadeio P.F., Longo K.P., Snider R.M. Discovery of a potent substance P antagonist: recognition of the key molecular determinant. J Med Chem. 1992;**35**(26):4911–3. PubMed PMID: 1282570.
9. McLean S., Ganong A., Seymour P.A., Snider R.M., Desai M.C., Rosen T., Bryce D.K., Longo K.P., Reynolds L.S., Robinson G., Schmidt A.W., Siok C., Heym J. Pharmacology of CP-99,994; a nonpeptide antagonist of the tachykinin neurokinin-1 receptor. J Pharmacol Exp Ther. 1993;**267**(1):472–9. PubMed PMID: 7693914.