(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol ([^{11}C]SCH 23390)

[^{11}C]SCH 23390

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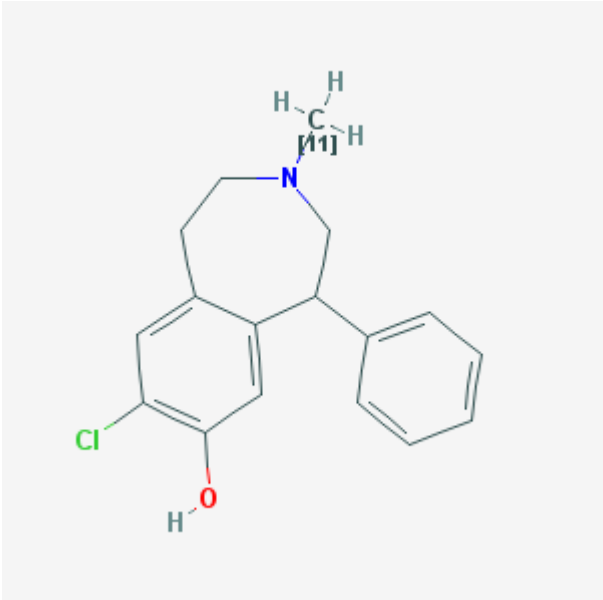
Chemical name:	(R)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol
Abbreviated name:	[^{11}C]SCH 23390, [^{11}C]SCH
Synonym:	
Agent Category:	Compound
Target:	Dopamine D_1 receptor
Target Category:	Receptor
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{11}C
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans



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Background

[PubMed]

Dopamine, a neurotransmitter, plays an important role in the mediation of movement, cognition, and emotion (1, 2). Dopamine receptors are involved in the pathophysiology of neuropsychiatric diseases, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia (3). Five subtypes of dopamine receptors, $D_{1\text{-}5}$, were well-characterized pharmacologically and biochemically (4). These five subtypes were classified into two subfamilies of D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) dopamine receptors. D_1-like and D_2-like receptors exert synergistic as well as opposite effects at the biochemical and overall system levels. A great majority of striatal D_1 and D_2 receptors are localized postsynaptically on the caudate-putamen neurons and to a lesser extent presynaptically on nigrostiatal axons.

(*R*)-(+)-8-Chloro-2,3,4,5-tetrahydro-3-[^{11}C]methyl-5-phenyl-1*H*-3-benzazepin-7-ol ([^{11}C]SCH 23390) was found to be a selective, high-affinity antagonist of D_1 receptors. SCH 23390 was found to have marginal effect on D_2, α_1-adrenergic, muscarinic and histaminergic receptors and only a slight effect on 5-HT_{2A} receptors (5). [^{11}C]SCH 23390 positron emission tomography (PET) has been used to study D_1 receptor occupancy and density in neuropsychiatric disorders and aging in humans.

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Related Resource Links:

- Chapters in MICAD (Dopamine receptors)
- Gene information in NCBI (D_1 receptor)
- Articles in Online Mendelian Inheritance in Man (OMIM) (D_1 receptor)
- Clinical trials (Dopamine receptors)
- Drug information in Food and Drug Administration (Dopamine receptors)

Synthesis

[PubMed]

[^{11}C]SCH 23390, was synthesized by alkylation of the desmethyl compound SCH 24518 ((R)-(+)-8-chloro-2,3,4,5-tetrahydro-5-phenyl-1H-3-benzazepin-7-ol) with [^{11}C]methyl iodide (6). Reaction in acetone with subsequent normal-phase LC separation resulted in

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80% radiochemical yield, based on [^{11}C]methyl iodide, with a total synthesis time of 35-40 min and a radiochemical purity greater than 99%. The averaged specific activity was 11.1 GBq/mmol (300 Ci/mmol) at end of synthesis (EOS).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

SCH 23390 was reported to have selective binding affinity to D_1 (striatum) and 5-HT_{2A} (frontal cortex) receptor sites in homogenates of rat brain membranes (7). The K_i values for D_1 ([^{3}H]piflutixol), D_2 ([^{3}H]spiroperidol) in the striatal membranes and 5-HT_{2A} ([^{3}H]spiroperidol) in the cortical membranes were 1.3 nM, 880 nM and 30 nM, respectively. It has a K_i value of 690 nM for the α_1-adrenergic receptor in rat forebrain membrane. The affinity for the 5-HT_{2A} receptor is about 10-fold lower than that for the D_1 receptor, suggesting that specific [^{11}C]SCH 23390 binding visualized by PET represents mainly binding to D_1 receptors. The K_d value of [^{3}H]SCH 23390 was 0.53 nM for D_1(8). The B_{max} value of [^{3}H]SCH 23390 for D_1 was 69 pmol/g tissue.

Using human putamen homogenates, the K_d values of [^{3}H]SCH 23390 and [^{3}H]raclopride, a D_2 antagonist, were 1.6 ± 0.22 nM (1.1 ± 0.38 nM with 40 nM ketanserin, a 5-HT_{2A} antagonist) and 2.0 ± 0.2 nM, respectively (9). The D_1 receptor binding density (B_{max}) was 12.7 ± 3.8 and 9.9 ± 2.1 pmol/g tissue for [^{3}H]SCH 23390 without and with 40 nM ketanserin, respectively. The B_{max} of [^{3}H]raclopride for $D_{2/3}$ receptor was 13.3 ± 0.9 pmol/g tissue. Using frontal cortex membranes, the B_{max} for D_1 was 6.7 ± 3.9 and 3.3 ± 0.82 pmol/g tissue without and with 40 nM ketanserin, respectively. Ketanserin had little effect on the K_d (2.1 - 2.4 nM). There was little specific binding of raclopride in the cortex membranes. Therefore, part of the [^{3}H]SCH 23390 bindings to the putamen and frontal cortex was due to 5-HT_{2a} receptor sites.

Hyttel (10) reported that the B_{max} and K_d of dopamine D_1 and D_2 receptors in striatum was estimated in rats of different ages (from 3.5 to 25 months) using [^{3}H]SCH 23390 and [^{3}H]spiperone as ligands. The density of D_1 and D_2 receptors decreased with age from 3.5 months' values of 990 ± 50 and 350 ± 11 pmol/g tissue to 25 months' values of 690 ± 35 (30% decrease) and 240 ± 7 pmol/g tissue (31% decrease), respectively. However, the K_d vaukes remained constant. The decreases in density of D_1 and D_2 receptors were parallel. Thus, the ratio between the density of D_1 and D_2 receptors remained constant throughout life

Hess et al (11) demonstrated that D_1 receptor density ([^{3}H]SCH 233900) was reduced by 43% in postmortem caudate brains from 8 schizophrenic patients as compared with 8 normal subjects from 281.5 ± 20.5 to 161.4 ± 22.1 fmol/mg protein. In contrast, schizophrenic patients exhibited a 56% increase in D_2 receptor density from 119.8 ± 13.7 to 186.7 ± 33.0 fmol/mg protein as measured by [^{3}H]spiperone in the presence of 40 nM ketanserin. These resulted in a highly significant difference in the ratio of D_2/D_1 receptor density between schizophrenic patients (1.29 ± 0.29) and controls (0.42 ± 0.03).

Animal Studies

Rodents

[PubMed]

Biodistribution studies in mice showed a high accumulation of radioactivity in the intestines (1.38% injected dose (ID)/g), followed by the liver (1.06% ID/g), kidney (0.40% ID/g), lung (0.22% ID/g), and brain (0.17% ID/g) at 60 min after injection of [^{11}C]SCH 23390. There was a rapid accumulation of the tracer in the striata within the first ten min (4.88% ID/g), followed by a slow decrease of radioactivity to 2.25% ID/g at 60 min. In contrast, radioactivity in the cerebellum decreased continuously from 1 min (3.10% ID/g) to 60 min (0.10% ID/g). The striatum-to-cerebellum ratios were 1.3, 3.1, 6.1, and 23.4 at 1, 10, 30, and 60 min, respectively.

Suzuki et al (12) reported that the binding potential (B_{max}/K_d) of [^{11}C]SCH 23390 as measured by PET in the rat striata decreased as a function of age by a maximum of 26%, whereas the binding potential of [^{11}C]raclopride decreased by 36%. These PET results confirmed the decreases in density of D_1 and $D_{2/3}$ receptors were parallel in aging rats.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[[PubMed]

The distributions of dopamine D_1 and D_2 receptors in 6 monkeys were compared directly using PET (13). The binding potentials of [^{11}C]SCH 23390 for dopamine D_1 receptors and [^{11}C]raclopride for dopamine D_2 receptors were calculated in monkey striatum volumes of interest using cerebellum as a non-binding reference region. The D_1 binding potential for [^{11}C]SCH 23390 was 1.30 ± 0.04 in monkey striata, whereas the D_2 binding potential for [^{11}C]raclopride was 1.96 ± 0.44. There were distinct gradients in the distributions of the two binding sites in monkey brain: D_1 binding predominated in the antero-ventral striatum, whereas D_2 binding was relatively greater in the dorsal-posterior striatum.

Human Studies

[PubMed]

[^{11}C]SCH 23390 PET studies of D_1 receptor distribution in human brain were reported, showing a major localization of radioactivity in the striatum. Striatum-to-cerebellum ratio and kinetic constants are commonly used as analytical parameters in [^{11}C]SCH 23390

PET studies with good reproducibility (14-16). Farde et al. (17) reported on [^{11}C]SCH 23390 PET studies in 2 patients with schizophrenia and in 3 normal subjects. PET brain scans of normal subjects showed that a high accumulation of radioactivity was in the putamen, followed by the neocortex and cerebellum at 5 - 60 min after injection of 100 MBq (2.7 mCi) [^{11}C]SCH 23390. The putamen-to-cerebellum ratio was 3 at 25 min. There was a marked accumulation of radioactivity in the neocortex for [^{11}C]SCH 23390 but not for [^{11}C]raclopride ($D_{2/3}$ receptors), suggesting the presence of 5-HT_{2A} binding sites. Only about 1.2% of injected [^{11}C]SCH 23390 remained in the brain at 4.5 min. Only 15% of radioactivity remained intact in blood at 42 min. PET scans of schizophrenic patients was similar to those obtained in the normal controls. [^{11}C]SCH 23390 PET was able to assess striatal dopamine receptor occupancies in patients treated with various antipsychotic drugs (18).

The effects of age on the binding of [^{11}C]SCH 23390 for D_1 receptor sites were studied in 17 healthy male subjects in age from 20 to 72 years old (19). The binding potential of the D_1 receptors in the striatum and frontal cortex decreased with age by 35% and 39%, respectively. In another study with 8 men and 10 women (22-74 years old) (20), there was an age dependent decrease of D_1 receptor binding potential in the caudate, putamen, and occipital cortex by 6.9%/decade, 7.4%/decade, and 8.6%/decade, respectively. There was no difference in D_1 binding potentials between men and women.

In Huntington's disease, there was a significant reduction in both the D_1 ([^{11}C]SCH 23390) and D_2 ([^{11}C]raclopride) binding potentials in the striatum (21-23). A great majority (90%) of patients was not on any medication affecting the dopamine and serotonin system. Medications were withdrawn for 1 to 14 days prior to PET. In Parkinson's disease, there was no significant difference in D_1 receptor accumulation in the pathologic striatum compared with the contralateral striatum (24). On the other hand, there was a significant increase in D_2 binding potential in the striatum contralateral to the symptoms as compared with the opposite striatum. None of the patients was on any anti-Parkinsonism medication.

Kosaka et al. performed [^{11}C]NNC112 and [^{11}C]SCH23390 PET imaging in six patients with schizophrenia in severe residual phase with chronic antipsychotic treatment and twelve healthy age-matched controls on the same subjects. The D_1 binding potential (BP_{ND})values of both tracers in the frontal cortex, anterior cingulate, temporal cortex and striatum of the patients were significantly lower (21-31%) than those of the healthy controls ($P < 0.001$).

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[^{11}C]SCH 23390 PET is useful for objective monitoring of D_1 receptor density and drug occupancy in patients with dopaminergic disorders. Internal dosimetry data for [^{11}C]SCH 23390 in humans are not available in the literature.

References

1. Carbon M., Ghilardi M.F., Feigin A., Fukuda M., Silvestri G., Mentis M.J., Ghez C., Moeller J.R., Eidelberg D. *Learning networks in health and Parkinson's disease: reproducibility and treatment effects.* Hum Brain Mapp. 2003;19(3):197–211. PubMed PMID: 12811735.
2. Chesselet M.F., Delfs J.M. *Basal ganglia and movement disorders: an update.* Trends Neurosci. 1996;19(10):417–22. PubMed PMID: 8888518.
3. Seeman P., Bzowej N.H., Guan H.C., Bergeron C., Reynolds G.P., Bird E.D., Riederer P., Jellinger K., Tourtellotte W.W. *Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's, and Huntington's diseases.* Neuropsychopharmacology. 1987;1(1):5–15. PubMed PMID: 2908095.
4. Stoof J.C., Kebabian J.W. *Two dopamine receptors: biochemistry, physiology and pharmacology.* Life Sci. 1984;35(23):2281–96. PubMed PMID: 6390056.
5. Hyttel J., Arnt J., van den Berghe M. *Selective dopamine D1 and D2 receptor antagonists.* Psychopharmacol Ser. 1989;7:109–22. PubMed PMID: 2574447.
6. Halldin C., Stone-Elander S., Farde L., Ehrin E., Fasth K.J., Langstrom B., Sedvall G. *Preparation of 11C-labelled SCH 23390 for the in vivo study of dopamine D-1 receptors using positron emission tomography.* Int J Rad Appl Instrum [A]. 1986;37(10):1039–43. PubMed PMID: 3027000.
7. Hyttel J. *SCH 23390 - the first selective dopamine D-1 antagonist.* Eur J Pharmacol. 1983;91(1):153–4. PubMed PMID: 6225651.
8. Billard W., Ruperto V., Crosby G., Iorio L.C., Barnett A. *Characterization of the binding of 3H-SCH 23390, a selective D-1 receptor antagonist ligand, in rat striatum.* Life Sci. 1984;35(18):1885–93. PubMed PMID: 6387355.
9. Hall H., Farde L., Sedvall G. *Human dopamine receptor subtypes--in vitro binding analysis using 3H-SCH 23390 and 3H-raclopride.* J Neural Transm. 1988;73(1):7–21. PubMed PMID: 2969950.
10. Hyttel J. *Parallel decrease in the density of dopamine D1 and D2 receptors in corpus striatum of rats from 3 to 25 months of age.* Pharmacol Toxicol. 1989;64(1):55–7. PubMed PMID: 2526948.
11. Hess E.J., Bracha H.S., Kleinman J.E., Creese I. *Dopamine receptor subtype imbalance in schizophrenia.* Life Sci. 1987;40(15):1487–97. PubMed PMID: 2951573.
12. Suzuki M., Hatano K., Sakiyama Y., Kawasumi Y., Kato T., Ito K. *Age-related changes of dopamine D1-like and D2-like receptor binding in the F344/N rat striatum revealed by positron emission tomography and in vitro receptor autoradiography.* Synapse. 2001;41(4):285–93. PubMed PMID: 11494399.
13. Rosa-Neto P., Doudet D.J., Cumming P. *Gradients of dopamine D1- and D2/3-binding sites in the basal ganglia of pig and monkey measured by PET.* Neuroimage. 2004;22(3): 1076–83. PubMed PMID: 15219579.
14. Chan G.L., Holden J.E., Stoessl A.J., Doudet D.J., Wang Y., Dobko T., Morrison K.S., Huser J.M., English C., Legg B., Schulzer M., Calne D.B., Ruth T.J. *Reproducibility of the distribution of carbon-11-SCH 23390, a dopamine D1 receptor tracer, in normal subjects.* J Nucl Med. 1998;39(5):792–7. PubMed PMID: 9591577.

15. Hirvonen J., Nagren K., Kajander J., Hietala J. *Measurement of cortical dopamine d1 receptor binding with 11C[SCH23390]: a test-retest analysis.* J Cereb Blood Flow Metab. 2001;21(10):1146–50. PubMed PMID: 11598491.
16. Sossi V., Holden J.E., Chan G., Krzywinski M., Stoessl A.J., Ruth T.J. *Analysis of four dopaminergic tracers kinetics using two different tissue input function methods.* J Cereb Blood Flow Metab. 2000;20(4):653–60. PubMed PMID: 10779009.
17. Farde L., Halldin C., Stone-Elander S., Sedvall G. *PET analysis of human dopamine receptor subtypes using 11C-SCH 23390 and 11C-raclopride.* Psychopharmacology (Berl). 1987;92(3):278–84. PubMed PMID: 2957716.
18. Farde L., Hall H. *Positron emission tomography--examination of chemical transmission in the living human brain. Development of radioligands.* Arzneimittelforschung. 1992;42(2A):260–4. PubMed PMID: 1316756.
19. Suhara T., Fukuda H., Inoue O., Itoh T., Suzuki K., Yamasaki T., Tateno Y. *Age-related changes in human D1 dopamine receptors measured by positron emission tomography.* Psychopharmacology (Berl). 1991;103(1):41–5. PubMed PMID: 1826059.
20. Wang Y., Chan G.L., Holden J.E., Dobko T., Mak E., Schulzer M., Huser J.M., Snow B.J., Ruth T.J., Calne D.B., Stoessl A.J. *Age-dependent decline of dopamine D1 receptors in human brain: a PET study.* Synapse. 1998;30(1):56–61. PubMed PMID: 9704881.
21. Sedvall G., Karlsson P., Lundin A., Anvret M., Suhara T., Halldin C., Farde L. *Dopamine D1 receptor number--a sensitive PET marker for early brain degeneration in Huntington's disease.* Eur Arch Psychiatry Clin Neurosci. 1994;243(5):249–55. PubMed PMID: 8172940.
22. Andrews T.C., Weeks R.A., Turjanski N., Gunn R.N., Watkins L.H., Sahakian B., Hodges J.R., Rosser A.E., Wood N.W., Brooks D.J. *Huntington's disease progression. PET and clinical observations.* Brain. 1999;122(Pt 12):2353–63. PubMed PMID: 10581228.
23. Ginovart N., Lundin A., Farde L., Halldin C., Backman L., Swahn C.G., Pauli S., Sedvall G. *PET study of the pre- and post-synaptic dopaminergic markers for the neurodegenerative process in Huntington's disease.* Brain. 1997;120(Pt 3):503–14. PubMed PMID: 9126061.
24. Rinne J.O., Laihinen A., Nagren K., Bergman J., Solin O., Haaparanta M., Ruotsalainen U., Rinne U.K. *PET demonstrates different behaviour of striatal dopamine D-1 and D-2 receptors in early Parkinson's disease.* J Neurosci Res. 1990;27(4):494–9. PubMed PMID: 1981915.