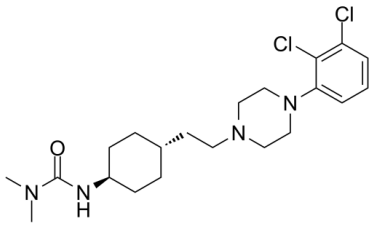
Data Sheet

Product Name:	Cariprazine
Cat. No.:	CS-1569
CAS No.:	839712-12-8
Molecular Formula:	C21H32Cl2N4O
Molecular Weight:	427.41
Target:	5-HT Receptor; Dopamine Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	10 mM in DMSO



BIOLOGICAL ACTIVITY:

Cariprazine is a novel antipsychotic drug candidate that exhibits high affinity for the **D_3** (**K_i**=0.085 nM) and **D_2** (**K_i**=0.49 nM) receptors, and moderate affinity for the **5-HT_{1A}** receptor (**K_i**=2.6 nM). IC50 & Target: Ki: 0.49 nM (D2 receptor), 0.085 nM (D3 receptor), 2.6 nM (5-HT1A receptor)[1] **In Vitro:** Cariprazine stimulates inositol phosphate (IP) formation with a high potency (pEC_{50} 8.5) with relatively low efficacy (E_{max} 30%)[2]. Cariprazine, a novel candidate antipsychotic, demonstrated approximately 10-fold higher affinity for human D_3 versus human D_{2L} and human D_{2S} receptors (pK_i 10.07, 9.16, and 9.31, respectively). Cariprazine displays high affinity at human serotonin (5-HT) type 2B receptors (pK_i 9.24) with pure antagonism. Cariprazine has lower affinity at human and rat hippocampal 5-HT_{1A} receptors (pK_i 8.59 and 8.34, respectively) and demonstrates low intrinsic efficacy. Cariprazine displays low affinity at human 5-HT_{2A} receptors (pK_i 7.73). Moderate or low affinity for histamine H_1 and 5-HT_{2C} receptors (pK_i 7.63 and 6.87, respectively) suggest Cariprazine's reduced propensity for adverse events related to these receptors[2]. Cariprazine is over sixfold more potent (EC_{50}=1.4 nM) than Aripiprazole (EC_{50}=9.2 nM) in inhibiting isoproterenol-induced cAMP production in HEK-293 cells[4]. **In Vivo:** Administration of Cariprazine (30 μg/kg) reduces the striatal uptake of both radioligands to the level of nonspecific binding compared with baseline PET measurements. Cariprazine has negligible effect on the time-activity curves in the cerebellum. At doses of 5.0 and 30 μg/kg, Cariprazine causes a dose-dependent dopamine D_2/D_3 receptor occupancy of ~45% and ~80% for both antagonist [^{11}C] raclopride and agonist radioligand [^{11}C]MNPA. Receptor occupancy of dopamine D_2/D_3 receptors calculated using the transient equilibrium and the MRTM2 methods ranged from 5% at the lowest dose (1.0 μg/kg) to 94% at the highest dose (300 μg/kg)[1]. The effects of 5 doses of Cariprazine (ranging from 0.005 to 0.15 mg/kg) are examined on EPM behavior of wild-type mice. Whereas lower doses of Cariprazine (0.005 to 0.02 mg/kg) do not alter the time spent in open arms, the two higher doses (0.08 and 0.15 mg/kg) lead to a significant decline of this measure (ANOVA, ($F(5,52)=4.20$; $p=0.0032$)). Moreover, the two higher doses of Cariprazine also lead to a significant decrease in the total number of arm entries ($F(5,52)=7.21$; $p=0.0001$)) but this decrease in the total number of arm entries is largely accounted for by a significant decrease in the number of closed arm entries ($F(5,52)=11.75$; $p=0.0001$)). The two highest doses of Cariprazine (0.08 and 0.15 mg/kg) have significant effects on locomotor activity, but doses ranging from 0.005 to 0.02 mg/kg do not affect anxiety-like behavior or locomotor activity in the EPM test[3]. A significant ($P<0.01$) reduction in ouabain-induced hyperactivity is observed after acute i.p. administration of all doses of Cariprazine (mean±SEM: 0.06 mg/kg, 64.2±3.88; 0.25 mg/kg, 72.7±11.67; 0.5 mg/kg, 40.6±5.32; 1 mg/kg, 19.5±8.78) and lithium (40.4±12.78), compared with ouabain injection alone (114.6±14.33). The highest Cariprazine dose produced significant sedation (72% inhibition for Cariprazine 1.0 mg/kg aCSF vs. saline aCSF; $P<0.05$)[4].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [2]These assays are done in 50 mM Tris (pH 7.4), 100 mM NaCl, 7 mM $MgCl_2$, 1 mM EDTA, and 1 mM DTT. Assay tubes (final volume 250 μL) contain 50 μM (striatum and hippocampus) or 1 μM (D_2 and D_3 cell membrane) GDP, the ligand to be examined, and membrane suspension (250 μg tissue/tube for the striatum and hippocampus and 20 μg protein/tube for hD_2 and hD_3

membranes). Samples are preincubated for 10 min at 30°C. After the addition of 50 pM [^{35}S]GTPγS, membranes are incubated for an additional 60 min at 30°C. Nonspecific binding is determined in the presence of 10 μM GTPγS; basal binding is determined in the presence of buffer only. The assay is terminated by rapid filtration through UniFilter GF/B using a harvester, and the membranes washed four times with 1 mL of ice-cold buffer. After drying (40°C for 1 h), 40 μL of Microscint is added to the filters, and the bound radioactivity is determined by a TopCount NXT counter[2]. **Cell Assay:** Cariprazine is prepared in DMSO and stored, and then diluted with appropriate medium[2].[2]Cells are seeded on a 24-well tissue culture plate in 500 μL of medium. Fifty microliters of medium containing 0.55 μCi myo-[^{3}H]inositol is added (final concentration 1 μCi/mL) and incubated for 18-20 h. Cells are then washed three times with buffer containing 140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 5 mM HEPES, 5 mM Na-HEPES, 20 mM glucose, and 10 mM LiCl (pH 7.4). Cells are then incubated for an additional 60 min (37°C) in medium with test compounds alone (agonist test) or alongside 1000 nM (±)-Quinpirole (antagonist test). Medium is then aspirated off, cells are lysed by adding 400 μL of 0.1 M HCl/2 mM $CaCl_2$, and supernatants are frozen at −72°C. After thawing and centrifugation at 1000g for 10 min, 200 μL of each supernatant is loaded on 250 μL of AG1-X8 (formate form) anion exchange column. Effluent is discarded, and columns are washed twice in 1.5 mL of distilled water. IPs are eluted with 2.5 mL of 1 M ammonium formate/0.1 M formic acid directly into scintillation vials, 10 mL of Optiphase HiSafe 3 is added, and the radioactivity is determined in a TriCarb 4900 scintillation counter[2]. **Animal Administration:** Cariprazine is dissolved in saline, filter sterilized (Mice)[3];Cariprazine is dissolved in 0.9% saline (Rats)[4].[3][4]Mice[3]
Experiments are performed on wild-type C57Bl/6J mice. In tests of cognitive functions, it is essential to employ concentrations of drugs that have no effects on emotional behavior and that do not impair locomotor activity. Whether Cariprazine (administered at a dose range of 0.005 to 0.15 mg/kg) is first tested affected the behavior of mice in the EPM, a test of anxiety-related behavior that is also critically dependent upon normal locomotor activity. Animals are exposed to an EPM apparatus designed for mice (leg height: 45 cm, arm length: 35 cm, lane width: 5 cm, wall height: 15 cm). Testing (under 100 lux lighting) is performed between 1 and 4 PM. Mice are placed in the center of the maze and their time spent in open arms and the number of closed and open arm entries during a 5 min test period is recorded. Measures of the time spent in open arms and the number of open arm entries served as a measure of anxiety-like behavior. The number of closed arm entries served as a measure of locomotor activity.
Rats[4]
Adult male Sprague-Dawley rats (150-300 g) are used. Cariprazine is dissolved in 0.9% saline and administered at 0.06, 0.25, 0.5, and 1.0 mg/kg via intraperitoneal (i.p.) injection 1 h before i.c.v. injection of ouabain and daily thereafter for 7 days. Open field activity is assessed immediately following the i.c.v. injection and again after 7 days (the activity is noted 10-14 h after the last i.p. injection of Cariprazine).

References:

[1]. Seneca N, et al. Occupancy of dopamine D2 and D3 and serotonin 5-HT1A receptors by the novel antipsychotic drug candidate, cariprazine (RGH-188), in monkey brain measured using positron emission tomography. Psychopharmacology (Berl). 2011 Dec;218(3):579-8

[2]. Kiss B, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther. 2010 Apr;333(1):328-40.

[3]. Zimnisky R, et al. Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse. Psychopharmacology (Berl). 2013 Mar;226(1):91-100

[4]. Gao Y, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor β-arrestin interactions. Pharmacol Res Perspect. 2015 Feb;3(1):e00073.

CAIndexNames:

Urea, N'-[trans-4-[2-[4-(2,3-dichlorophenyl)-1-piperazinyl]ethyl]cyclohexyl]-N,N-dimethyl-

SMILES:

O=C(N[C@H]1CC[C@H](CCN2CCN(C3=CC=CC(Cl)=C3Cl)CC2)CC1)N(C)C

Caution: Product has not been fully validated for medical applications. For research use only.

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