Cariprazine hydrochloride

Cat. No.: HY-14763A

CAS No.: 1083076-69-0

Molecular Formula: $C_{21}H_{33}Cl_3N_4O$

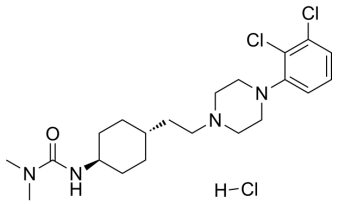
Molecular Weight: 463.87

Target: Dopamine Receptor; 5-HT Receptor

Pathway: GPCR/G Protein; Neuronal Signaling

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 6.67 mg/mL (14.38 mM; Need ultrasonic)

H_2O : 2.86 mg/mL (6.17 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	2.1558 mL	10.7789 mL	21.5578 mL
5 mM	0.4312 mL	2.1558 mL	4.3116 mL
10 mM	0.2156 mL	1.0779 mL	2.1558 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.67 mg/mL (1.44 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.67 mg/mL (1.44 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.67 mg/mL (1.44 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cariprazine hydrochloride is a novel antipsychotic agent 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).

IC_{50} & Target

D_2 Receptor	D_3 Receptor	5-HT_{1A} Receptor
0.49 nM (Ki)	0.085 nM (Ki)	2.6 nM (Ki)

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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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].

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PROTOCOL

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].

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Cell Assay [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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration [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). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Neurosci. 2021 Dec 9.
- ACS Chem Neurosci. 2020 Jan 15;11(2):173-183.

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REFERENCES

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