

产品名称: **Cariprazine (hydrochloride)**  
 产品别名: **RGH188 hydrochloride; 盐酸卡利拉嗪**

生物活性:														
Description		Cariprazine hydrochloride is a novel antipsychotic drug candidate that exhibits high affinity for the D <sub>3</sub> (K <sub>i</sub> =0.085 nM) and D <sub>2</sub> (K <sub>i</sub> =0.49 nM) receptors, and moderate affinity for the 5-HT <sub>1A</sub> receptor (K <sub>i</sub> =2.6 nM).												
IC <sub>50</sub> & 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 (pEC50 8.5) with relatively low efficacy (Emax 30%)[2]. Cariprazine, a novel candidate antipsychotic, demonstrated approximately 10-fold higher affinity for human D3 versus human D2L and human D2S receptors (pKi 10.07, 9.16, and 9.31, respectively). Cariprazine displays high affinity at human serotonin (5-HT) type 2B receptors (pKi 9.24) with pure antagonism. Cariprazine has lower affinity at human and rat hippocampal 5-HT1A receptors (pKi 8.59 and 8.34, respectively) and demonstrates low intrinsic efficacy. Cariprazine displays low affinity at human 5-HT2A receptors (pKi 7.73). Moderate or low affinity for histamine H1 and 5-HT2C receptors (pKi 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 (EC50=1.4 nM) than Aripiprazole (EC50=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 D2/D3 receptor occupancy of ~45% and ~80% for both antagonist [ <sup>11</sup> C] raclopride and agonist radioligand [ <sup>11</sup> C]MNPDA. Receptor occupancy of dopamine D2/D3 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].												
		In Vitro: DMSO : 6.67 mg/mL (14.38 mM; Need ultrasonic)												
		<table><tr><td rowspan="2">Preparing</td><td>Solvent Concentration</td><td>1 mg</td><td>5 mg</td><td>10 mg</td></tr><tr><td>1 mM</td><td>2.1558 mL</td><td>10.7789 mL</td><td>21.5578 mL</td></tr></table>				Preparing	Solvent Concentration	1 mg	5 mg	10 mg	1 mM	2.1558 mL	10.7789 mL	21.5578 mL
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	<b>Stock Solutions</b>	5 mM	0.4312 mL	2.1558 mL	4.3116 mL
		10 mM	0.2156 mL	1.0779 mL	2.1558 mL
<b>Solvent&amp;Solubility</b>	<p>*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。</p> <p>储备液的保存方式和期限：-80℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。</p> <p><b><i>In Vivo:</i></b></p> <p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 <b>In Vitro</b> 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 0.67 mg/mL (1.44 mM); Clear solution</p> <p>此方案可获得 ≥ 0.67 mg/mL (1.44 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 6.7000003 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 0.67 mg/mL (1.44 mM); Clear solution</p> <p>此方案可获得 ≥ 0.67 mg/mL (1.44 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 6.7000003 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil</p> <p>Solubility: 0.67 mg/mL (1.44 mM); Clear solution</p> <p>此方案可获得 ≥ 0.67 mg/mL (1.44 mM, 饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例，取 100 μL 6.7000003 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。</p>				
<b>References</b>	<p>[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. <i>Psychopharmacology (Berl)</i>. 2011 Dec;218(3):579-8</p> <p>[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. <i>J Pharmacol Exp Ther</i>. 2010 Apr;333(1):328-40.</p> <p>[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. <i>Psychopharmacology (Berl)</i>. 2013 Mar;226(1):91-100.</p> <p>[4]. Gao Y, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor β-arrestin interactions. <i>Pharmacol Res Perspect</i>. 2015 Feb;3(1):e00073.</p> <p>[5]. Citrome L. Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. <i>Adv Ther</i>.</p>				

**实验参考:**

<b>Cell Assay</b>	<p>Cells are seeded on a 24-well tissue culture plate in 500 <math>\mu</math>L of medium. Fifty microliters of medium containing 0.55 <math>\mu</math>Ci myo-[3H]inositol is added (final concentration 1 <math>\mu</math>Ci/mL) and incubated for 18-20 h. Cells are then washed three times with buffer containing 140 mM NaCl, 5 mM KCl, 2 mM <math>\text{CaCl}_2</math>, 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 (<math>\pm</math>)-Quinpirole (antagonist test). Medium is then aspirated off, cells are lysed by adding 400 <math>\mu</math>L of 0.1 M HCl/2 mM <math>\text{CaCl}_2</math>, and supernatants are frozen at -72°C. After thawing and centrifugation at 1000g for 10 min, 200 <math>\mu</math>L of each supernatant is loaded on 250 <math>\mu</math>L 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].</p>
<b>Animal Administration</b>	<p>Mice[3]</p> <p>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.</p> <p>Rats[4]</p> <p>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).</p>
<b>Kinase Assay</b>	<p>These assays are done in 50 mM Tris (pH 7.4), 100 mM NaCl, 7 mM <math>\text{MgCl}_2</math>, 1 mM EDTA, and 1 mM DTT. Assay tubes (final volume 250 <math>\mu</math>L) contain 50 <math>\mu</math>M (striatum and hippocampus) or 1 <math>\mu</math>M (D2 and D3 cell membrane) GDP, the ligand to be examined, and membrane suspension (250 <math>\mu</math>g tissue/tube for the striatum and hippocampus and 20 <math>\mu</math>g protein/tube for hD2 and hD3 membranes). Samples are preincubated for 10 min at 30°C. After the addition of 50 pM [35S]GTP<math>\gamma</math>S, membranes are incubated for an additional 60 min at 30°C. Nonspecific binding is determined in the presence of 10 <math>\mu</math>M GTP<math>\gamma</math>S; 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 <math>\mu</math>L of Microscint is added to the filters, and the bound radioactivity is determined by a TopCount NXT counter[2].</p>
	<p>[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</p>

<p><b>References</b></p>	<p><a href="#"><u>positron emission tomography. Psychopharmacology (Berl). 2011 Dec;218(3):579-8</u></a></p> <p>[2]. <a href="#"><u>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.</u></a></p> <p>[3]. <a href="#"><u>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.</u></a></p> <p>[4]. <a href="#"><u>Gao Y, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor <math>\beta</math>-arrestin interactions. Pharmacol Res Perspect. 2015 Feb;3(1):e00073.</u></a></p> <p>[5]. <a href="#"><u>Citrome L. Cariprazine in schizophrenia: clinical efficacy, tolerability, and place in therapy. Adv Ther. 2013 Feb;30(2):114-26.</u></a></p>
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源叶生物