产品名称：CTEP(RO4956371)
产品别名：CTEP；mGluR5 inhibitor

生物活性：

Description	CTEP (RO 4956371) is a novel, long-acting, orally bioavailable allosteric antagonist of mGlu5 receptor with IC_{50} of 2.2 nM, and shows > 1000-fold selectivity over other mGlu receptors.
IC_{50} & Target	IC50: 2.2 nM (mGlu5 receptor)
In Vitro	CTEP (RO 4956371) inhibits quisqualate-induced Ca^{2+} mobilization with an IC_{50} of 11.4 nM and [^{3}H]IP accumulation with an IC_{50} of 6.4 nM in HEK293 cells stably expressing human mGlu5. CTEP (RO 4956371) inhibits the constitutive activity of human mGlu5 by approximately 50% with an IC_{50} of 40.1 nM in HEK293 cells stably expressing human mGlu5[1].
In Vivo	CTEP (RO 4956371) is significantly active at doses of 0.1 mg/kg and 0.3 mg/kg in treatment of anxiety in mouse. CTEP (RO 4956371) significantly increases drinking time at doses of 0.3 mg/kg and 1.0 mg/kg in the Vogel conflict drinking test in rat, whereas it has no effect at lower doses. The half-life of CTEP (RO 4956371) (oral) is 18 h, and the B/P ratio based on total drug concentrations in plasma and whole brain homogenates is 2.6 in mice. After single oral doses of 4.5 and 8.7 mg/kg CTEP (RO 4956371) formulated as microsuspension in a saline/Tween vehicle administrated to adult C57BL/6 mice is rapidly absorbed and achieves close to maximal exposure after approximately 30 min. Chronic administration in adult mice with a dose of 2 mg/kg p.o. every 48 h for 2 months reaches a minimal CTEP (RO 4956371) brain exposure of 240 ng/g. CTEP (RO 4956371) fully displaces [3H]ABP688 in mouse brain regions known to express mGlu5, and 50% displacement is achieved with doses producing an average compound concentration of 77.5 ng/g measured in whole brain homogenate[1]. CTEP (RO 4956371) (2 mg/kg, p.o. bid) achieves uninterrupted mGlu5 occupancy per 48 hours in mice. CTEP (RO 4956371) (2 mg/kg, p.o.) treatment corrects elevated hippocampal long-term depression, excessive protein synthesis, and audiogenic seizures in the Fmr1 knockout mouse[2].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL (255.25 mM)** **H_2O : < 0.1 mg/mL** (insoluble) * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5525 mL	12.7626 mL	25.5252 mL
5 mM	0.5105 mL	2.5525 mL	5.1050 mL
10 mM	0.2553 mL	1.2763 mL	2.5525 mL

*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。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

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 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——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

	1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (6.38 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.38 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: 2.5 mg/mL (6.38 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (6.38 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 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。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.38 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.38 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。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Lindemann L, et al. CTEP: a novel, potent, long-acting, and orally bioavailable metabotropic glutamate receptor 5 inhibitor. J Pharmacol Exp Ther. 2011 Nov;339(2):474-86. [2]. Michalon A, et al. Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. Neuron. 2012 Apr 12;74(1):49-56.

实验参考：

Animal Administration	Adult male Sprague-Dawley rats (body weight approximately 180-210 g) and male NMRI mice (body weight approximately 25 g) are supplied by Charles River. Rats are group-housed and mice are-single housed in separate holding rooms at controlled temperature (20-22°C) and 12-h light/dark cycle (lights on 6:00 AM). Animals are allowed ad libitum access to food and water, with the exception of those used in the Vogel conflict drinking test, where access to water is limited during the training sessions as described below. All formulations are prepared immediately before use in vehicle, consisting of 0.9% NaCl (w/v) and 0.3% Tween 80 (v/v) solution for oral administration of CTEP (RO 4956371), MPEP, MTEP, and fenobam; 0.9% NaCl solution for MPEP and MTEP intravenously; and 30% N-methylpyrrolidone, 42% hydroxypropyl-γ-cyclodextrin, and 28% water for fenobam intravenously. The volume of administration for oral dosing is 5 mL/kg for rats, 10 mL/kg for mice, and 2.5 mL/kg for intravenous applications and 10 mL/kg for subcutaneous applications in mice. [1]
Kinase Assay	For all filtration radioligand binding assays, membrane preparations expressing the target receptors or receptor combinations are resuspended in radioligand binding buffer (15 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 1.25 mM $CaCl_2$, and 1.25 mM $MgCl_2$, pH 7.4), and the membrane suspension is mixed with the appropriate concentrations of radioligand and nonlabeled drugs in 96-well plates in a total volume of 200 μL and incubated for 60 min at the appropriate temperature. At the end of the incubation, membranes are filtered onto Whatman Unifilter preincubated with 0.1% polyethyleneimine in ish buffer (50 mM Tris-HCl, pH 7.4) with a Filtermate 196 harvester and washed three times with ice-cold ish buffer. Radioactivity captured on the filter is quantified on a Topcount microplate scintillation counter with quenching correction after the addition of 45 μL of

	MicroScint 40 per well and shaking for 20 min. The concentration of membranes and incubation time is determined for each assay in pilot experiments. [1]
References	[1]. Lindemann L, et al. CTEP: a novel, potent, long-acting, and orally bioavailable metabotropic glutamate receptor 5 inhibitor. J Pharmacol Exp Ther. 2011 Nov;339(2):474-86. [2]. Michalon A, et al. Chronic pharmacological mGlu5 inhibition corrects fragile X in adult mice. Neuron. 2012 Apr 12;74(1):49-56.