CTEP

Cat. No.: HY-15445

CAS No.: 871362-31-1

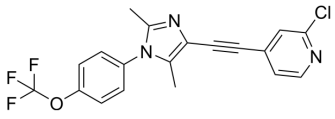
Molecular Formula: $C_{19}H_{13}ClF_3N_3O$

Molecular Weight: 391.77

Target: mGluR

Pathway: GPCR/G Protein; Neuronal Signaling

Storage: 4°C, sealed storage, away from moisture and light
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture and light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (255.25 mM)
* "≥" 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

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: ≥ 2.5 mg/mL (6.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.38 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.38 mM); Clear solution

BIOLOGICAL ACTIVITY

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. CTEP is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups.

IC_{50} & Target

mGlu5 Receptor
2.2 nM (IC_{50})

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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 [^{3}H]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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sleep. 2020 Nov 12;43(11):zsaa087.
- Research Square Print. September 2nd, 2022.

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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.

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