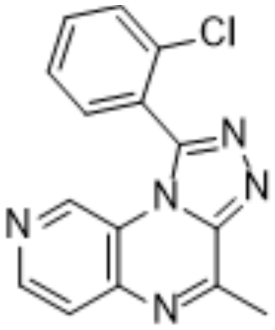
PDE2/PDE10-IN-1



Cat. No.:	HY-U00427
CAS No.:	1426833-08-0
Molecular Formula:	$C_{15}H_{10}ClN_5$
Molecular Weight:	295.73
Target:	Phosphodiesterase (PDE)
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month

SOLVENT & SOLUBILITY

In Vitro

DMSO : 12.5 mg/mL (42.27 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.3815 mL	16.9073 mL	33.8146 mL
	5 mM	0.6763 mL	3.3815 mL	6.7629 mL
	10 mM	0.3381 mL	1.6907 mL	3.3815 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: ≥ 1.25 mg/mL (4.23 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.25 mg/mL (4.23 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.25 mg/mL (4.23 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PDE2/PDE10-IN-1 is a phosphodiesterase 2 (PDE2) and PDE10 inhibitor with IC_{50}s of 29 and 480 nM, respectively.

IC_{50} & Target

hPDE2A	rPDE10A	hPDE4D	hPDE11A
29 nM (IC_{50})	480 nM (IC_{50})	5890 nM (IC_{50})	6920 nM (IC_{50})

In Vitro

PDE2/PDE10-IN-1 (Compound 6) inhibits PDE2 and PDE10, respectively, with an IC_{50} value of 29 and 480 nM. PDE2/PDE10-IN-1 also inhibits PDE11A and PDE4D with IC_{50}s of 6920 nM and 5890 nM, respectively. In addition PDE2/PDE10-IN-1 does not

	show significant inhibition of a panel of CYP450 enzymes (CYP1A2, 2C9, 2D6, 2C19, and 3A4). PDE2/PDE10-IN-1 is also inactive up to a concentration of 125 μg/mL in a bacterial mutagenicity assay[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The PK properties of PDE2/PDE10-IN-1 are studied in rats after 2.5 mg/kg i.v. and 10 mg/kg p.o. administration. After i.v. administration, a rapid clearance is observed ($t_{1/2}$=0.47 h), which is not expected based on the in vitro metabolic stability in rat liver microsomes (rLMs). Interestingly, PDE2/PDE10-IN-1 shows much slower clearance after p.o. administration ($t_{1/2}$ =2.36 h), resulting in good bioavailability and a maximum plasma concentration (C_{max}) of 997 ng/mL. PDE2/PDE10-IN-1 is assessed for its potential to cross the blood–brain barrier in rats after 10 mg/kg s.c. administration. PDE2/PDE10-IN-1 shows good formulatability with 10 to 20% HPβCD at pH>3.5. The brain concentration for PDE2/PDE10-IN-1 after 1 h administration is in the range of 370-895 ng/g with high brain free fractions and brain/plasma ratios. More specifically, PDE2/PDE10-IN-1, which is orally bioavailable, occupies PDE2 with an ED_{50} of 21 mg/kg[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats[1] Male Sprague-Dawley rats are fed with PDE2/PDE10-IN-1 (i.v., 2.5 mg/kg; p.o., 10 mg/kg). After administration, the clearance is observed. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Rombouts FJ, et al. Pyrido[4,3-e][1,2,4]triazolo[4,3-a]pyrazines as Selective, Brain Penetrant Phosphodiesterase 2 (PDE2) Inhibitors. ACS Med Chem Lett. 2015 Jan 15;6(3):282-6.

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