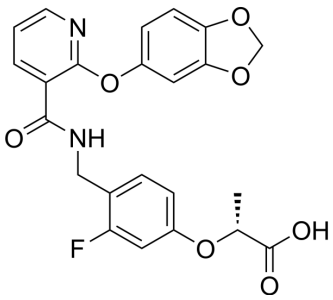
CP671305

Cat. No.:	HY-101803
CAS No.:	445295-04-5
Molecular Formula:	$C_{23}H_{19}FN_2O_7$
Molecular Weight:	454.4
Target:	Phosphodiesterase (PDE)
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (220.07 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2007 mL	11.0035 mL	22.0070 mL
	5 mM	0.4401 mL	2.2007 mL	4.4014 mL
	10 mM	0.2201 mL	1.1004 mL	2.2007 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 (5.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CP671305 is a potent, orally active, selective inhibitor of phosphodiesterase-4-D, and possesses high activities.

In Vitro

CP-671,305 is identified as a substrate of MRP2 and BCRP, but not MDR1. CP-671,305 is a substrate of human OATP2B1 with a high affinity (K_m=4 μM) but not a substrate for human OATP1B1 or OATP1B3. CP-671,305 displays high affinity (K_m=12 μM) for rat hepatic Oatp1a4[1]. CP-671,305 does not exhibit competitive inhibition of the five major cytochrome P450 enzymes, namely CYP1A2, 2C9, 2C19, 2D6 and 3A4 (IC_{50}s > 50 μM). Likewise, no time-dependent inactivation of the five major cytochrome P450 enzymes is discernible with CP-671,305[2].

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

In Vivo	CP-671,305 pharmacokinetics are largely unaltered, and compromised biliary clearance of CP-671,305 is compensated by increased urinary clearance[1]. CP-671,305 demonstrates generally favourable pharmacokinetic properties, systemic plasma clearance after intravenous administration is low in Sprague-Dawley rats (9.60 ± 1.16 mL/min/kg), beagle dogs (2.90 ± 0.81 mL/min/kg) and cynomolgus monkeys (2.94 ± 0.87 mL/min/kg) resulting in plasma half-lives > 5 h. Moderate to high bioavailability in rats (43-80%), dogs (45%) and monkeys (26%) is observed after oral dosing. In rats, oral pharmacokinetics are dose dependent over the dose range studied (10 and 25 mg/kg)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Jugular vein cannulated and bile duct-exteriorized male Sprague-Dawley rats (230-250 g) are used in the assay. All animals are fasted overnight before dosing, whereas access to water is provided ad libitum. Animals are fed following collection of the 2-h blood samples. CP-671,305 (3 mg/kg) in glycerol formal is administered intravenously (i.v.) via the jugular vein to three rats over 30 s, and serial plasma samples are collected before dosing and 0.033, 0.15, 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. All plasma samples are kept frozen until analysis. In addition, an i.v. dose of 3 mg/kg is also given to bile duct-exteriorized rats (n=3), where plasma, bile, and urine samples are collected on ice for up to 24 h and stored at -20°C until analysis. For the DDI studies, cyclosporin A (20 mg/kg in glycerol formal) is administered i.v. 30 min before intravenous administration of CP-671,305. Rifampicin (50 mg/kg) in saline is administered i.v. 5 min before the administration of CP-671,305. Plasma samples from the various pharmacokinetic studies are generated by centrifugation at 3000 rpm for 10 min at 4°C. Samples are stored at -20°C, pending analysis by LC-MS/MS. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Kalgutkar AS, et al. Role of transporters in the disposition of the selective phosphodiesterase-4 inhibitor (+)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid in rat and human. Drug Metab Dispos. 2007 Nov;35(11):2111-8. Epub 2007 Aug 8.

[2]. Kalgutkar AS, et al. Disposition of CP-671, 305, a selective phosphodiesterase 4 inhibitor in preclinical species. Xenobiotica. 2004 Aug;34(8):755-70.

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