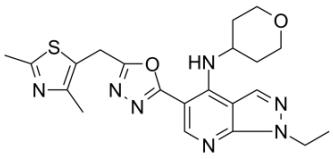
GSK356278

Cat. No.:	HY-106003
CAS No.:	720704-34-7
Molecular Formula:	$C_{21}H_{25}N_7O_2S$
Molecular Weight:	439.53
Target:	Phosphodiesterase (PDE)
Pathway:	Metabolic Enzyme/Protease
Storage:	-20°C, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (stored under nitrogen)



BIOLOGICAL ACTIVITY

Description

GSK356278 is a potent, selective, orally bioavailable and brain-penetrant inhibitor of phosphodiesterase 4 (PDE4), with pIC_{50}s of 8.6, 8.8, and 8.7 for human PDE4A, PDE4B, and PDE4D, respectively. GSK356278 has anti-inflammatory activity, and exhibits anxiolytic and cognition-enhancing effects[1].

IC_{50} & Target

PDE4A	PDE4B	PDE4D
8.6 (pIC_{50})	8.8 (pIC_{50})	8.7 (pIC_{50})

In Vitro

GSK356278 competes with [^{3}H]rolipram for the high affinity rolipram binding site (HARBS) with a pK_i of 8.6 in a competitive filtration-binding assay to the recombinant human PDE4B2B enzyme expressed in yeast membranes[1].
GSK356278 bounds to the HARBS in rats, mice, marmosets, and ferrets with pK_is of 7.9, 7.8, 8.4, and 8.5, respectively[1].
GSK356278 inhibits LPS-induced release of TNF-α in human whole blood, with a pIC_{50} of 7.6[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

GSK356278 (0.003-30 mg/kg; p.o.) shows anti-inflammatory activity in rodents at exposures that does not induce pica feeding[1].
GSK356278 (0.1-0.1 mg/kg; p.o.) demonstrates efficacy in a nonhuman primate model of anxiety at exposures that do not induce emesis[1].
GSK356278 (4 doses at 0.03, 0.1, 0.3, and 1.0 mg/kg for 6 weeks; p.o.) enhances performance in a nonhuman primate object retrieval test[1].GSK356278 exhibits oral bioavailability (rat 91%, monkey 23%) and C_{max} (rat 205, monkey 41 nM) following oral administration (rat 1, monkey 0.2 mg/kg)[1].
GSK356278 exhibits terminal elimination half-lives (rat 2.2, monkey 1.5 h) due to moderate blood clearance (rat 40, monkey 16 mL/min/kg) combined with volumes of distribution (rat 6.3, monkey 2.1 L/kg) following intravenous administration (rat 1, monkey 0.2 mg/kg)[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male Lewis rats (320-400 g) are treated with lipopolysaccharide (LPS)[1]
Dosage:	0.003-3 mg/kg
Administration:	P.o. administration 30 minutes prior to the LPS challenge
Result:	Reduced the level of neutrophilia in a dose-dependent manner, with an ED_{50} of 0.09 mg/kg.

Animal Model:	Male CD rats[1]
Dosage:	1 mg/kg (Pharmacokinetic Analysis)
Administration:	I.v. and p.o. administration
Result:	Oral bioavailability (91%), C_{max} (205 nM), $T_{1/2}$ (2.2 h).

REFERENCES

[1]. Rutter AR, et, al. GSK356278, a potent, selective, brain-penetrant phosphodiesterase 4 inhibitor that demonstrates anxiolytic and cognition-enhancing effects without inducing side effects in preclinical species. J Pharmacol Exp Ther. 2014 Jul;350(1):153-63.

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