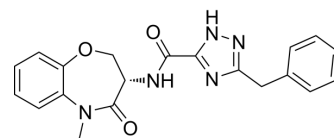


GSK2982772

Cat. No.:	HY-101760		
CAS No.:	1622848-92-3		
Molecular Formula:	C ₂₀ H ₁₉ N ₅ O ₃		
Molecular Weight:	377.4		
Target:	RIP kinase		
Pathway:	Apoptosis		
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 : 250 mg/mL (662.43 mM; Need ultrasonic)
 H₂O : < 0.1 mg/mL (ultrasonic;warming;heat to 60°C) (insoluble)

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	2.6497 mL	13.2485 mL	26.4971 mL
	5 mM	0.5299 mL	2.6497 mL	5.2994 mL
	10 mM	0.2650 mL	1.3249 mL	2.6497 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.5 mg/mL (6.62 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 2.08 mg/mL (5.51 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
 Solubility: ≥ 2.08 mg/mL (5.51 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK2982772 is a potent, orally active and ATP competitive RIP1 kinase inhibitor with IC₅₀ values of 16 nM and 20 nM for human and monkey RIP1, respectively^[1].

IC₅₀ & Target

IC₅₀: 16 nM (human RIP1 FP)
 IC₅₀: 20 nM (monkey RIP1 FP)
 IC₅₀: 2 μM (rat RIP1 FP)

	IC50: 2.5 μ M (mouse RIP1 FP) ^[1]
In Vitro	GSK2982772 shows more than 1,000-fold selectivity for ERK5 over a panel of over 339 kinases at 10 μ M. In stimulated cellular systems, GSK2982772 is also able to reduce spontaneous production of cytokines (IL-1 β and IL-6) in a concentration-dependent fashion from ulcerative colitis explant tissue in overnight incubations. GSK2982772 produces a weak concentration dependent inhibition of hERG in human embryonic kidney (HEK-293) cells, with an estimated IC ₅₀ of 195 μ M, and also shows a weak activation of the human Pregnane X receptor (hPXR) with an EC ₅₀ of 13 μ M ^[1] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GSK2982772 is dosed orally 15 min prior to TNF and shows 68, 80, and 87% protection from temperature loss over 6 h, at doses of 3, 10, and 50 mg/kg, respectively. In the corresponding TNF/zVAD model, GSK2982772 shows 13, 63, and 93% protection from temperature loss over 3 h. GSK2982772 displays a good free fraction in blood in rats (4.2%), dogs (11%), cynomolgus monkeys (11%), and humans (7.4%). The inhibitor has a good pharmacokinetic profile across both rats and monkeys. GSK2982772 distributes into a range of tissues including the colon, liver, kidney, and heart at concentrations comparable to those of blood. However, GSK2982772 has low brain penetration in rat (4%) despite possessing good cell permeability (21 \times 10 ⁻⁶ cm/s) ^[1] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration ^[1]

Mice: A total of 7 mice per dose group are orally predosed with saline or GSK2982772 at doses of 3, 10, and 50 mg/kg 15 min before i.v. administration of mouse TNF (30 μ g/ mouse). Temperature loss in the mice is measured by a rectal probe. The study is terminated after 6 h when the control group lost 7 $^{\circ}$ C^[1].

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

CUSTOMER VALIDATION

- Biochem Pharmacol. 2020 Feb;172:113751.

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REFERENCES

[1]. Harris PA, et al. Discovery of a First-in-Class Receptor Interacting Protein 1 (RIP1) Kinase Specific Clinical Candidate (GSK2982772) for the Treatment of Inflammatory Diseases. J Med Chem. 2017 Feb 23;60(4):1247-1261.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898

Fax: 609-228-5909

E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA