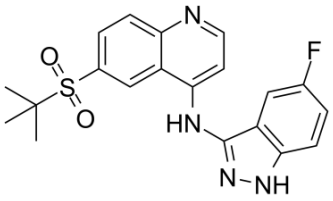
GSK583

Cat. No.:	HY-100339
CAS No.:	1346547-00-9
Molecular Formula:	$C_{20}H_{19}FN_4O_2S$
Molecular Weight:	398.45
Target:	RIP kinase
Pathway:	Apoptosis

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 : ≥ 100 mg/mL (250.97 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5097 mL	12.5486 mL	25.0972 mL
5 mM	0.5019 mL	2.5097 mL	5.0195 mL
10 mM	0.2510 mL	1.2549 mL	2.5097 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 (6.27 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK583 is a highly potent, orally active and selective inhibitor of RIP2 Kinase, with IC_{50} of 5 nM. GSK583 inhibits both TNF-α and IL-6 production with an IC_{50} value of 200 nM.

IC_{50} & Target

IC50: 5 nM (RIP2K)[1]

In Vitro

GSK583 (1 μM) exhibits excellent selectivity in a panel of 300 kinases, including p38α and VEGFR2. GSK583 potently and dose dependently inhibits MDP-stimulated tumor necrosis factor-alpha (TNFα) production with an IC_{50} of 8 nM. GSK583 demonstrates only a modest reduction in potency when profiled in a similar MDP-induced TNFα production assay in human whole blood (IC_{50} = 237 nM) and rat whole blood (IC_{50} = 133 nM)[1].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GSK583 (0.1, 1, and 10 mg/kg, p.o.) inhibits serum KC (the rodent orthologue of IL-8) levels in rats in a dose-dependent manner, with an IC_{50} derived from rat blood concentrations of 50 nM (or 20 ng/mL). Similarly, GSK583 inhibits serum KC levels and recruitment of neutrophils into the peritoneal cavity in mice in a dose-dependent manner, with an IC_{50} of 37 nM (15 ng/mL) derived from mouse blood concentration[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	A fluorescent polarization based binding assay is developed to quantitate interaction of novel test compounds at the ATP binding pocket of RIP2K by competition with a fluorescently labeled ATP competitive ligand. Full length FLAG His tagged RIP2K is purified from a baculovirus expression system and is used at a final assay concentration of twice the KD apparent. A fluorescent labeled ligand that is reversible and competitive with the inhibitors is used at a final assay concentration of 5 nM. Both the enzyme and ligand are prepared in solutions in 50 mM HEPES pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM DTT, and 1 mM CHAPS. Test compounds are prepared in 100% DMSO, and 100 nL is dispensed to individual wells of a multiwell plate. Next, 5 µL of RIP2K is added to the test compounds at twice the final assay concentration and incubated at room temperature for 10 min. Following the incubation, 5 µL of the fluorescent labeled ligand solution is added to each reaction at twice the final assay concentration and incubated at room temperature for at least 10 min. Finally, samples are read on an instrument capable of measuring fluorescent polarization. Test compound inhibition is expressed as percent (%) inhibition of internal assay controls. For concentration response experiments, normalized data are fit using the following four parameter logistic equation: y = A + ((B-C))/(1+(10x)/(10C)D), where y is the % activity (% inhibition) at a specified compound concentration, A is the minimum % activity, B is the maximum % activity, C = log10(IC_{50}), D = Hill slope, x = log10(compound concentration [M]), and pIC_{50} = (−C). MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female C57Bl/6 mice (for cytokine analyses) or male Balb/c mice (for peritoneal neutrophil analyses) (n=10/treatment group) are dosed orally 15 min prior to MDP challenge with vehicle or GSK583 (0.1, 1, or 10 mg/kg). For peritoneal neutrophil analysis, mice are sacrificed at 4 h post-MDP challenge (30 µg, i.p.) and peritoneal fluid is collected by lavage. Peritoneal neutrophils are quantified by FACS analysis. Rats[1] Female Crl:CD(SD) rats (n=8/treatment group) are dosed orally with vehicle or GSK583 15 min prior to MDP challenge (150 µg/rat, IV). At 2 h post MDP challenge, rats are sacrificed and terminal serum is prepared from blood collected via cardiac stick. Serum cytokine levels (IL-6, IL-8 or KC, IL-1β, and TNFα) are quantified by the MSD platform. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Biomater Sci. 2019 Jul 1;7(7):2702-2715.
- J Immunol. 2017 May 1;198(9):3729-3736.
- Research Square Preprint. 2020 Dec.

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REFERENCES

[1]. Haile PA et al. The Identification and Pharmacological Characterization of 6-(tert-Butylsulfonyl)-N-(5-fluoro-1H-indazol-3-yl)quinolin-4-amine (GSK583), a Highly Potent and Selective Inhibitor of RIP2 Kinase. J Med Chem, 2016 May 26, 59(10):4867-80.

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