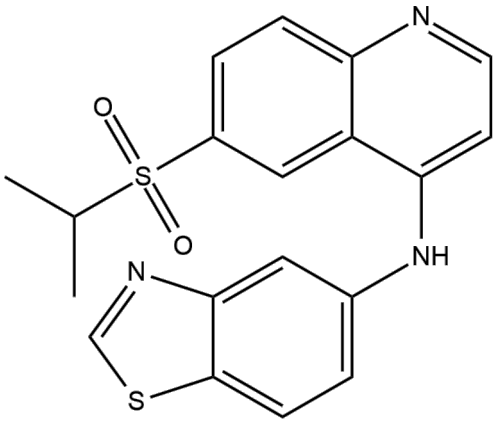
Product Data Sheet

Product Name: GSK-872
Cat. No.: GC19175

Chemical Properties

Cas. No.	1346546-69-7		
SMILES	O=S(C1=CC=C2N=CC=C(NC3=CC=C(SC=N4)C4=C3)C2=C1)(C(C)C)=O		
Formula	$C_{19}H_{17}N_3O_2S_2$	M.Wt	383.49
Solubility	DMSO : ≥ 100 mg/mL (260.76 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Cell experiment [1]:	
Cell lines	Mouse proximal renal tubular epithelial primary cells

Product Data Sheet

Preparation Method	Mouse proximal renal tubular epithelial primary cells were cultivated in DMEM/F12 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1% penicillin-streptomycin at 37°C in an incubator with 5% CO_2. Cells were seeded in a 96-well plate at a density of 3×10^3 cells/well for 24h, with three replicates for each treatment. Cells were treated with 0.5μM GSK-872 1h prior to the addition of 40μg/ml LPS for 24h. Control cells were treated with an equal volume of DMSO, the cell viability was determined.
Reaction Conditions	0.5μM; 1h
Applications	GSK-872 treatment enhanced cell viability of mouse proximal renal tubular epithelial primary cells exposed to LPS.
Animal experiment [2]:	
Animal models	Male Sprague Dawley rats

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Preparation Method	Male Sprague Dawley rats (3 months old; 250-300g) were maintained in a pathogen-free room at 21°C under a 12h light/12h dark artificial lighting cycle, with free access to food. GSK-872 (100μg) or SP600125 (10μg) was dissolved in vehicle (1% DMSO with 0.1M PBS; 10μl). Rats were injected 1h before I/R slowly by microliter syringe on right side using the coordinates: 1.5mm posterior, 1.0mm lateral and 3.5mm below the horizontal plane. Control rats were given an equal volume of vehicle. Anesthesia was induced and maintained in 1.4% isoflurane in 100% oxygen. Both vertebral arteries were permanently electro-cauterized and the bilateral common carotid arteries (CCAs) were freed. Rats were allowed to recover for 24h. Both CCAs were occluded for 20min with aneurysm clips to induce global cerebral ischemia. Rectal temperature was maintained at 36.5°C to 37.5°C throughout the procedures. Cerebral blood flow (CBF) before and after clamping the bilateral CCAs was monitored using a laser Doppler blood flow monitor. The rats brain tissue was rapidly removed for analysis.
Dosage form	100μg; once; i.c.v.
Applications	GSK-872 administration reduced the number of neuron deaths and the expression of RIPK3, p-JNK and IL-6 in rats with I/R.

References:

[1] Zhang S, Li R, Dong W, et al. RIPK3 mediates renal tubular epithelial cell apoptosis in endotoxin-induced acute kidney injury[J]. Molecular Medicine Reports, 2019, 20(2): 1613-1620.

[2] Hu W, Wu X, Yu D, et al. Regulation of JNK signaling pathway and RIPK3/AIF in necroptosis-mediated global cerebral ischemia/reperfusion injury in rats[J]. Experimental Neurology, 2020, 331: 113374.

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Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

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Background

GSK-872 is a potent Receptor-interacting protein kinase 3 (RIPK3) inhibitor with an IC_{50} value of 1.3nM[1]. GSK-872 protects cells from necroptotic apoptosis by inhibiting the RIP1/RIP3/MLKL pathway and inhibits the activation of the NLRP3 inflammasome[2]. GSK-872 has been widely used to alleviate the early brain damage following subarachnoid hemorrhage in rats[3].

In vitro, GSK-872 (10μM) pretreatment for 4 hours significantly improved fibrosis in rat cardiac fibroblasts, reduced the oxidation and phosphorylation levels of CaMKII, and caused rectification of CaMKIIδ alternative splicing anomalies[4]. 0.5μM of GSK-872 treatment for 1 hour alleviated the apoptosis of mouse proximal renal tubular epithelial primary cells induced by 40μg/ml lipopolysaccharide (LPS)[5]. Treatment with 1μM GSK-872 for 24 hours significantly reduced cell damage in human astrocytes under oxygen-glucose deprivation/reoxygenation (OGD/Re) conditions and inhibited lactate dehydrogenase leakage[6].

In vivo, GSK-872 treatment via a single intraperitoneal injection at a dose of 2mg/kg for 1 hour alleviated the infiltration of monocytes, endothelial cell necrosis and Kir4.1 down-regulation of astrocytes in the hippocampus of mice treated with LPS[7]. A single intracerebroventricular injection of 100μg dose of GSK-872 for 1 hour improved brain injury in rats after ischemia/reperfusion (I/R) and reduced the expression of inflammatory cytokines[8].

References:

[1] Mandal P, Berger S B, Pillay S, et al. RIP3 induces apoptosis independent of pronecrotic kinase activity[J]. Molecular cell, 2014, 56(4): 481-495.

[2] Liu M, Li H, Yang R, et al. GSK872 and necrostatin-1 protect retinal ganglion cells against necroptosis through inhibition of RIP1/RIP3/MLKL pathway in glutamate-induced retinal excitotoxic model of glaucoma[J]. Journal of neuroinflammation, 2022, 19(1): 262.

[3] Chen T, Pan H, Li J, et al. Inhibiting of RIPK3 attenuates early brain injury following subarachnoid hemorrhage: Possibly through alleviating necroptosis[J]. Biomedicine & pharmacotherapy, 2018, 107: 563-570.

Product Data Sheet

[4] Zhang J, Cao J, Qian J, et al. Regulatory mechanism of CaMKII δ mediated by RIPK3 on myocardial fibrosis and reversal effects of RIPK3 inhibitor GSK'872[J]. Biomedicine & Pharmacotherapy, 2023, 166: 115380.

[5] Zhang S, Li R, Dong W, et al. RIPK3 mediates renal tubular epithelial cell apoptosis in endotoxin-induced acute kidney injury[J]. Molecular Medicine Reports, 2019, 20(2): 1613-1620.

[6] Zhou X Y, Lin B, Chen W, et al. The brain protection of MLKL inhibitor necrosulfonamide against focal ischemia/reperfusion injury associating with blocking the nucleus and nuclear envelope translocation of MLKL and RIP3K[J]. Frontiers in Pharmacology, 2023, 14: 1157054.

[7] Huang W Y, Lai Y L, Liu K H, et al. TNFα-mediated necroptosis in brain endothelial cells as a potential mechanism of increased seizure susceptibility in mice following systemic inflammation[J]. Journal of Neuroinflammation, 2022, 19(1): 29.

[8] Hu W, Wu X, Yu D, et al. Regulation of JNK signaling pathway and RIPK3/AIF in necroptosis-mediated global cerebral ischemia/reperfusion injury in rats[J]. Experimental Neurology, 2020, 331: 113374.

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