GDC-2394

Cat. No.: HY-148258

CAS No.: 2238822-07-4

Molecular Formula: $C_{20}H_{25}N_5O_4S$

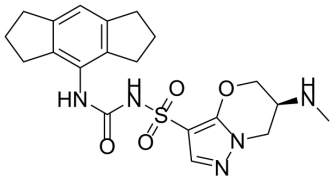
Molecular Weight: 431.51

Target: Interleukin Related; Caspase; NOD-like Receptor (NLR)

Pathway: Immunology/Inflammation; Apoptosis

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (115.87 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3174 mL	11.5872 mL	23.1744 mL
	5 mM	0.4635 mL	2.3174 mL	4.6349 mL
	10 mM	0.2317 mL	1.1587 mL	2.3174 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: ≥ 2.08 mg/mL (4.82 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.82 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.82 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GDC-2394 is an orally active and selective NLRP3 inhibitor, and also inhibits IL-1β with IC_{50}s of 0.4 μM (human IL-1β) and 0.1 μM (mouse IL-1β). GDC-2394 inhibits NLRP3-induced caspase-1 activity without inhibiting NLRC4-dependent inflammasome activation[1][2].

In Vitro

GDC-2394 (20 μM; 30 min) inhibits NLRP3-induced apoptosis associated speck-like protein containing CARD (ASC) speck formation in THP-1 cells[1].
GDC-2394 (1 nM-10 μM; 7 d) inhibits human macrophage IL-1β and IL-18 production after activation of the NLRP3 inflammasome[1].

GDC-2394 (0-20 μM; 30 min) inhibits NLRP3-dependent caspase-1 activation (IC_{50}=51 nM) in THP-1 cells, also inhibits NLRP3-dependent IL-1β release (IC_{50}=63 nM) and NLRC4-dependent IL-1β release (IC_{50}>20 μM) in mouse bone marrow-derived macrophages (mBMDMs)[1].

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

In Vivo

GDC-2394 (compound 20) (1 mg/kg, 10 mg/kg; p.o.; single dose) inhibits production of IL-1β in an acute mouse peritonitis model[1].

GDC-2394 (25 mg/kg; once daily for 7 d) reduces paw swelling and pain in a functional rat model of gouty arthritis[1].

Preclinical PK of GDC-2394[1].

Species	Mouse	Rat	Dog	Cyno
CL_p (mL/min/kg)	10.1	1.3	11.7	4.1
V_{ss} (L/kg)	0.72	0.29	0.67	0.18
$T_{1/2}$ (h)	1.2	4.4	0.99	0.89
%F (1 mg/kg)	80	33	78	53

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

Animal Model:	Acute mouse peritonitis model[1]
Dosage:	1 mg/kg and 10 mg/kg
Administration:	Oral gavage; 2 h later treated with 1.25 μg LPS (i.p.) followed by 1 mg monosodium urate crystals (i.p.) a further 2 h later.
Result:	Resulted in a dose-dependent decrease in peritoneal IL-1β concentrations after MSU treatment, and decreased the level of IL-1β by 66.8 and 81.3% at 1 and 10 mg/kg compared with the control.

Animal Model:	Functional rat model of gouty arthritis[1]
Dosage:	25 mg/kg
Administration:	Interventional injection; once daily for 7 days
Result:	Significantly inhibited knee swelling after 48 h.

REFERENCES

[1]. McBride C, et al. Overcoming Preclinical Safety Obstacles to Discover (S)-N-((1,2,3,5,6,7-Hexahydro-s-indacen-4-yl)carbamoyl)-6-(methylamino)-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine-3-sulfonamide (GDC-2394): A Potent and Selective NLRP3 Inhibitor. J Med Chem. 2022 Oct 24.

[2]. Stafford, et al. Preparation of hexahydroindacenylcarbamoyldihydropyrazolooxazinesulfonamide derivatives and analogs for use as interleukin-1 activity inhibitors: World Intellectual Property Organization, WO2018136890[P]. 2018-07-26.

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

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