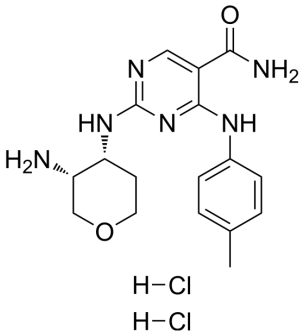
GSK143 dihydrochloride

Cat. No.:	HY-12736A
CAS No.:	2341796-81-2
Molecular Formula:	$C_{17}H_{24}Cl_2N_6O_2$
Molecular Weight:	415.32
Target:	Syk; PERK
Pathway:	Protein Tyrosine Kinase/RTK; Cell Cycle/DNA Damage
Storage:	4°C, sealed storage, away from moisture and light * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture and light)



SOLVENT & SOLUBILITY

In Vitro

H_2O : 100 mg/mL (240.78 mM; Need ultrasonic)
DMSO : ≥ 50 mg/mL (120.39 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4078 mL	12.0389 mL	24.0778 mL
5 mM	0.4816 mL	2.4078 mL	4.8156 mL
10 mM	0.2408 mL	1.2039 mL	2.4078 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 (6.02 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.02 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.02 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK143 dihydrochloride is an orally active and highly selective spleen tyrosine kinase (SYK) inhibitor with a pIC_{50} of 7.5. GSK143 dihydrochloride inhibits phosphorylated Erk (pErk: pIC_{50}=7.1)[1]. GSK143 dihydrochloride reduces inflammation and prevents recruitment of immune cells in the intestinal muscularis in mice[2][3].

IC_{50} & Target

pIC50: 7.5 (SYK) and 7.1 (pErk)[1]

In Vitro

GSK143 dihydrochloride (compound 20) inhibits ZAP-70 (pIC_{50}=4.7), LCK (pIC_{50}=5.3), LYN (pIC_{50}=5.4), JAK1/2/3 (pIC_{50} =5.8/5.8/5.7), Aurora B (pIC_{50}=4.8), hWB (pIC_{50}=6.6), hERG (pIC_{50}=4.7)[1].
GSK143 dihydrochloride (10-10000 nM; every 24 hours for 3 days) has an IC_{50} of 323 nM in CLL cells. GSK 143 dihydrochloride (1 μM; 30 mins) abrogates early signalling events including SYK phosphorylation and calcium flux[2].
GSK143 dihydrochloride (0.1-10 μM; for 30 min) reduces cytokine expression in bone marrow derived macrophages in a concentration-dependent manner[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[2]

Cell Line:	Chronic lymphocytic leukaemia (CLL) cells
Concentration:	10, 100, 1000, 10000 nM
Incubation Time:	Every 24 hours for 3 days
Result:	Had an IC_{50} of 323 nM.

In Vivo

GSK143 (0.1-10 mg/kg; orally; 1.5 hours) reduces inflammation and prevents recruitment of immune cells in the intestinal muscularis of 1 mg/kg[3].
GSK143 (3, 10, 30, 100 mg/kg; oral; 1 hour before ovalbumin challenge) reduces the cutaneous reverse passive Arthus reaction in a dose dependent manner by approximately 50% and 70% at 10 mg/kg and 30 mg/kg, respectively[2].
GSK143 (iv of 1 mg/kg; po of 3 mg/kg) has a $T_{1/2}$ of 4.2 hours, low clearance (16 mL/min/kg), moderate bioavailability of 30% and a V_{ss} of 4.1 L/kg in rats[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Wild type C57NL/BL6 mice, 10-12 weeks old[3]
Dosage:	0.1, 1, 3, 10 mg/kg
Administration:	Orally; 1.5 hours before intestinal manipulation (IM)
Result:	Reduced inflammation and prevented recruitment of immune cells in the intestinal muscularis.

Animal Model:	Male CD rats (175-200 g)[1]
Dosage:	1 mg/kg of iv; 3 mg/kg of po (Pharmacokinetic Analysis)
Administration:	IV or PO
Result:	Had a $T_{1/2}$ of 4.2 hours, low clearance (16 mL/min/kg), moderate bioavailability of 30% and a V_{ss} of 4.1 L/kg.

REFERENCES

[1]. John Liddle, et al. Discovery of GSK143, a Highly Potent, Selective and Orally Efficacious Spleen Tyrosine Kinase Inhibitor. Bioorg Med Chem Lett. 2011 Oct 15;21(20):6188-94.

[2]. Abraham M Varghese, et al. Highly Selective SYK Inhibitor, GSK143, Abrogates Survival Signals in Chronic Lymphocytic Leukaemia. Br J Haematol. 2018 Sep;182(6):927-930.

[3]. Sjoerd H W van Bree, et al. Inhibition of Spleen Tyrosine Kinase as Treatment of Postoperative Ileus. Gut. 2013 Nov;62(11):1581-90.

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

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