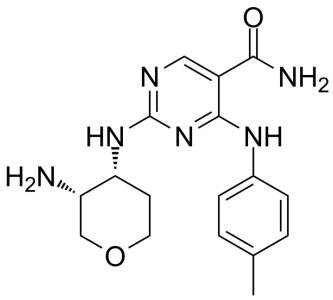
GSK143

Cat. No.:	HY-12736
CAS No.:	1240390-27-5
Molecular Formula:	$C_{17}H_{22}N_6O_2$
Molecular Weight:	342.4
Target:	Syk; PERK
Pathway:	Protein Tyrosine Kinase/RTK; Cell Cycle/DNA Damage
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

GSK143 is an orally active and highly selective spleen tyrosine kinase (SYK) inhibitor with a pIC_{50} of 7.5. GSK143 inhibits phosphorylated Erk (pErk: pIC_{50}=7.1)[1]. GSK143 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 (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 (10-10000 nM; every 24 h for 3 days) has an IC_{50} of 323 nM in CLL cells. GSK 143 (1 μM; 30 mins) abrogates early signalling events including SYK phosphorylation and calcium flux[2].

GSK143 (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 h 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.

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