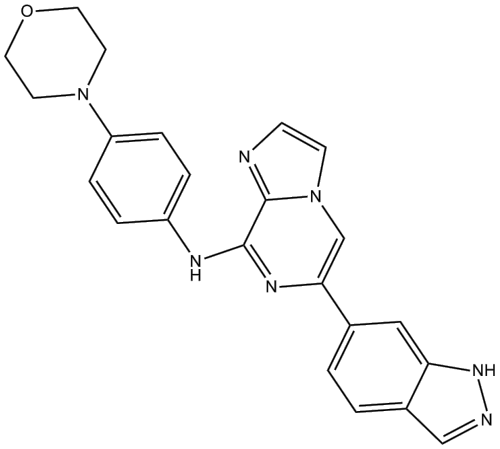
Product Data Sheet

Product Name: GS-9973
Cat. No.: GC16430

Chemical Properties

Cas. No.	1229208-44-9		
Chemical Name	6-(1H-indazol-6-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine		
SMILES	C12=NC=CN1C=C(C3=CC=C(C=NN4)C4=C3)N=C2NC5=CC=C(N6CCOCC6)C=C5		
Formula	$C_{23}H_{21}N_7O$	M.Wt	411.46
Solubility	≥ 20.55mg/mL in DMSO	Storage	Desiccate 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

Kinase experiment [1]:

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Kinase assays	Full-length baculovirus-expressed Syk kinase activity was measured in a Lance-based assay format in a final volume of 25 µL containing 25 mM Tris-HCl, pH 7.5, 5 mM β-glycerophosphate, 2 mM DTT, 0.1 mM Na3VO4, 10 mM MgCl2, 0.5 µM Promega PTK biotinylated peptide substrate 1, 0.01% casein, 0.01% Triton X-100, 0.25% glycerol, and 40 mM ATP (Km for ATP) incubated at room temperature for 60 mins. Reactions were stopped with the addition of 30 mM EDTA containing 30 µL of SA-APC and 4 nM PT-66 antibody and the plates were measured on a Perkin-Elmer Envision. IC50 values for test compounds were determined using a four-parameter linear regression algorithm.

Cell experiment [1]:

Cell lines	MV-4-11 cells
Preparation method	The solubility of this compound in DMSO is > 20.6 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	10 µM; 72 hrs
Applications	GS-9973 selectively inhibited Syk in cells, and potently suppressed BCR-mediated activation and proliferation of B-cells as well as immune-complex-induced cytokine production in monocytes.

Animal experiment [1]:

Animal models	Rat collagen-induced arthritis (CIA) model

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Dosage form	1 ~ 10 mg/kg; p.o.; b.i.d.
Applications	In a rat CIA model, GS-9973 (1 ~ 10 mg/kg; p.o.; b.i.d.) significantly reduced ankle inflammation. Moreover, GS-9973 also showed disease-modifying activity in several histological measurements, including inhibition of pannus formation, cartilage damage, bone resorption, as well as periosteal bone formation with the ED50 values ranging from 1.2 to 3.9 mg/kg.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Currie KS, Kropf JE, Lee T, et al. Discovery of GS-9973, a selective and orally efficacious inhibitor of spleen tyrosine kinase. J Med Chem, 2014, 57(9): 3856-3873.

Background

GS-9973 is a selective inhibitor of Syk with IC50 value of 7.7 nM [1].

Spleen tyrosine kinase (Syk) is a cytoplasmic tyrosine kinase that is expressed mainly in hematopoietic cells and acts as a mediator of immunoreceptor signaling. Syk can be used for therapy of autoimmune, oncology indications and allergy [1].

GS-9973 is an orally bioavailable and selective Syk inhibitor. GS-9973 showed good absorption potential and high bioavailability. In monocytes, GS-9973 inhibited immune-complex-stimulated cytokine production and BCR-mediated proliferation and activation of B-cells [1]. In chronic lymphocytic leukemia (CLL) cells, GS-9973 significantly reduced pAkt and ribosomal S6 phosphorylation. These results suggested that GS-9973 inhibited B-cell receptor (BCR) mediated signaling pathways. In CLL samples, the combination of GS-9973 and idelalisib synergistically reduced CLL cell viability [2].

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In chronic lymphocytic leukemia patients, GS-9973 inhibited adenopathy and reduced lymph node [3].

References:

[1]. Currie KS, Kropf JE, Lee T, et al. Discovery of GS-9973, a selective and orally efficacious inhibitor of spleen tyrosine kinase. J Med Chem, 2014, 57(9): 3856-3873.
[2]. Burke RT1, Meadows S, Loriaux MM, et al. A potential therapeutic strategy for chronic lymphocytic leukemia by combining Idelalisib and GS-9973, a novel spleen tyrosine kinase (Syk) inhibitor. Oncotarget, 2014, 5(4): 908-915.
[3]. Sharman J, Hawkins M, Kolibaba K, et al. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. Blood, 2015, 125(15): 2336-2343.

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