AS-605240

Cat. No.: HY-10109

CAS No.: 648450-29-7

Molecular Formula: $C_{12}H_7N_3O_2S$

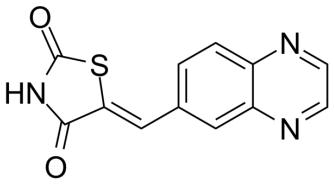
Molecular Weight: 257.27

Target: PI3K; Autophagy

Pathway: PI3K/Akt/mTOR; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 3.33 mg/mL (12.94 mM; ultrasonic and warming and heat to 80°C)

H_2O : 2.78 mg/mL (10.81 mM; ultrasonic and warming and adjust pH to 10 with NaOH and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.8870 mL	19.4348 mL	38.8697 mL
	5 mM	0.7774 mL	3.8870 mL	7.7739 mL
	10 mM	0.3887 mL	1.9435 mL	3.8870 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 0.5% CMC-Na >> 0.5% Tween-80
   Solubility: 6.25 mg/mL (24.29 mM); Suspened solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (9.72 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (9.72 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AS-605240 is a specific and orally active inhibitor of the PI3Kγ, with an IC_{50} of 8 nM, and a K_i of 7.8 nM.

IC_{50} & Target

PI3Kγ 7.8 nM (Ki)	PI3Kγ 8 nM (IC_{50})	PI3Kα 60 nM (IC_{50})	PI3Kβ 270 nM (IC_{50})
PI3Kδ 300 nM (IC_{50})	Autophagy		

In Vitro	AS-605240 is an isoform-selective inhibitor of PI3Kγ with over 30-fold selectivity for PI3Kδ and β, and 18- and 7.5-fold selectivity over PI3Kα, respectively. AS-605240 shows an inhibitory effect on C5a-mediated PKB phosphorylation in RAW264 mouse macrophages with an IC_{50} of 0.09 μM. AS-605240 blocks PKB phosphorylation induced by MCP-1 and has little or no effect after stimulation with CSF-1. AS-605240 inhibits MCP-1-mediated phosphorylation of PKB and its downstream substrates GSK3α and β in a concentration-dependent manner. AS605240 suppresses in a dose-dependent manner the proliferation of BDC2.5 $CD4^+$ T cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AS-605240 (30 mg/kg BW, per os, every 12 h) markedly decreases FoxM1 expression in mouse lungs and fails to restore vascular integrity[1]. AS-605240 reduces RANTES-induced peritoneal neutrophil recruitment, with ED_{50} of 9.1 mg/kg. In the CCL5 model, AS-605240 shows an ED_{50} value of 10 mg/kg, in correlation with the percentage of reduction of neutrophil recruitment observed in $Pik3cg^{-/-}$ mice. AS-605240 (50 mg/kg, p.o.) substantially reduces clinical and histological signs of joint inflammation to a similar extent to that of $Pik3cg^{-/-}$ mice[2]. AS605240 (30 mg/kg, i.p.) suppresses intracellular PAkt in splenocytes of NOD mice and delays diabetes onset. AS605240 also prevents autoimmune diabetes in prediabetic NOD mice, and suppresses autoreactive T cells while increasing Tregs in NOD mice. AS605240 (30 mg/kg, i.p.) reverses hyperglycemia in newly hyperglycemic NOD mice, reverses hyperglycemia in early diabetic NOD mice through Tregs and suppresses T-cell infiltration in pancreatic islets while increasing Tregs[3]. AS605240 (25, 50 mg/kg) markedly reduces total cell count and numbers of macrophages, neutrophils and lymphocytes in rats. AS605240 significantly reduces the levels of TNF-α and IL-1β in BALF to 132.7±11.2 pg/mL and 49.2±11.3 pg/mL in 25 mg/kg AS605240 + BLM group and 131.3±10.7 and 49.6±8.8 pg/mL in 50 mg/kg AS605240 + BLM group, respectively. AS605240 inhibits prefibrotic cytokines production in bleomycin-induced pulmonary fibrosis. AS605240 inhibits phosphorylation of Akt of inflammatory cells in bleomycin-induced pulmonary fibrosis model[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Human PI3Kγ (100 ng) is incubated at RT with kinase buffer (10 mM $MgCl_2$, 1 mM β-glycerophosphate, 1 mM DTT, 0.1 mM Na_3VO_4, 0.1% Na Cholate and 15 M ATP/100 nCi γ[^{33}P]ATP, final concentrations) and lipid vesicles containing 18 M PtdIns and 250 M of PtdSer (final concentrations), in the presence of inhibitors or DMSO. Kinase reaction is stopped by adding 250 g of Neomycin-coated Scintillation Proximity Assay (SPA) bead and proceeded. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [3]	A total of 5×10^5 BDC2.5 splenocytes and 50 μg/mL BDC2.5-peptide are incubated in vitro in a 96-well round-bottom plate for 48 h. Then the cultures are pulsed with 1 μCi of tritiated thymidine [^{3}H] to determine cell proliferation. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [4]	In this study, rats are bred for one week to affirm body weight and then randomLy divided into four experimental groups: (a) control group (rats are given vehicle only); (b) BLM group (rats are induced with BLM); (c) BLM + 25 mg/kg AS605240 group (rats are induced with BLM and then administrated with 25 mg/kg AS605240); (d) BLM + 50 mg/kg AS605240 group (the same protocol as the former group except a different dose of 50 mg/kg AS605240). In addition, five rats are given 50 mg/kg AS605240 only to detect whether AS605240 has any side effect simultaneously as the previous four groups. Rats in (c), (d) and AS605240-given-only group are administered orally 25, 50 and 50 mg/kg AS605240 by gavage while rats in control group and BLM group are given only equivalent saline at day-1 (the day rats are given BLM is marked as day-0). The same dosage is maintained once everyday for 28 days. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Syst. 2020 Jan 22;10(1):66-81.e11.

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- Drug Des Devel Ther. 2023 Apr 27;17:1275-1288.
- J Neurochem. 2022 Jun;161(6):478-491.
- Molecules. 2020 Apr 23;25(8):1980.

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REFERENCES

[1]. Huang X, et al. Endothelial p110γPI3K Mediates Endothelial Regeneration and Vascular Repair After Inflammatory Vascular Injury. Circulation. 2016 Mar 15;133(11):1093-103.

[2]. Camps M, et al. Blockade of PI3Kgamma suppresses joint inflammation and damage in mouse models of rheumatoid arthritis. Nat Med. 2005 Sep;11(9):936-43.

[3]. Azzi J, et al. The novel therapeutic effect of phosphoinositide 3-kinase-γ inhibitor AS605240 in autoimmune diabetes. Diabetes. 2012 Jun;61(6):1509-18. Epub 2012 Mar 8.

[4]. Wei X, et al. A phosphoinositide 3-kinase-gamma inhibitor, AS605240 prevents bleomycin-induced pulmonary fibrosis in rats. Biochem Biophys Res Commun. 2010 Jun 25;397(2):311-7. Epub 2010 May 26.

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