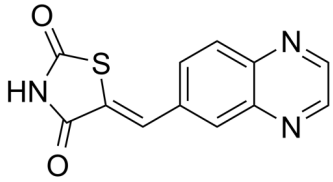
Data Sheet

Product Name:	AS-605240
Cat. No.:	CS-0084
CAS No.:	648450-29-7
Molecular Formula:	$C_{12}H_7N_3O_2S$
Molecular Weight:	257.27
Target:	Autophagy; PI3K
Pathway:	Autophagy; PI3K/Akt/mTOR
Solubility:	DMSO : 5.8 mg/mL (22.54 mM; Need warming)



BIOLOGICAL ACTIVITY:

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.
IC50 & Target: IC50: 8 nM (PI3Kγ), 60 nM (PI3Kα), 270 nM (PI3Kβ), 300 nM (PI3Kδ)[2]
Ki: 7.8 nM (PI3Kγ)[2]
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].
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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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. **Animal Administration:** AS605240 is dissolved in a vehicle (5% Tween-80).[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.

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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