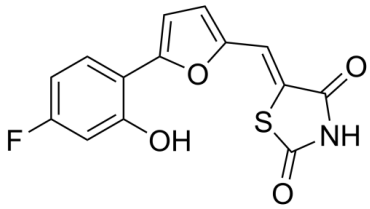
Data Sheet

Product Name:	AS-252424
Cat. No.:	CS-3164
CAS No.:	900515-16-4
Molecular Formula:	$C_{14}H_8FNO_4S$
Molecular Weight:	305.28
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO : 25 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

AS-252424 is a potent and selective **PI3Kγ** inhibitor with an **IC_{50}** of 30±10 nM. IC50 & Target: IC50: 30±10 nM (PI3Kγ), 935±150 nM (PI3Kα), 20 μM (PI3Kβ), 20 μM (PI3Kδ)[1] ***In Vitro:*** AS-252424 also inhibits PI3Kα, PI3Kβ and PI3Kδ with IC_{50}s of 935±150 nM, 20 μM and 20 μM, respectively. AS-252424 inhibits MCP-1-mediated chemotaxis in wild-type primary monocytes in a concentration-dependent manner with an IC_{50} value of 52 μM, as well as in the monocytic cell line THP-1 with an IC_{50} value of 53 μM. In the human monocytic cell line THP-1, MCP-1 binding to the GPCR chemokine receptor CCR2, strongly induces phosphorylation of PKB/Akt, which is effectively inhibited by AS-252424 at IC_{50} values as low as 0.4 μM. In contrast, induction of PKB/Akt phosphorylation by colony stimulating factor (CSF-1), binding to the growth factor receptor c-fms, is only blocked by AS-252424 at IC_{50} values as high as 4.7 μM[1]. ***In Vivo:*** Oral administration of AS-252424 in a mouse model of acute peritonitis leads to a significant reduction of leukocyte recruitment. To evaluate the efficacy of AS-252424 to block leukocyte migration in vivo, it is tested in a mouse model of thioglycollate-induced peritonitis. Oral administration of AS-252424 at 10 mg/kg results in moderate reduction of neutrophil recruitment (35%±14%), almost matching the result observed in PI3Kγ-deficient mice. Given the short oral half-life of AS-252424 ($t_{1/2}$=1 h) and relative high clearance (2.25 L/kg per h), investigations at later time points (24-48 h) to assess macrophage and monoycyte recruitment are not undertaken. The modest pharmacokinetic properties do not appear to be caused by rapid oxidative metabolism (microsomal metabolism after 1 h: 16% (rat), 10% (human))[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]A PI3Kγ lipid kinase assay, based on the neomycin-coated scintillation proximity assay (SPA) bead technology, is performed in 384-well plates using ATP/[γ^{33}P]ATP and PtdIns. Kinase assays for IC_{50} value determinations with PI3Kα, PI3Kβ, and PI3Kδ are carried out[1].

Cell Assay: [1]After 3 h of starvation in serum-free medium, **Raw-264 macrophages** are pretreated with inhibitors (e.g., **AS-252424, 1 nM, 10 nM, 100 nM, 1 μM, 10 μM and 100 μM**) or DMSO for 30 min and stimulated for 5 min with 50 nM C5a. PKB/Akt phosphorylation is monitored using phospho-Ser-473 Akt specific antibody and standard ELISA protocols[1].

Animal Administration: [1]Mice[1]

PI3Kγ knockout (KO) mice are used. **Oral administration of AS-252424 at 10 mg/kg** is performed in PI3Kγ-deficient mice.

References:

[1]. Pomel V, et al. Furan-2-ylmethylene thiazolidinediones as novel, potent, and selective inhibitors of phosphoinositide 3-kinase gamma. J Med Chem.

2006 Jun 29;49(13):3857-71.

CAIndexNames:

2,4-Thiazolidinedione, 5-[[5-(4-fluoro-2-hydroxyphenyl)-2-furanyl]methylene]-, (5Z)-

SMILES:

O=C(NC/1=O)SC1=C/C2=CC=C(C3=CC=C(F)C=C3O)O2

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