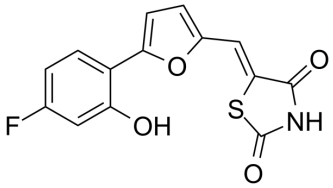
AS-252424

Cat. No.:	HY-13532
CAS No.:	900515-16-4
Molecular Formula:	$C_{14}H_8FNO_4S$
Molecular Weight:	305.28
Target:	PI3K
Pathway:	PI3K/Akt/mTOR
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 : 25 mg/mL (81.89 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2757 mL	16.3784 mL	32.7568 mL
	5 mM	0.6551 mL	3.2757 mL	6.5514 mL
	10 mM	0.3276 mL	1.6378 mL	3.2757 mL

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

BIOLOGICAL ACTIVITY

Description

AS-252424 is a potent and selective PI3Kγ inhibitor with an IC_{50} of 30±10 nM.

IC_{50} & Target

PI3Kγ	PI3Kα	PI3Kδ	PI3Kβ
30 nM (IC_{50})	935 nM (IC_{50})	20 μM (IC_{50})	20 μM (IC_{50})

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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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 monocyte 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Biol Chem. 2020 May 22;295(21):7431-7441.
- J Mol Med (Berl). 2018 Feb;96(2):119-133.
- Molecules. 2020 Apr 23;25(8):1980.

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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.

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