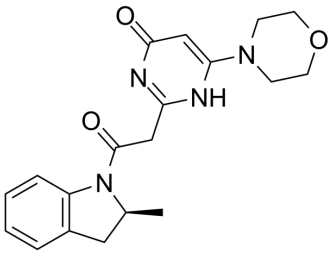
SAR-260301

Cat. No.:	HY-15837
CAS No.:	1260612-13-2
Molecular Formula:	$C_{19}H_{22}N_4O_3$
Molecular Weight:	354.4
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 : 125 mg/mL (352.71 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.8217 mL	14.1084 mL	28.2167 mL
	5 mM	0.5643 mL	2.8217 mL	5.6433 mL
	10 mM	0.2822 mL	1.4108 mL	2.8217 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (5.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SAR-260301 is an orally available and selective PI3Kβ inhibitor with an IC_{50} of 23 nM[1][2].

IC_{50} & Target

PI3Kβ 23 nM (IC_{50})	PI3Kδ 468 nM (IC_{50})	PI3Kα 1539 nM (IC_{50})	PI3Kγ 10000 nM (IC_{50})
Vps34 183 nM (IC_{50})	PI3KC2γ 3812 nM (IC_{50})	pAkt 49 nM (IC_{50})	DNA-PK 2000 nM (IC_{50})

In Vitro	In the UACC-62 tumor cell line assay, SAR-260301 inhibits pAktS473 with a measured IC_{50} at 0.06 μM and an estimated IC_{90} at 2 μM[1]. In MEF-3T3-myr-p110β mechanistic model, SAR260301 inhibits PI3Kβ-dependent proliferation/viability in low serum conditions with an IC_{50} of 196 nM. In PTEN-deficient human prostate tumor cells, SAR260301 inhibits LNCaP cell proliferation in low and high serum conditions with IC_{50} values of 2.9 and 5.0 μM, respectively, after 4-day treatment, whereas it is inactive in these conditions in PC3 cells at concentrations up to 10 μM, despite target engagement. After prolonged treatment, SAR260301 at 3 or 10 μM inhibits PC3 cell proliferation in low serum conditions, with a cytostatic effect achieved for 14 days, despite some cell death induction observed at 10 μM. SAR260301 also leads to antitumor activities in PTEN-deficient/BRAF-mutant human melanoma cells, inhibiting cell proliferation with IC_{40} values of 6.5 and 3.3 μM for UACC-62 and WM-266.4, respectively, after 4-day treatment[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	SAR-260301 displays antitumor efficacy in human PTEN-deficient melanoma models in mice as a single agent. SAR-260301 treatment leads to a statistically significant tumor growth inhibition as measured by a ΔT/ΔC of 39% (p = 0.054 versus control mice) on day 15 post-tumor implantation. SAR-260301 is well tolerated at the active dose, with no sign of toxicity and no body weight loss. Oral administration of SAR-260301 reveals sustained target inhibition (≥50%) of pAkt-S473 for at least 7 h. SAR-260301 has moderate terminal elimination half-life ($t_{1/2}$=0.87 h, 1.4 h, 2.5 h, 0.87h, 6.9 h and 4.5 h for female SCID mice (3 mg/kg, iv), mice (10 mg/kg, po), mice (100 mg/kg, po), female nude rats (3 mg/kg, iv), rat (10 mg/kg, po), male beagle dogs (10 mg/kg, po))[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Cell proliferation is measured by quantifying intracellular ATP using CellTiter-Glo kit. Cells seeded into 96-well black microplates in complete medium, are treated with single or combined agents (e.g., SAR260301) 0.3 nM-30 μM (0.1% DMSO final concentration) for 96 hours[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] SAR-260301 is evaluated for its antitumor effects in UACC-62 melanoma subcutaneous xenografts in SCID mice. Tumors are allowed to reach at least 150 mm^3 before treatment, and tumor volume is measured regularly over the treatment period. Mice are treated orally with SAR-260301 at the dose of 150 mg/kg using a bidaily (BID) schedule in order to favor sustained pathway inhibition and allow comparison with the study performed in PC3 model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Certal V, et al. Discovery and optimization of pyrimidone indoline amide PI3Kβ inhibitors for the treatment of phosphatase and tensin homologue (PTEN)-deficient cancers. J Med Chem. 2014 Feb 13;57(3):903-20.

[2]. Bonnevaux H, et al. Concomitant Inhibition of PI3Kβ and BRAF or MEK in PTEN-Deficient/BRAF-Mutant Melanoma Treatment: Preclinical Assessment of SAR260301 Oral PI3Kβ-Selective Inhibitor. Mol Cancer Ther. 2016 Jul;15(7):1460-71.

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