Product Data Sheet

Product Name: SAR-100842
Cat. No.: GC31785

Chemical Properties

Cas. No.	1195941-38-8		
SMILES	O=C(C1(NC(C2=CC=C(OC)C(OCCC3=CC=CC(C)=C3)=C2)=O)CC4=C(C=CC=C4)C1)O		
Formula	$C_{27}H_{27}NO_5$	M.Wt	445.51
Solubility	DMSO : ≥ 83.3 mg/mL (186.98 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	SAR-100842		

Protocol

Cell experiment [1]:

Cell lines

Preparation Method	SAR-100842 were dissolved into 100% DMSO to 10 mM stock and further diluted in serum free media.cells were serum starved and incubated in vehicle or varying concentrations of drug for 24 hours. Lower wells contained DMEM with or without attractants (1-5% FBS or 5-10 μM LPA). 4T1-Luc2 or MDA-MB-231T cells were added to the upper wells at a concentration of 2×105 cells/mL in serum-free DMEM containing vehicle or SAR-100842 and incubated for 4 hours in a humidified chamber at 37⊿in 5% CO2. The top chamber was removed and the cells that had migrated to the bottom of the membrane were stained using Diff Quick Staining kit. Using an inverted brightfield microscope with a 10× objective, the number of cells that had migrated through the membrane was counted in three fields in the center of each filter.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Reaction Conditions	0.5-50μM for 24, 48, 72 hours
Applications	50 μM SAR-100842 reduced the migration of MDA-MD-231T cells through a collagen membrane by 1.92-fold and 3.15-fold to FBS and LPA chemoattractants, respectively. In 4T1-Luc2 cells 50 μM SAR-100842 reduced migration by 10.8-fold and 13.6-fold to FBS and LPA, respectively.

Animal experiment [1]:

Animal models	6-8 week old athymic nu/nu mice
Preparation Method	Mice received 30 mg/kg SAR-100842 by oral gavage twice daily for the duration of the experiment. 6-8 week old athymic nu/nu mice received either 1.0×10^6 SKVO3 cells or 3.5×10^6 OVCAR5 cells in an intraperitoneal injection. On day two post cell injection, mice were randomized to three groups. Group one began vehicle on day 2, group two began 30 mg/kg SAR-100842 twice daily on day two for the duration of the experiment, and group three began 30 mg/kg SAR-100842 twice daily on day 10 for the duration of the experiment. On day 70 post cell injection all mice were euthanized and necropsied. Liver, abdominal lymph nodes or masses, omentum, peritoneum and any other organ suspected of harboring tumor were collected, fixed in 10% NBF and prepared for histological analysis.
Dosage form	30 mg/kg twice daily, oral

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Applications	In the SKOV3 model treated early with SAR-100842, Only a weak reduction in diaphragm, kidney and lymph node metastases was evident ; none of these reductions were maintained in the group that started treatment on day 10 post-injection. For the OVCAR5 model, metastases were observed at day 70 post-injection on the omentum, liver, diaphragm, pancreas and peritoneum. Of these, SAR-100842 apparently reduced diaphragm tumor deposits, both surface and invasive, but was without significant effect in other locations.

References:

[1]: Brooks D, Zimmer A, Wakefield L, et al. Limited fibrosis accompanies triple-negative breast cancer metastasis in multiple model systems and is not a preventive target[J]. Oncotarget, 2018, 9(34): 23462.

Background

SAR-100842 is a potent, selective oral antagonist of the LPAR1, for diffuse cutaneous systemic sclerosis [1]. SAR-100842 is safe, moderately effective, and well-tolerated in patients[1].

SAR-100842(10 μM) showed weak inhibitory activity (25-30%) on the impact on Gαq signal transduction in an RH7777 cell line exogenously expressing the LPA1 receptor. SAR-100842 was able to fully inhibit the LPA driven Gαi signaling with an IC50 of 52.5 ± 12 nM. SAR-100842 (IC50 31 ± 8.5 nM) fully inhibited the LPA mediated G-protein signalling subsequently leads to recruitment and activation of β-arrestin. SAR-100842 showed a significant inhibition of Gα12/13 signalling at 1 and 10 μM in MeT-5A cell line [2]. 50 μM SAR-100842 reduced the migration of

Product Data Sheet

MDA-MD-231T cells through a collagen membrane to FBS and LPA chemoattractants, respectively. In 4T1-Luc2 cells 50 μM SAR-100842 reduced migration to FBS and LPA, respectively [3].

SAR-100842 (30 mg/kg BID) reversed significantly dermal thickness, inhibited myofibroblast differentiation and skin collagen content in the mouse model of bleomycin-induced skin fibrosis. SAR-100842 significantly reduced the expression of CXCL-1 and IL-13, associated with the TH-2 cytokine milieu found in Systemic Sclerosis (SSc) [4]. SAR-100842 has a half-life of 4.9 h and a Cmax of 5600 ng/mL after a 30 mg/kg oral dosing in mice [1].

References:
[1]. Allanore Y, Distler O, Jagerschmidt A, et al. Lysophosphatidic acid receptor 1 antagonist SAR100842 for patients with diffuse cutaneous systemic sclerosis: a double-blind, randomized, eight-week placebo-controlled study followed by a sixteen-week open-label extension study[J]. Arthritis & Rheumatology, 2018, 70(10): 1634-1643.
[2]. Ellery J, Dickson L, Cheung T, et al. Identification of compounds acting as negative allosteric modulators of the LPA1 receptor[J]. European journal of pharmacology, 2018, 833: 8-15.
[3]. Brooks D, Zimmer A, Wakefield L, et al. Limited fibrosis accompanies triple-negative breast cancer metastasis in multiple model systems and is not a preventive target[J]. Oncotarget, 2018, 9(34): 23462.
[4]. Illiano S, Ledein L, Bidouard J P, et al. OP0228 Protective Effect of LPA1 and 3 Receptor Antagonism in Experimental Skin Fibrosis is Linked to LPA Activity in Dermal Fibroblasts of SSC Patients[J]. Annals of the Rheumatic Diseases, 2013, 72(Suppl 3): A129-A129.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA