Data Sheet (Cat.No.T6278)

TargetMol

Sotrastaurin

Chemical Properties

CAS No. : 425637-18-9

Formula: C25H22N6O2

Molecular Weight: 438.48

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	Sotrastaurin (AEB071) is a potent pan-PKC inhibitor with Kis of 0.95 nM for PKCα, 0.64 nM for PKCβI, 2.1 nM for PKCδ, 3.2 nM for PKCε, 1.8 nM for PKCη, and 0.22 nM for PKCθ.
Targets(IC50)	PKC
In vitro	In cell-free kinase assays, Sotrastaurin (AEB071) inhibited PKC, with K(i) values in the subnanomolar to low nanomolar range. Upon T-cell stimulation, AEB071 markedly inhibited in situ PKC catalytic activity. In primary human and mouse T cells, AEB071 treatment effectively abrogated at low nanomolar concentration markers of early T-cell activation [1]. Growth inhibition was observed in GNAQ/GNA11-mutant cells with AEB071 versus no activity in wild-type cells. In the GNAQ-mutant cells, AEB071 decreased phosphorylation of myristoylated alanine-rich C-kinase substrate, a substrate of PKC, along with ERK1/2 and ribosomal S6, but persistent AKT activation was present [2].
In vivo	Daily oral dosing of Sotrastaurin (80 mg/kg, tid) resulted in statistically significant inhibition of tumor growth compared with vehicle-treated animals, corresponding to 17% tumor volume change, treated over the control group [2]. The combination therapy resulted in a significantly enhanced reduction in tumor volume when compared to either AEB071 or BYL719 alone. There was even a greater effect when compared to vehicle control [3].
Kinase Assay	Classical and novel PKC isotypes were assayed by scintillation proximity assay technology. In brief, the assay was performed in 20 mM Tris-HCl buffer, pH 7.4, and 0.1% bovine serum albumin by incubating 1.5 μM of the peptide substrate with 10 μM [33P] ATP, 10 mM Mg(NO3)2, 0.2 mM CaCl2, and PKC at a protein concentration varying from 25 to 400 ng/ml, and lipid vesicles containing 30 mol% phosphatidylserine, 5 mol% diacylglycerol (DAG), and 65 mol% phosphatidylcholine at a final lipid concentration of 0.5 μM. Incubation was performed for 60 min at room temperature. The reaction was stopped by adding 50 μl of a mixture containing 100 mM EDTA, 200 μM ATP, 0.1% Triton X-100, and 0.375 μg/well streptavidin-coated scintillation proximity assay beads in PBS without Ca2+ and Mg2+. Incorporated radioactivity was measured in a MicroBetaTrilux counter for 1 min. In situ Thr-219 autophosphorylation status analysis of PKC was done by a phospho-site-specific antibody [1].
Cell Research	Jurkat cells (5×10^6 cells) were pretreated for 4 h with 500 nM AEB071 and loaded for 30 min at 37°C in the dark with 5 μM fura-2 acetoxymethyl ester. Dye excess was removed

Cell Research	by washing in Hanks' balanced salt solution. Samples were prewarmed to 37°C and baseline Ca2+ levels were determined for 100 s on a Spex Fluorolog 2 spectrofluorometer equipped with two excitation monochrometers and a Cooper system. At this point, anti-CD3 antibody was added to a final concentration of 10 μg/ml, and data were collected over 6.5 min. The maximal and minimal Ca2 levels were determined by adding an excess of ionomycin and EGTA. Experiments were performed at least four times with similar outcomes [1].
Animal Research	6-8 week nu/nu SCID female mice bearing subcutaneously injected 92.1 tumors (7 mice/group) of 100mm3 diameter were treated with vehicle, AEB071 (80mg/kg/d) TID and or BYL719 orally (50mg/kg/d) QD as single agents and in combination, 5 days/week for 2 weeks. After 2 weeks, two animals from each group were sacrificed and tumors were collected to analyze for Western blot. For Omm1 xenografts, 6-8 weeks athymic female mice bearing subcutaneously injected Omm1 tumors (7 mice/group) of 100 mm3 diameter were treated with vehicle, AEB071 (80mg/kg/d) TID and or BYL719 orally (50mg/kg/d) QD as single agents and in combination, 5 days/week for 3 weeks. Tumors were homogenized with grinding resins kits as per manufacturer's instructions. Tumors were collected to analyze for H&E and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. Tumors were measured every 2 to 3 days with calipers, and tumor volumes were calculated by the formula 4/3 × r3 [r = (larger diameter + smaller diameter)/4. Toxicity was monitored by weight loss [3].

Solubility Information

Solubility	DMSO: 81 mg/mL (184.73 mM),Sonication is recommended. Ethanol: 2 mg/mL (4.56 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 3.3 mg/mL (7.53 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.2806 mL	11.403 mL	22.8061 mL
5 mM	0.4561 mL	2.2806 mL	4.5612 mL
10 mM	0.2281 mL	1.1403 mL	2.2806 mL
50 mM	0.0456 mL	0.2281 mL	0.4561 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Evenou JP, et al. The potent protein kinase C-selective inhibitor AEB071 (sotrastaurin) represents a new class of immunosuppressive agents affecting early T-cell activation. J Pharmacol Exp Ther. 2009 Sep;330(3):792-801.
Naylor TL, et al. Protein kinase C inhibitor sotrastaurin selectively inhibits the growth of CD79 mutant diffuse large B-cell lymphomas. Cancer Res. 2011 Apr 1;71(7):2643-53.
Musi E, et al. The phosphoinositide 3-kinase α selective inhibitor BYL719 enhances the effect of the protein kinase C inhibitor AEB071 in GNAQ/GNA11-mutant uveal melanoma cells. Mol Cancer Ther. 2014 May;13(5):1044-53.

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