Product Data Sheet

Product Name: Retaspimycin
Cat. No.: GC10327

Chemical Properties

Cas. No.	857402-23-4		
Chemical Name	[(3R,5S,6R,7S,8E,10S,11S,12Z,14E)-6,20,22-trihydroxy-5,11-dimethoxy-3,7,9,15-tetramethyl-16-oxo-21-(prop-2-enylamino)-17-azabicyclo[16.3.1]docosa-1(22),8,12,14,18,20-hexaen-10-yl] carbamate		
SMILES	CC1CC(C(C(C=C(C(C(C=CC=C(C(=O)NC2=CC(=C(C(=C2O)C1)NCC=C)O)C)OC)OC(=O)N)C)C)O)OC		
Formula	$C_{31}H_{45}N_3O_8$	M.Wt	587.7
Solubility	Soluble in DMSO	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	Retaspimycin		

Protocol

Cell experiment:

Cell proliferation is studied using the cell proliferation reagent WST-1. Briefly, 8 × 103 cells are seeded in triplicate in 96-well plates and treated for 5 days, with either trastuzumab or Retaspimycin as indicated. Viable cells are estimated on the basis of their ability to metabolize tetrazolium salt WST-1 to formazan by mitochondrial dehydrogenases. Quantification of the formazan dye directly correlates with the number of metabolically active cells and is analyzed by a scanning microplate reader. Results are shown as means ± SE[3].

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Animal experiment:

RPMI-8226 cells are harvested from cultures grown in vitro in RPMI medium 1640 supplemented with heat-inactivated 10% (wt/vol) FBS and 100 units/mL penicillin/streptomycin at 37°C under a humidified 95%/5% (vol/vol) mixture of air and CO2. Cells are washed twice by using sterile Hepes-buffered saline (HBS) and suspended in HBS to a concentration of 1 × 108 viable cells per mL. Twelve female Nu/Nu nude mice (≈20 g) are used in the assay. RPMI-8226 cells (1 × 107 cells per mouse) are implanted in the right flank. When tumor volume reaches ≈200-500 mm3 (≈4 weeks postimplantation), animals receive a single i.v. dose of 50 mg/kg Retaspimycin via the tail vein. At 4, 24, and 48 h posttreatment, the animals are killed with carbon dioxide, and tumors are removed and stored at −80°C until analyzed. Four animals are used for each time point. Tumor samples are homogenized in an ice-cold, nitrogen-sparged 1:1 solution of MeOH:150 mM citrate, 0.2% (wt/vol) EDTA, and 0.2% (wt/vol) ascorbate (pH 3.0) for 1 min in an ice/water bath with a homogenizer at 17,500 rpm. Samples are centrifuged for 5 min at 4°C at 18,000 × g. The supernatants are diluted 1:1 with ice-cold, nitrogen-sparged 75 mM citrate, 0.1% (wt/vol) EDTA, and 0.1% (wt/vol) ascorbate (pH 3) containing 25 ng/mL deuterated 17-AAG as internal standard and analyzed by LC-MS/MS analysis. The standard curve is prepared for Retaspimycin, 17-AAG, and 17-AG in 1:1 MeOH:150 mM citrate, 0.2% (wt/vol) EDTA, and 0.2% (wt/vol) ascorbate (pH 3.0); diluted 1:1 with ice-cold, nitrogen-sparged 75 mM citrate, 0.1% (wt/vol) EDTA, and 0.1% (wt/vol) ascorbate (pH 3.0) containing 25 ng/mL deuterated 17-AAG as internal standard; and analyzed by LC-MS/MS[1].

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References:

[1]. Sydor JR, et al. Development of 17-allylamino-17-demethoxygeldanamycin hydroquinone hydrochloride (IPI-504), an anti-cancer agent directed against Hsp90. Proc Natl Acad Sci U S A. 2006 Nov 14;103(46):17408-13. Epub 2006 Nov 7.
[2]. Floris G, et al. The heat shock protein 90 inhibitor IPI-504 induces KIT degradation, tumor shrinkage, and cell proliferation arrest in xenograft models of gastrointestinal stromal tumors. Mol Cancer Ther. 2011 Oct;10(10):1897-908.
[3]. Scaltriti M, et al. Antitumor activity of the Hsp90 inhibitor IPI-504 in HER2-positive trastuzumab-resistant breast cancer. Mol Cancer Ther. 2011 May;10(5):817-24.

Background

Retaspimycin is a water-soluble hydroquinone hydrochloride salt inhibitor of Hsp90 [1].

Hsp90 is a member of the Hsp family. The other members of this protein family are Hsp40, Hsp70 and so on. These proteins act as molecule chaperons and participate in many cellular processes. When cells are exposed in stress, some proteins become unstable, accumulate to form aggregates and subsequently cause cell apoptosis. In this situation, Hsps will help their client proteins folding correctly, accompany them to be translocated to the correct location and thus prevent the cells from apoptosis. Hsps are required for cancer

cells development. They are found to overexpress in a variety of cancer cells. Therefore, the inhibitors of Hsp are thought to be attractive therapy for cancer treatment. As an inhibitor of Hsp90, retaspimycin works through binding to the ATP-binding pocket of Hsp90 N-terminal [1].

In both RPMI-8826 and MM1.S cells, treatment of retaspimycin resulted in degradation of the Hsp90 client proteins, for instance, c-RAF and Her2. It also caused increased levels of Hsp70. Besides that, retaspimycin is found to prevent RPMI-8826 cells from secreting the immunoglobulin light chain. In breast cancer cells which are resistant to trastuzumab, treatment of retaspimycin potently caused Her2 degradation and resulted in tumor growth suppression and cell apoptosis [1].

Retaspimycin is often used as combination therapy with other drugs in cancer treatment. In mice bearing GIST-882 (gastrointestinal stromal tumor) xenografts, the administration of retaspimycin associated with imatinib showed a significant effect with a 66% tumor regression. In mice bearing GIST-PSW xenografts, both the combination treatment of retaspimycin and imatinib or sunitinib showed effective antitumor activities in reducing tumor burden. When used alone, retaspimycin reduced tumor volumes by 84% and 69% in GIST-PSW and GIST-882 mice models, respectively. Moreover, retaspimycin is found to decrease the mitotic activity in these two models. However, the antimitotic effects of retaspimycin were less significant than of imatinib or sunitinib or the combination treatment [2].

References:
[1]. Hanson B E, Vesole D H. Retaspimycin hydrochloride (IPI-504): a novel heat shock protein inhibitor as an anticancer agent. 2009.
[2]. Floris G, Debiec-Rychter M, Wozniak A, et al. The heat shock protein 90 inhibitor IPI-504 induces KIT degradation, tumor shrinkage, and cell proliferation arrest in xenograft models of gastrointestinal stromal tumors. Molecular cancer therapeutics, 2011, 10(10): 1897-1908.