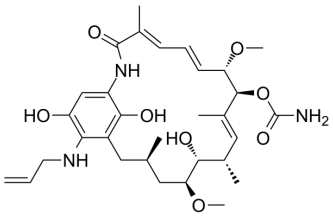
Retaspimycin

Cat. No.:	HY-15263
CAS No.:	857402-23-4
Molecular Formula:	$C_{31}H_{45}N_3O_8$
Molecular Weight:	587.7
Target:	HSP
Pathway:	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Retaspimycin is a potent inhibitor of Hsp90, with EC_{50}s of 119 nM for both Hsp90 and Grp9.	
IC_{50} & Target	HSP90 119 nM (EC50)	GRP94 119 nM (EC50)
In Vitro	Retaspimycin is a potent inhibitor of Hsp90, with EC_{50}s of 119 nM for both Hsp90 and Grp9. Retaspimycin (IPI-504) is cytocoxic to human multiple myeloma (MM) cell lines, with EC_{50}s of 307 ± 51 nM and 306 ± 38 nM, respectively, for MM1.s and RPMI-8226 cells[1]. Retaspimycin (IPI-504, 10-100 nM) suppresses the growth of both trastuzumab-sensitive and -resistant cells in a dose-dependent manner. Retaspimycin (0-500 nM) decreases HER2 protein expression and suppresses both Akt and MAPKs pathways in both sensitive and trastuzumab-resistant cells[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	Retaspimycin (IPI-504, 50 mg/kg, i.v.) causes selective tumor retention in RPMI-8226 tumor-bearing mice[1]. Retaspimycin (IPI-504, 100 mg/kg, p.o., 3 times per week) reduces the tumor volume by 69% and and 84% of baseline values in GIST-882 and GIST-PSW xenografts, respectively. Furthermore, Retaspimycin in combination with imatinib inhibits tumor growth more significantly than Retaspimycin alone in GIST-PSW model, but no obvious difference is ovsrebed in the GIST-882 model. Retaspimycin also downregulates KIT in gastrointestinal stromal tumor (GIST)[2]. Retaspimycin (IPI-504, 50 mg/kg) shows antitumor activity in HCC1569 xenografts. IPI-504 (100 mg/kg, i.p.) effectively decreases the levels of HER2, p-Akt, and p-MAPKs in BT474R and BT474H1047R tumors[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Cell Assay [3]	Cell proliferation is studied using the cell proliferation reagent WST-1. Briefly, 8×10^3 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal	RPMI-8226 cells are harvested from cultures grown in vitro in RPMI medium 1640 supplemented with heat-inactivated 10%

Administration [1]	(wt/vol) FBS and 100 units/mL penicillin/streptomycin at 37°C under a humidified 95%/5% (vol/vol) mixture of air and CO_2. Cells are washed twice by using sterile Hepes-buffered saline (HBS) and suspended in HBS to a concentration of 1×10^8 viable cells per mL. Twelve female Nu/Nu nude mice (≈20 g) are used in the assay. RPMI-8226 cells (1×10^7 cells per mouse) are implanted in the right flank. When tumor volume reaches ≈200-500 mm^3 (≈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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Theranostics. 2019 Aug 12;9(20):5769-5783.
- Transl Oncol. 2019 Apr 3;12(6):801-809.

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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.

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