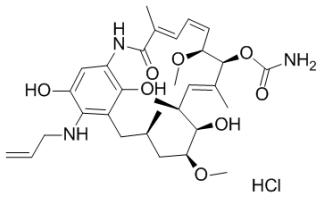
Retaspimycin Hydrochloride

Cat. No.:	HY-10210
CAS No.:	857402-63-2
Molecular Formula:	$C_{31}H_{46}ClN_3O_8$
Molecular Weight:	624.17
Target:	HSP
Pathway:	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 60 mg/mL (**96.13 mM;** Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6021 mL	8.0106 mL	16.0213 mL
	5 mM	0.3204 mL	1.6021 mL	3.2043 mL
	10 mM	0.1602 mL	0.8011 mL	1.6021 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: ≥ 3 mg/mL (4.81 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: 3 mg/mL (4.81 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Retaspimycin Hydrochloride is a potent and water-soluble inhibitor of **Hsp90** with **EC_{50}**s of 119 nM for both Hsp90 and Grp9.

IC_{50} & Target

EC50: 119 nM (Hsp90), 119 nM (Grp94)[3]

In Vitro

Retaspimycin (IPI-504) is a novel and highly soluble analog of 17AAG, an inhibitor of Hsp90. Retaspimycin can abrogate both the unfolded protein response element (UPRE) and ERSE-driven luciferase activity in non-treated U266 and MM.1s cells as well as in Tunicamycin (Tm)-treated cells. The IC_{50}s for the inhibition of reporter gene activity by

	Retaspimycin are 196±56 nM in U266 and 472±177 nM in MM.1s for UPRE-luc activity and 213±140 nM for the ERSE-driven activity in MM.1s cells. Retaspimycin treatment leads to a dose-dependent decrease of p50ATF6 with EC_{50} of 237 nM, consistent with the reporter-gene assay. The level of sXBP1 is decreased in the presence of Retaspimycin with an apparent EC_{50} between 300 nM and 1 μM[1]. Incubation of Retaspimycin (IPI-504) potently suppresses both Akt and MAPKs phosphorylation in both sensitive and Trastuzumab-resistant cells. Total levels of Akt decreased in all 4 cell lines (BT474, SKBR-3, HCC1569, and HCC1569) in a dose-dependent manner. However, levels of total MAPKs are not significantly altered with Retaspimycin treatment[2].
In Vivo	Retaspimycin (IPI-504) and Trastuzumab independently induce tumor regression of Trastuzumab-sensitive BT474 cell-derived xenografts. Xenografts derived from BT474R cells continue to grow in the presence of Trastuzumab but are still sensitive to Retaspimycin. When used in combination, Retaspimycin and Trastuzumab add only marginal benefits to Retaspimycin monotherapy. Retaspimycin (100 mg/kg) as a single agent is more efficacious than Trastuzumab in inhibiting tumor growth in HCC1569 xenografts. The combination is not significantly superior to Retaspimycin used as a single agent[2].

PROTOCOL

Cell Assay [1]	Hela cells are grown in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum, 1 ug/mL streptomycin and 1 ug/mL penicillin. U266 and MM.1s are cultured in RPMI 1640 medium containing 15% fetal bovine serum, 1 mM pyruvate, 1 ug/mL streptomycin, and 1 ug/mL penicillin. All the cell lines are maintained at 37°C in a humidified 5% CO_2 atmosphere. Viability studies are performed using the vital mitochondrial function stain Alamar Blue. After cells are incubated in 96-well plates (200 μL) ± Retaspimycin, 20 μL of Alamar Blue is added and incubated for 4-6 h at 37°C. The Alamar Blue reduction is monitored using an Envision plate reader at λ_{EM}=544 nm and λ_{EM}=590 nm. The ratios obtained from drug-treated cells versus vehicle treated cells are quantified and plotted against drug concentration to give EC_{50} values. Caspase-3 and 7 activities are detected using the Caspase Glow kit[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] For all the experiments, 2×10^7 cells are injected into the right flanks of 10 mice for each experimental condition. Established tumors are treated with Trastuzumab, Retaspimycin, or the combination as following: Trastuzumab (10 mg/kg in sterile PBS) or sterile PBS (control) is given intraperitoneally twice weekly. Retaspimyci (100 mg/kg) is administered intraperitoneally thrice weekly. Retaspimyci, Trastuzumab, and the combination treatments are tolerable. No significant toxicity is noticed among the treatment arms. Tumor growth is measured with digital calipers as indicated and tumor volume is determined using the formula: $(\text{length}\times\text{width}^2)\times(\pi/6)$. At the end of the experiments, the animals are anesthetized with 1.5% isofluorane-air mixture and killed by cervical dislocation. Results are depicted as means of tumor volume±SE. 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]. Patterson J, et al. IPI-504, a novel and soluble HSP-90 inhibitor, blocks the unfolded protein response in multiple myeloma cells. Cancer Chemother Pharmacol. 2008 May;61(6):923-32.

[2]. 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.

[3]. 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.

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