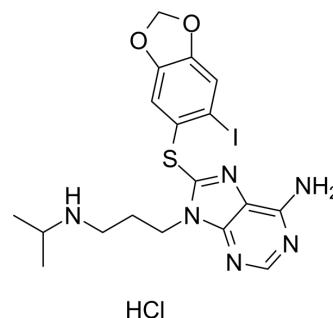


Zelavespib hydrochloride

Cat. No.:	HY-11038B
CAS No.:	2095432-24-7
Molecular Formula:	C ₁₈ H ₂₂ ClIN ₆ O ₂ S
Molecular Weight:	548.83
Target:	HSP
Pathway:	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro	H ₂ O : 15.38 mg/mL (28.02 mM; Need ultrasonic)					
	Preparing Stock Solutions	Solvent	Mass	1 mg	5 mg	10 mg
		Concentration				
		1 mM		1.8221 mL	9.1103 mL	18.2206 mL
		5 mM		0.3644 mL	1.8221 mL	3.6441 mL
	10 mM		0.1822 mL	0.9110 mL	1.8221 mL	
Please refer to the solubility information to select the appropriate solvent.						
In Vivo	1. Add each solvent one by one: PBS Solubility: 14.29 mg/mL (26.04 mM); Clear solution; Need ultrasonic					

BIOLOGICAL ACTIVITY

Description	Zelavespib (PU-H71) hydrochloride is a potent Hsp90 inhibitor, with an IC ₅₀ of 51 nM in MDA-MB-468 cells.
IC₅₀ & Target	HSP90 51 nM (IC ₅₀ , MDA-MB-468 cells)
In Vitro	Zelavespib hydrochloride is a potent Hsp90 inhibitor, with an IC ₅₀ of 51 nM in MDA-MB-468 cells. Zelavespib inhibits the growth of several tumor cells, such as MDA-MB-468, MDA-MB-231 and HCC-1806 cells, with IC ₅₀ s of 65 ± 8 nM, 140 ± 5 nM and 87 ± 3 nM, respectively, and such inhibition is associated with a G2-M block arrest. Zelavespib (10-1000 nM) induces significant apoptosis in triple-negative breast cancers (TNBCs). Zelavespib (0.5, 1 μM) also downregulates oncoproteins involved in the invasive potential of TNBCs ^[1] . Zelavespib (0.5 μM) decreases and depletes the BCR signaling kinases. Zelavespib (0.25-10 μM) is cytotoxic to CLL cells but shows minimal effects on PBMC or resting B cells. In addition, Zelavespib (0-1 μM) reduces CLL viability via the induction of mitochondrial apoptosis, and antagonizes the survival signals from CLL microenvironment at 0.5 μM ^[2] . Zelavespib (0.05 μM) induces apoptosis of MDA-MB-231, BT-474, and MCF7 cells, and such induction is enhanced by TNF-α. Zelavespib (0.05 μM) degrades IKKβ, and down-regulates the NF-κB transcriptional

	<p>activity induced by TNF-α treatment^[3].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Zelavespib hydrochloride (75 mg/kg, i.p.) causes intratumor accumulation, extends down-regulation of anti-tumor driving molecules, completes and retains responses at nontoxic doses in MDA-MB-468 tumor-bearing mice. Zelavespib (75 mg/kg 3\timesweek, i.p.) suppresses the growth of tumors, and such an effect is associated with down-regulation of several Hsp90-regulated malignancy driving proteins^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Kinase Assay ^[1]	<p>Measurements are performed in black 96-well microtiter plates. In short, cell lysates are prepared by rupturing cellular membranes by freezing at -70°C and dissolving the cellular extract in HFB [20 mM Hepes (K), pH 7.3, 50 mM KCl, 5 mM MgCl₂, 20 mM Na₂MoO₄, 0.01% Nonidet P-40] with added protease and phosphatase inhibitors (Zelavespib, etc.). Saturation curves are recorded in which fluorescently labeled geldanamycin (Cy3B-GM) (3 nM) is treated with increasing amounts of cellular lysates. The amount of lysate that results in polarization (mP) readings corresponding to 90%-99% bound ligand is chosen for the competition study. Here, each 96-well plate contains 3 nM Cy3B-GM, cellular lysate and tested Hsp90 inhibitor in a final volume of 100 μL. The plate is left for 24 h on a shaker at 4°C, and the fluorescence polarization (FP) values in mP are recorded. EC₅₀ values are determined as the competitor concentrations at which 50% of the Cy3B-GM is displaced. FP measurements are performed on an Analyst GT microplate reader^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Cell Assay ^[1]	<p>The antiproliferative effects of select Hsp90 inhibitors is evaluated using the CellTiter-Glo Luminescent Cell Viability Assay kit. Briefly, exponentially growing MDA-MB-468, MDA-MB-231, and HCC-1806 cells are seeded into black 96-well microtiter plates and incubated in medium containing either vehicle control (DMSO) or Zelavespib for the indicated time at 37°C. Plates containing 3 replicate wells per assay condition are seeded at a density of 8 \times 10³ cells for each cell line in 100 μL medium. After exposure of cells to the Hsp90 inhibitors, plates are equilibrated to room temperature (20-25°C) for approximately 30 min, and 100 μL CellTiter-Glo reagent are added to each well. Plates are mixed for 2 min on an orbital shaker and then incubated for 15 min to 2 h at room temperature. The luminescence signal in each well is measured in an Analyst GT microplate reader. The percentage cell growth inhibition is calculated by comparing luminescence readings obtained from treated versus control cells, accounting for initial cell population (time 0). The IC₅₀ is calculated as the drug concentration that inhibits cell growth by 50%^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[1]	<p>Mice^[1]</p> <p>Mice bearing MDA-MB-468 tumors reaching a volume of 100-150 mm³ are treated i.p. using different doses and schedules: Group 01 (n = 8) PBS; group 02 (n = 8) Zelavespib at 50 mg/kg on alternate days; group 03 (n = 8) Zelavespib at 50 mg/kg 5xqd ; group 04 (n = 8) Zelavespib at 75 mg/kg 3 week; group 05 (n = 8) Zelavespib at 75 mg/kg on alternate days. Mice bearing HCC-1806 or MDA-MB-231 xenografted tumors receive Zelavespib at 75 mg/kg on alternate days. Tumor volume is determined by measurement with Vernier calipers, and tumor volume is calculated as the product of its length \times width² \times 0.4. Tumor volume is expressed on indicated days as the median tumor volume \pm SD indicated for groups of mice^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

REFERENCES

- [1]. Caldas-Lopes E, et al. Hsp90 inhibitor PU-H71, a multimodal inhibitor of malignancy, induces complete responses in triple-negative breast cancer models. *Proc Natl Acad Sci U S A*. 2009 May 19;106(20):8368-73.
- [2]. Guo A, et al. HSP90 stabilizes B-cell receptor kinases in a multi-client interactome: PU-H71 induces CLL apoptosis in a cytoprotective microenvironment. *Oncogene*. 2017 Jun 15;36(24):3441-3449.

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