Pimitespib

Cat. No.: HY-15785

CAS No.: 1260533-36-5

Molecular Formula: $C_{25}H_{26}N_8O$

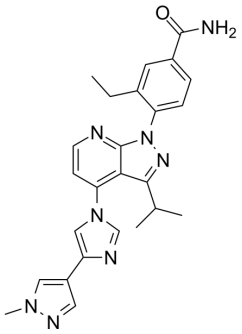
Molecular Weight: 454.53

Target: HSP

Pathway: Cell Cycle/DNA Damage; Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (275.01 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2001 mL	11.0004 mL	22.0007 mL
5 mM	0.4400 mL	2.2001 mL	4.4001 mL
10 mM	0.2200 mL	1.1000 mL	2.2001 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: ≥ 2.08 mg/mL (4.58 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.58 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.58 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pimitespib (TAS-116) is an oral bioavailable, ATP-competitive, highly specific HSP90α/HSP90β inhibitor (K_is of 34.7 nM and 21.3 nM, respectively) without inhibiting other HSP90 family proteins such as GRP94[1]. Pimitespib demonstrates less ocular toxicity[2].

IC_{50} & Target

HSP90α	HSP90β
34.7 nM (Ki)	21.3 nM (Ki)

In Vitro

Pimitespib binds not only to the conventional-binding pockets as existing Hsp-90 inhibitors, but also to a novel-binding pocket. Such a unique binding mode makes Pimitespib highly specific for Hsp-90α/β without inhibiting other Hsp-90 family proteins such as GRP94 in endoplasmic reticulum or TRAP-1 in mitochondria[3].

Pimitespib (0-5 μM, 48 hours) inhibits human retinal pigment epithelial ARPE-19 cell lines and NCI-H929 MM cells growth[2].

More significant degradation of p-C-Raf and p-MEK1/2, HSP90 client proteins and key RAS/RAF/MEK pathway regulators, is triggered by Pimitespib (0.125-1 μM, 24 hours) than 17-AAG in INA6 and NCI-H929 MM cells[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[2]

Cell Line:	Human retinal pigment epithelial ARPE-19 cell lines and NCI-H929 MM cells
Concentration:	0-5 μM
Incubation Time:	48 hours
Result:	Inhibited NCI-H929 MM cells growth with an IC_{50} of 0.35 μM.

Western Blot Analysis[2]

Cell Line:	MM cell lines INA6 and NCI-H929 cells
Concentration:	0.125-1 μM
Incubation Time:	24 hours
Result:	Targeted potently HSP90 client proteins including C-Raf and MEK1/2; as well as inhibited upregulation of HSP27 and overcomes 17-AAG resistance mechanisms.

In Vivo

Pimitespib (12.0 mg/kg, p.o., 14 days) shows antitumor activity without inducing eye injury in rats. Pimitespib is distributed less in retina than in plasma in rats; consequently, Pimitespib does not produce any detectable photoreceptor injury[1].

Pimitespib triggers enhanced in vivo anti-MM activities, both alone and in combination with PS-341 (BTZ), with a favorable safety profile. Mice treated with Pimitespib (10 mg/kg and 15 mg/kg, orally, 38 days), BTZ, or Pimitespib plus BTZ show significantly enhance growth inhibition versus the vehicle control group. Median overall survival of treated animals (Pimitespib, orally, 10 mg/kg=33 days, 15 mg/kg=37 days, BTZ=36 days, and the combination=56.5 days) is significantly longer than vehicle control[2].

The favorable pharmacokinetic profile of Pimitespib is reflected in its dose-dependent antitumor activity; the T/C (tumor volume of Pimitespib-treated mice vs. vehicle-treated mice) is 47%, 21%, and 9% for doses of 3.6 mg/kg, 7.1 mg/kg, and 14.0 mg/kg, respectively. Pimitespib is orally absorbed and has a bioavailability of almost 100% in mice, and 69.0% in rats. Pimitespib has moderate terminal elimination half-life ($t_{1/2}$=8.2 h, 2.5 h, 4.4 h and 2.2 h for mouse (3.6 mg/kg, p.o.), mouse (7.1 mg/kg, p.o.), mouse (14.0 mg/kg, p.o.), rat (4 mg/kg, p.o.)). Pimitespib is more rapidly eliminated from retina ($t_{1/2}$=3.4 hours) than the other HSP90 inhibitors ($t_{1/2}$=7.1-19.1 hours)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male F344 nude rats (6 weeks old) with established NCI-H1975 xenografts (6 weeks old)[1]
Dosage:	12.0 mg/kg
Administration:	Oral administration; daily; two weeks
Result:	Led to tumor shrinkage. Showed antitumor activity without inducing eye injury in rats and did not cause ocular toxicity at the effective dose in the NCI-H1975 rat xenograft model.

Animal Model:	CB17 SCID mice (48-54 days old) with murine xenograft model[2]

Dosage:	10 and 15 mg/kg
Administration:	Oral administration; 5 days a week; for 28 days
Result:	Enhanced significantly growth inhibition versus the vehicle control group. The delay in tumor growth was greater in the combination-treated group compared with either monotherapy cohort.

Animal Model:	Mice, Rats, and Dogs[1]
Dosage:	3.0 mg/kg for dogs, 4.0 mg/kg for rats, 3.6, 7.1 and 14.0 mg/kg for mice
Administration:	Oral administration; daily; 20 days
Result:	Absorbed orally and had a bioavailability of almost 100% in mice, 69.0% in rats, and 73.9% in dogs without special formulation.

CUSTOMER VALIDATION

- Cancer Med. 2022 Oct 6.
- JTO Clin Res Rep. 2023 Jan 24.

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REFERENCES

[1]. Ohkubo S, et al. TAS-116, a highly selective inhibitor of heat shock protein 90α and β, demonstrates potent antitumor activity and minimal ocular toxicity in preclinical models. Mol Cancer Ther. 2015 Jan;14(1):14-22.

[2]. Suzuki R, et al. Anti-tumor activities of selective HSP90α/β inhibitor, TAS-116, in combination with PS-341 in multiple myeloma. Leukemia. 2015 Feb;29(2):510-4.

[3]. Utsugi T. New challenges and inspired answers for anticancer drug discovery and development. Jpn J Clin Oncol. 2013 Oct;43(10):945-53.

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