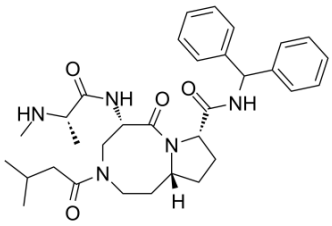
Xevinapant

Cat. No.:	HY-15454
CAS No.:	1071992-99-8
Molecular Formula:	$C_{32}H_{43}N_5O_4$
Molecular Weight:	561.71
Target:	IAP
Pathway:	Apoptosis
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 : ≥ 100 mg/mL (178.03 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7803 mL	8.9014 mL	17.8028 mL
5 mM	0.3561 mL	1.7803 mL	3.5606 mL
10 mM	0.1780 mL	0.8901 mL	1.7803 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: ≥ 2.5 mg/mL (4.45 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.45 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.45 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Xevinapant (AT-406) is a potent and orally bioavailable Smac mimetic and an antagonist of IAPs, and it binds to XIAP, cIAP1, and cIAP2 proteins with K_i of 66.4, 1.9, and 5.1 nM, respectively.

IC_{50} & Target

Ki: 66.4 nM (XIAP), 1.9 nM (cIAP1), 5.1 nM (cIAP2)

In Vitro

Xevinapant mimic closely the AVPI peptide in both hydrogen bonding and hydrophobic interactions with XIAP, with

	additional hydrophobic contacts with W323 of XIAP. Xevinapant is more sensitive to these IAPs than Smac AVPI peptide with 50-100 fold binding affinities. Xevinapant (1 μM) completely restores the activity of caspase-9, which is suppressed by 500 nM XIAP BIR3 in a cell-free system. In MDA-MB-231 cell, Xevinapant induces rapid cellular cIAP1 degradation and also pulls down the cellular XIAP protein. Xevinapant effectively inhibits lots of human cancer cell lines and shows IC_{50} of 144 and 142 nM in MDA-MB-231 cell and SK-OV-3 ovarian cell, with low toxicity against normal-like human breast epithelial MCF-12F cells and primary human normal prostate epithelial cells. Xevinapant induces apoptosis in MDA-MB-231 cell by inducing activation of caspase-3 and cleavage of PARP[1]. Xevinapant displays single agent activity in ovarian cancer cell lines. The IC_{50} values of AT-406 in these ovarian cancer cells range from 0.05-0.5 μg/mL. Xevinapant exhibits anti-ovarian cancer efficacy both as a single agent and in combination with carboplatin. Xevinapant (30 μg/mL) induced degradation of XIAP in the drug sensitive ovarian cancer cell lines[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Xevinapant has good pharmacokinetic properties and oral bioavailability in mice, rats, non-human primates, and dogs. In the MDA-MB-231 xenograft, Xevinapant effectively induces cIAP1 degradation and processing of procaspase-8, cleavage of PARP in tumor tissues at 100 mg/kg with well toleration even at 200 mg/kg. Xevinapant induces significant tumor growth inhibition with p of 0.0012 at 100 mg/kg[2]. Xevinapant (30, 100 mg/kg, p.o.) decreases the plasma and tumor in tumor-bearing mice[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are seeded in 96-well flat bottom cell culture plates at a density of 3-4×10^3 cells/well with Xevinapant and incubated for 4 days. The rate of cell growth inhibition after treatment with different concentrations of Xevinapant is determined by assaying with WST-8. WST-8 is added to each well to a final concentration of 10%, and then the plates are incubated at 37°C for 2-3 hours. The absorbance of the samples is measured at 450 nm using a TECAN ULTRA reader. Concentration of AT-406 that inhibits cell growth by 50% (IC_{50}) is calculated by comparing absorbance in the untreated cells and the cells treated with Xevinapant. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	SCID mice (8-10 per group) bearing MDA-MB-231 xenograft tumors are treated with different doses of compound 2, or 7.5 mg/kg of Taxotere or vehicle control daily, 5 days a week for 2 weeks. Tumor sizes and animal weights are measured 3 times a week during the treatment and twice a week after the treatment. Data are presented as mean tumor volumes±SEM. Statistical analyses are performed by two-way ANOVA and unpaired two-tailed t test, using Prism. $P < 0.05$ is considered statistically significant. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Med Chem. 2019 Oct 24;62(20):9188-9200.
- Biochim Biophys Acta Mol Basis Dis. 2019 Jun 26;1865(10):2618-2632.

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REFERENCES

[1]. Cai Q, et al. A potent and orally active antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in clinical development for cancer treatment. J Med Chem. 2011 Apr 28;54(8):2714-26.

[2]. Brunckhorst MK, et al. AT-406, an orally active antagonist of multiple inhibitor of apoptosis proteins, inhibits progression of human ovarian cancer. Cancer Biol Ther.

2012 Jul;13(9):804-11.

[3]. Zhang T, et al. Physiologically based pharmacokinetic and pharmacodynamic modeling of an antagonist (SM-406/AT-406) of multiple inhibitor of apoptosis proteins (IAPs) in a mouse xenograft model of human breast cancer. Biopharm Drug Dispos. 2013 Sep;34(6):

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