

产品名称: **AT406 (SM-406)**
 产品别名: **AT-406; Debio-1143**

生物活性:				
Description	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 Ki of 66.4, 1.9, and 5.1 nM, respectively.			
	IC ₅₀ & Target			
In Vitro	AT-406 mimic closely the AVPI peptide in both hydrogen bonding and hydrophobic interactions with XIAP, with additional hydrophobic contacts with W323 of XIAP. AT-406 is more sensitive to these IAPs than Smac AVPI peptide with 50-100 fold binding affinities. AT-406 (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, AT-406 induces rapid cellular cIAP1 degradation and also pulls down the cellular XIAP protein. AT-406 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. AT-406 induces apoptosis in MDA-MB-231 cell by inducing activation of caspase-3 and cleavage of PARP[1]. AT-406 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. AT-406 exhibits anti-ovarian cancer efficacy both as a single agent and in combination with carboplatin. AT-406 (30 μg/mL) induced degradation of XIAP in the drug sensitive ovarian cancer cell lines[2].			
In Vivo	AT-406 has good pharmacokinetic properties and oral bioavailability in mice, rats, non-human primates, and dogs. In the MDA-MB-231 xenograft, AT-406 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. AT-406 induces significant tumor growth inhibition with p of 0.0012 at 100 mg/kg[2]. SM-406 (30, 100 mg/kg, p.o.) decreases the plasma and tumor in tumor-bearing mice[3].			
Solvent&Solubility	In Vitro: DMSO : ≥ 100 mg/mL (178.03 mM) * "≥" means soluble, but saturation unknown.			
		Solvent / Mass / Concentration	1 mg	5 mg
	Preparing	1 mM	1.7803 mL	8.9014 mL
	Stock Solutions	5 mM	0.3561 mL	1.7803 mL
		10 mM	0.1780 mL	0.8901 mL
*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液，一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。 储备液的保存方式和期限 -80℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用， -20℃ 储存时，请在 1 个月内使用。 In Vivo: 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (4.45 mM); Clear solution				

	<p>此方案可获得 ≥ 2.5 mg/mL (4.45 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中, 混合均匀向上述体系中加入 50 μL Tween-80, 混合均匀; 然后继续加入 450 μL 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂: 10% DMSO\rightarrow 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.45 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (4.45 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中, 混合均匀。</p> <p>3.请依序添加每种溶剂: 10% DMSO \rightarrow90% corn oil Solubility: ≥ 2.5 mg/mL (4.45 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (4.45 mM, 饱和度未知) 的澄清溶液, 此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例, 取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。</p>
References	<p>[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.</p> <p>[2]. Brunkhorst 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.</p> <p>[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):</p>
实验参考:	
Cell Assay	<p>Cells are seeded in 96-well flat bottom cell culture plates at a density of $3-4 \times 10^3$ cells/well with AT-406 and incubated for 4 days. The rate of cell growth inhibition after treatment with different concentrations of AT-406 is determined by assaying with (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulphophenyl)-2H-tetrazolium monosodium salt (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 AT-406. [1]</p>
Animal Administration	<p>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\pmSEM. Statistical analyses are performed by two-way ANOVA and unpaired two-tailed t test, using Prism. $P < 0.05$ is considered statistically significant. [1]</p>
Kinase Assay	<p>MDA-MB-231 cell lysates are prepared by solubilizing cells in ice cold buffer containing KCl (50 mM), EGTA (5 mM), $MgCl_2$ (2 mM) DTT (1 mM), 0.2% CHAPS and HEPES, (50 mM, pH 7.5), containing cocktail protease inhibitors, incubating on ice for 10 minutes, then freezing in liquid nitrogen. Cytochrome c and dATP are added to the cell lysates, which are then incubated at 30°C in a water bath for 60 minutes to activate caspase-9. Addition of recombinant XIAP BIR3 protein dose-dependently suppresses the activity of caspase-9. Different concentrations of a tested Smac</p>

	mimetic (1 nM-100 μ M) are added to determine the restoration of the activity of these caspases. [1]
References	<p>[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. <i>J Med Chem.</i> 2011 Apr 28;54(8):2714-26.</p> <p>[2]. Brunckhorst MK, et al. AT-406, an orally active antagonist of multiple inhibitor of apoptosis proteins, inhibits progression of human ovarian cancer. <i>Cancer Biol Ther.</i> 2012 Jul;13(9):804-11.</p> <p>[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. <i>Biopharm Drug Dispos.</i> 2013 Sep;34(6):</p>



源叶生物