碧云天网站 微信公众号
碧云天生物技术/Beyotime Biotechnology
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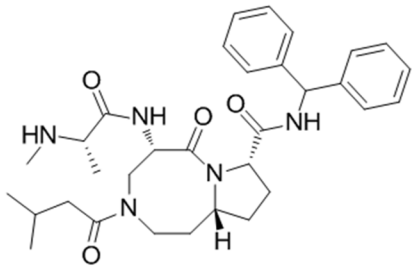
AT-406 (XIAP抑制剂)

产品编号	产品名称	包装
SC0038-10mM	AT-406 (XIAP 抑制剂)	10mM×0.2ml
SC0038-5mg	AT-406 (XIAP 抑制剂)	5mg
SC0038-25mg	AT-406 (XIAP 抑制剂)	25mg

产品简介：

➢ **化学信息：**

化学名	(5S,8S,10aR)-N-benzhydryl-5-[[(2S)-2-(methylamino) propanoyl]amino]-3-(3-methylbutanoyl)-6-oxo-1,2,4,5,8,9, 10,10a-octahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide
简称	AT-406
别名	AT 406, AT406 cpd, SM-406, SM 406, SM406cpd, DEBIO 1143
中文名	N/A
化学式	$C_{32}H_{43}N_5O_4$
分子量	561.71
CAS号	1071992-99-8
纯度	100.0%
溶剂/溶解度	Water <1mg/ml; DMSO >80mg/ml; Ethanol >80mg/ml
溶液配制	5mg加入0.89ml DMSO，或者每5.62mg加入1ml DMSO，配制成10mM溶液。SC0038-10mM用DMSO配制。



➢ **生物信息：**

产品描述	AT-406是有效的，拟Smac的，IAP(通过E3泛素连接酶起作用的凋亡蛋白抑制剂)拮抗剂，与XIAP-BIR3、cIAP1-BIR3和cIAP2-BIR3结合，Ki为66.4nM、1.9nM和5.1nM，比作用于Smac AVPI肽亲和力高50到100倍。Phase 1。				
信号通路	Apoptosis				
靶点	XIAP	cIAP1	cIAP2	—	—
IC50	66.4nM	1.9nM	5.1nM	—	—
体外研究	AT-406 is a Smac mimetic and appears to 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 (at 1μM) completely restores the activity of caspase-9, which is suppressed by 500nM 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 IC50 of 144 and 142nM 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.				
体内研究	AT-406 has good pharmacokinetic (PK) 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 100mg/kg with well toleration even at 200mg/kg. AT-406 induces significant tumor growth inhibition with p of 0.0012 at 100mg/kg.				
临床实验	AT-406 is currently in Phase I clinical trial in patients with advanced solid tumors and lymphomas.				
特征	N/A				

➢ **相关实验数据(此数据来自于公开文献，碧云天并不保证其有效性)：**

酶活性检测实验	
方法	FL-AT-406 (the fluorescently tagged AT-406) is employed to develop a set of new FP assays for determination of the binding affinities of Smac mimetics to XIAP, cIAP-1 and cIAP-2 BIR3 proteins. The Kd value of

	FL-AT-406 to each IAP protein is determined by titration experiments using a fixed concentration of FL-AT-406 and different concentrations of the protein up to full saturation. Fluorescence polarization values are measured using an Infinite M-1000 plate reader in Microfluor 2 96-well, black, round-bottom plates. To each well, FL-AT-406 (2, 1 and 1nM for experiments with XIAP BIR3, cIAP-1 BIR3 and cIAP-2 BIR3, respectively) and different concentrations of the protein are added to a final volume of 125μL in the assay buffer (100mM potassium phosphate, pH 7.5, 100μg/ml bovine γ-globulin, 0.02% sodium azide, with 4% DMSO). Plates are mixed and incubated at room temperature for 2-3 hours with gentle shaking. The polarization values in millipolarization units (mP) are measured at an excitation wavelength of 485nM and an emission wavelength of 530nM. Equilibrium dissociation constants (Kd) are then calculated by fitting the sigmoidal dose-dependent FP increases as a function of protein concentrations using Graphpad Prism 5.0 software. In competitive binding experiments for XIAP3 BIR3, AT-406 is incubated with 20nM XIAP BIR3 protein and 2nM FL-AT-406 in the assay buffer (100mM potassium phosphate, pH 7.5; 100μg/ml bovine γ-globulin; 0.02% sodium azide). In competitive binding experiments for cIAP1 BIR3 protein, 3nM protein and 1nM FL-AT-406 are used. In competitive binding experiments for cIAP2 BIR3, 5nM protein and 1nM FL-AT-406 are used. For each competitive binding experiment, polarization values are measured after 2-3 hours of incubation using an Infinite M-1000 plate reader. The IC50 value, the inhibitor concentration at which 50% of the bound tracer is displaced, is determined from the plot using nonlinear least-squares analysis. Curve fitting is performed using the PRISM software. A Ki value for AT-406 is calculated.

细胞实验	
细胞系	N/A
浓度	N/A
处理时间	N/A
方法	N/A

动物实验	
动物模型	N/A
配制	N/A
剂量	N/A
给药方式	N/A

- **参考文献：**

1. Cai Qian, Sun Haiying, Peng Yuefeng, 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. Journal of Medicinal Chemistry. 2011; 54(8):2714-2726.
2. Miura K, Fujibuchi W, Ishida K, et al. Inhibitor of apoptosis protein family as diagnostic markers and therapeutic targets of colorectal cancer. Surg Today. 2011 Feb;41(2):175-82.
3. Brunckhorst MK, Lerner D, Wang S, Yu Q. 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.
4. Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamic Properties of Oral AT-406 in Combination With Daunorubicin and Cytarabine in Patients With Poor-risk Acute Myelogenous Leukemia (Aml).
5. Dose Escalation Study of Safety and Tolerability of AT-406 in Patients With Advanced Solid Tumors and Lymphomas.

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—	说明书	1份

保存条件：

-20ºC保存，至少一年有效。如果溶于非DMSO溶剂，建议分装后-80ºC保存，预计6个月内有效。

注意事项：

- 本产品对人体有刺激性，操作时请小心，并注意适当防护以避免直接接触人体或吸入体内。
- 本产品仅限于专业人员的科学研究用，不得用于临床诊断或治疗，不得用于食品或药品，不得存放于普通住宅内。
- 为了您的安全和健康，请穿实验服并戴一次性手套操作。

使用说明：

1. 收到产品后请立即按照说明书推荐的条件保存。使用前可以在2,000-10,000g离心数秒，以使液体或粉末充分沉降至管底后再

开盖使用。

2. 对于10mM溶液，可直接稀释使用。对于固体，请根据本产品的溶解性及实验目的选择相应溶剂配制成高浓度的储备液(母液)后使用。
3. 具体的最佳工作浓度请参考本说明书中的体外、体内研究结果或其它相关文献，或者根据实验目的，以及所培养的特定细胞和组织，通过实验进行摸索和优化。
4. 不同实验动物依据体表面积的等效剂量转换表请参考如下网页：http://www.beyotime.com/support/animal-dose.htm

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