

Product Data Sheet

Product Name: AT-406 (SM-406)

Cat. No.: GC17448

Chemical Properties

Cas. No. 1071992-99-8

Chemical Name (5S,8S,10aR,Z)-N-benzhydryl-5-((Z)-((S)-1-hydroxy-2-(methylamino)propylidene)amino)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carbimidic acid

SMILES CC(CCC(N(C[C@@]/(N=C(O)/[C@](NC)([H])C)([H])C1=O)CC[C@@](N21)([H])CC[C@@]2([H])/C(O)=N/C(C3=CC=CC=C3)C4=CC=CC=C4)=O)C

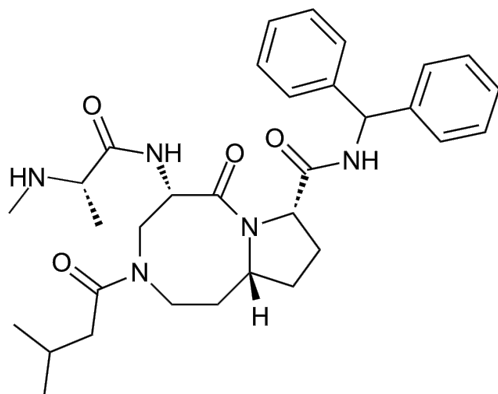
Formula $C_{32}H_{43}N_5O_4$ M.Wt 561.71

Solubility $\geq 27.65\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

Cell lines MDA-MB-231 breast cancer cell lines

Caution: Product has not been fully validated for medical applications. For research use only.

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Preparation method	Soluble in DMSO > 27.65mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37°C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.
Reacting condition	0.1,0.3,1,3μM for 24 hours(analysis of cell death), 1.5μM for 1,3,6,12,24hours(Western blot analysis of caspase processing and cleavage of PARP (poly (ADP-ribose) polymerase))
Applications	AT-406 was a potent and orally bioavailable antagonist of multiple inhibitor of apoptosis proteins (IAPs). AT-406 effectively antagonized XIAP BIR3 (XIAP: X-linked IAP BIR3: the third BIR domain) protein, induced rapid degradation of cIAP1 (cIAP1: cellular IAP1) protein in MDA-MB-231 cell. AT-406 was effective in inhibition of cell growth in approximately 15% of more than 100 human cancer cell lines and its activity was not limited to a single tumor type.
Animal experiment [2]:	
Animal models	SCID(severe combined immunodeficient) mice bearing human MDA-MB-231 xenograft tumor
Dosage form	30 and 100mg/kg(between pH3.0 and 9.0)for oral gavage, 10mg/kg(between pH4.5 and 9.0)for intravenous administration.
Application	AT-406 could lead to the cIAP1 degradation, pro-caspase 8 decrease, CL-PARP(cleaved PARP)accumulation and tumor growth inhibition in the mouse xenograft model.

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Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

- [1]. Cai Q, Sun H, Peng Y, 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]. Journal of medicinal chemistry, 2011, 54(8): 2714-2726.
- [2]. Zhang T, Li Y. et al. A 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):348-59.

Background

K(i): The Ki of XIAP, cIAP1, and cIAP2 proteins is 66.4, 1.9, and 5.1 nM, respectively.

AT-406 is also named as SM-406. AT-406 is a potent and orally bioavailable antagonist of multiple inhibitor of apoptosis proteins (IAPs). The inhibitor of apoptosis proteins (IAPs), originally identified in baculoviruses, are a family of apoptosis suppressor proteins which could bind and inhibit specific enzymes (caspases) such as caspase 3, 7, and 9, but not caspase 8 [1]. Growing evidence has showed that IAPs can regulate programmed cell death, apoptosis, cell division, cell cycle progression, and signal transduction pathways [1].

In vitro: The Ki of AT-406 against XIAP, cIAP1, and cIAP2 proteins is 66.4, 1.9, and 5.1 nM, respectively [2]. In human ovarian cancer cell lines, treatment with AT-406 for 48h could dose-dependently activate the apoptotic pathway. IC50 values of AT-406 in these ovarian cancer cells range from 0.05-0.5 µg/ml [3]. AT-406 could sensitize the response of ovarian cancer cells to carboplatin, a standard first-line chemotherapy for ovarian cancer [2].

In vivo: AT-406 exhibited good oral bioavailability in the mouse, rat, dog and non-human primates. In Rag-1 mice bearing intraperitoneally implanted OVCAR-3ip cells, AT-406 (100 mg/kg by oral gavage) significantly inhibited the progression of ovarian cancer and prolonged survival of the experimental

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mice both in single agent and in combination with carboplatin (40 mg/kg intraperitoneal injection) [2]. In xenograft mouse model of human breast cancer, 2-week treatment with 30 mg/kg or 100 mg/kg AT-406 effectively delayed the tumor growth [3].

Clinical trial: Oral treatment of AT-406 daily on days 1-5, initially every 14 days, later every 21 days was well tolerated at doses up to 900 mg in patients with different cancer types (Hurthle cell, melanoma, breast, rectal, hemangiopericytoma) [4].

References:

- [1].Schimmer A D. Inhibitor of apoptosis proteins: translating basic knowledge into clinical practice[J]. Cancer research, 2004, 64(20): 7183-7190.
- [2].Cai Q, Sun H, Peng Y, 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]. Journal of medicinal chemistry, 2011, 54(8): 2714-2726.
- [3].Zhang T, Li Y. et al. APhysiologically 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):348-59.
- [4].Hurwitz HI1, Smith DC, et al. Safety, pharmacokinetics, and pharmacodynamic properties of oral DEBIO1143 (AT-406) in patients with advanced cancer: results of a first-in-man study. Cancer ChemotherPharmacol. 2015 Apr;75(4):851-9.

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