Product Data Sheet

Product Name: AT-101
Cat. No.: GC11106

Chemical Properties

Cas. No.	90141-22-3		
Chemical Name	7-(8-formyl-1,6,7-trihydroxy-3-methyl-5-propan-2-ylnaphthalen-2-yl)-2,3,8-trihydroxy-6-methyl-4-propan-2-ylnaphthalene-1-carbaldehyde		
SMILES	CC1=C(C(=C2C(=C1)C(=C(C(=C2C=O)O)O)C(C)C)O)C3=C(C=C4C(=C3O)C(=C(C(=C4C(C)C)O)O)C=O)C		
Formula	$C_{30}H_{30}O_8$	M.Wt	518.55
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	AT-101		

Protocol

Cell experiment [1]:

Cell lines	CLL(Chronic lymphocytic leukemia) B cell
Preparation method	Soluble in DMSO > 10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months.
Reacting condition	1, 3, 10, 15, 20, 30μm for 24h; 20μm for 4, 8, 24 hours
Applications	AT-101 induced apoptosis in CLL B cells and overcomes microenvironment-mediated resistance while sparing normal stromal cells. AT-101 treatment resulted in cleavage of Mcl-1 (Myeloid cell leukemia-1) in a time- and dose-dependent fashion. The decrease in full-length Mcl-1 correlated well with annexin positivity and PARP(poly ADP-ribose polymerase) cleavage.

Animal experiment [2]:

Animal models	athymic nude mice with allografted intracranial medulloblastomas from Ptch+/-; p53-/- mouse

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Dosage form	20 or 40 mg/kg, daily administered, oral gavage
Application	Treatment with AT-101 obviously inhibited the growth of allografted medulloblastoma in mice. AT-101 might inhibit the growth of Hh(hedgehog)-driven medulloblastoma in vivo by suppressing the Hh pathway
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]. Balakrishnan K,Burger J, et al, AT-101 induces apoptosis in CLL B cells and overcomes stromal cell–mediated Mcl-1 induction and drug resistance.Blood,2009,113(1): 149–153.

[2]. Wang J1, Peng Y, et al, AT-101 inhibits hedgehog pathway activity and cancer growth. Cancer Chemother Pharmacol. 2015 Sep;76(3):461-9. doi: 10.1007/s00280-015-2812-x. Epub 2015 Jun 26.

Background

AT101, a natural product from cottonseed with a BH3-mimetic structure, was identified as a small molecule inhibitor of Bcl-2/Bcl-xL/Mcl-1 that potently induces apoptosis in various cancer cell lines [1].It is one of the world's first small molecule Bcl-2 inhibitors that has entered into clinical trials and is now in phase II clinical trials for hormone-refractory prostate cancer and other types of cancers [2, 3]. Few side effects of gossypol have been reported, with the major side effects of gossypol being nausea and vomiting in the third month of treatment or rashes earlier in the course of treatment [4]. Thus, AT101 is clinically safe [2, 3] and could be used as a potential inducer of apoptosis in cancer treatment.
As a BH3 mimetic, AT-101 binds to the hydrophobic surface binding groove BH3 of the anti-apoptotic proteins Bcl-2 and Bcl-xL, blocking their heterodimerization with pro-apoptotic members of the Bcl-2 family of proteins such as Bad, Bid, and Bim; this may result in the inhibition of tumor cell proliferation and the induction of tumor cell apoptosis. Preclinical studies revealed that gossypol not only interrupts the interaction between anti- and proapoptotic Bcl-2 family proteins but also induces BH3 protein (such as Puma and Noxa) up-regulation or down-regulates XIAP expression [5]. Thus, gossypol can induce apoptosis by activating apoptogenic factors other than the Bcl-2 family. AT-101 induced apoptosis in vitro through activation of caspase-9.
AT101 delayed onset of androgen-independent growth of VCaP prostate cancer xenografts in vivo. Gossypol can

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neutralize antiapoptotic Bcl-2 proteins and induced Bax activation [1]. However, the function of gossypol was not limited to effects on the interaction between anti- and proapoptotic Bcl-2 proteins. Some studies have demonstrated that gossypol could down-regulate Bcl-2, Bcl-xL, and XIAP expression [6] or induce Puma and Noxa expression. Therefore, the apoptotic effect of gossypol has been demonstrated to be attenuated by the presence of androgen in a prostate cancer xenograft mouse model.

References:

[1]. Meng Y, Tang W,Dai Y, et al. Natural BH3-mimetic (-)-gossypol chemosensitizes human prostate cancer via Bcl-xL inhibition accompanied by increase of Puma and Noxa.Molecular cancer therapeutics,2008,7(7): 2192–2202.

[2]. Liu G,Kelly W. K,Wilding G,et al. An Open-Label, Multicenter, Phase I/II Study of Single-Agent AT-101 in Men with Castrate-Resistant Prostate Cancer (CRPC).Clinical Cancer Research,2009,15(9): 3172–3176.

[3]. Van Poznak C, Seidman A. D,Reidenberg M,et al. Oral gossypol in the treatment of patients with refractory metastatic breast cancer: a phase I/II clinical trial,Breast Cancer ResTreat ,2001,66(3):239-48.

[4]. Qiu J,Levin L. R,Buck J,et al. Different pathways of cell killing by gossypol enantiomers.Exp Biol Med (Maywood) ,2002,227(6):398-401.

[5]. Balakrishnan K,Burger J. A,Wierda W. G,et al. AT-101 induces apoptosis in CLL B cells and overcomes stromal cell–mediated Mcl-1 induction and drug resistance.Blood,2009,113(1): 149–153.

[6].Sung B,Ravindran J,Prasad S,et al.Gossypol Induces Death Receptor-5 through Activation of the ROS-ERK-CHOP Pathway and Sensitizes Colon Cancer Cells to TRAIL.J Biol Chem,2010,285(46): 35418–35427.

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