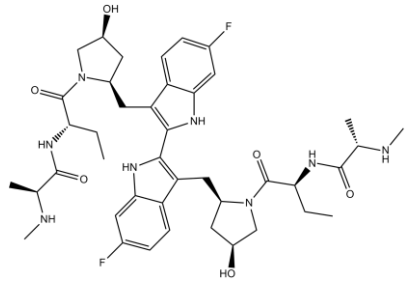
Product Data Sheet

Chemical Properties



Product Name:	Birinapant (TL32711)
Cas No.:	1260251-31-7
M.Wt:	806.94
Formula:	C42H56F2N8O6
Chemical Name:	(2S,2'S)-N,N'-((2S,2'S)-((3S,3'S,5R,5'R)-5,5'-((6,6'-difluoro-1H,1'H-[2,2'-biindole]-3,3'-diyl)bis(methylene))bis(3-hydroxypyrrolidine-5,1-diyl))bis(1-oxobutane-2,1-diyl))bis(2-(methylamino)propanamide)
Canonical SMILES:	CCC(C(=O)N1CC(CC1CC2=C(NC3=C2C=CC(=C3)F)C4=C(C5=C(N4)C=C(C=C5)F)CC6CC(CN6C(=O)C(CC)NC(=O)C(C)NC)O)O)NC(=O)C(C)NC
Solubility:	>40.3mg/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.
Shopping Condition:	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request

Biological Activity

Targets :	IAP
Pathways:	Apoptosis >> IAP

Description:

Birinapant, also called TL32711, is a potent antagonist for XIAP with Kd value of 45 nM and cIAP1 with Kd value <1 nM [1].
Birinapant not only binds to the isolated BIR3 domains of cIAP1, cIAP2, XIAP but the single BIR domain of ML-IAP with high affinity and degrades TRAF2-bound cIAP1 and cIAP2 rapidly accordingly inhibiting the activation of TNF-mediated NF- kB. Additionally, birinapantcan promote the formation of caspase-8: RIPK1 complex in response to TNF stimulation, which result in

downstream caspasesactivation [4].
In the inorganic SUM149- and SUM190-derived cells, which with differential XIAP expression (SUM149 wtXIAP, SUM190 shXIAP) and other high cIAP1/2 but low XIAP binding affinity bivalent Smac mimetic GT13402, XIAP inhibition are needed for increasing TRAIL potency. Opposite, single agent efficacy of Birinapant is owing to pan-IAP antagonism. Rapid cIAP1 degradation was caused by birinapant, as well as NF-κB activation, PARP cleavage andcaspase activation. While combined withTNF-α, showing strong combination activity, the combination was more effective than individual. The response in spheroid models was conserved, whereas in vivo birinapant inhibited tumor growth without adding TNF-α in vitro to resistant cell lines. In a parental cell line, TNF-αcombined withbirinapantinhibited the growth of a melanoma cell line with acquired resistance to the same extent of BRAF inhibition [1, 2].
Drug treatment increased the mean [18F]ICMT-11 tumor uptake with a peak at 24 hours for CPA (40 mg/kg; AUC40-60: 8.04 ± 1.33 and 16.05 ± 3.35 %ID/mL × min at baseline and 24 hours, respectively) and 6 hours for birinapant (15 mg/kg; AUC40-60: 20.29 ± 0.82 and 31.07 ± 5.66 %ID/mL × min, at baseline and 6 hours, respectively). Voxel-based spatiotemporal analysis of tumor-intrinsic heterogeneity showed that [18F] ICMT-11 could detect the discrete pockets of caspase-3 activation. Caspase-3 activation that measured ex vivo associated with the increased tumor [18F] ICMT-11, and early radiotracer uptake predicted apoptosis, distinct from the glucose metabolism with [18F] fluorodeoxyglucose-PET, which depicted the continuous loss of cell viability [3].

***Reference**:*

1.Allensworth JL, Sauer S, Lyerly HK, et al. Smac mimetic Birinapant induces apoptosis and enhances TRAIL potency in inflammatory breast cancer cells in an IAP-dependent and TNF-a-independent mechanism. Breast Cancer Research, 2013, 137:359-371.
2.Krepler C, Chunduru SK, Halloran MB, et al. The novel SMAC mimetic birinapant exhibits potent activity against human melanoma cells. Clinical Cancer Research, 2013, 19 (7): 1784-1794.
3.Nguyen QD, Lavdas I, Gubbins J, et al. Temporal and Spatial Evolution of Therapy-Induced Tumor Apoptosis Detected by Caspase-3–Selective Molecular Imaging. Clinical Cancer Research, 2013, 19 (14): 3914-3924.
4.Benetatos CA, Mitsuuchi Y, Burns JM, et al. Birinapant (TL32711), a Bivalent SMAC Mimetic, Targets TRAF2-Associated cIAPs, Abrogates TNF-Induced NF-kB Activation, and Is Active in Patient-Derived Xenograft Models. 2014, 13(4):867-879.

Protocol

Cell experiment:

Cell lines	SUM149 and SUM190 inflammatory breast cancer cell
Preparation method	Limited solubility. 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 conditions	24 h-96 h
Applications	Birinapant causes a significant degradation of cIAP1 and 2, which

was not enhanced by the addition of TRAIL. Birinapant is also more effective in increasing TRAIL potency than GT13402 in SUM149. In addition, Birinapant markedly decreases the viability of SUM190 cells in a dose-dependent manner.

Animal experiment [3]:

Animal models	Melanoma tumor xenotransplantation mice
Dosage form	Intra-peritoneal; 30mg/kg
Applications	Compared to vehicle control, cIAP1 protein is reduced to low levels at 3h post and this effect is sustained for 24 hours in the Birinapant treated mice. Staining for activated caspase-3 in biopsies of the same tumors shows a modest increase in apoptotic cells in the Birinapant treated mice compared to vehicle control, 24h post treatment.
Preparation method	Dissolved in 12.5% Captisol in distilled water.
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.

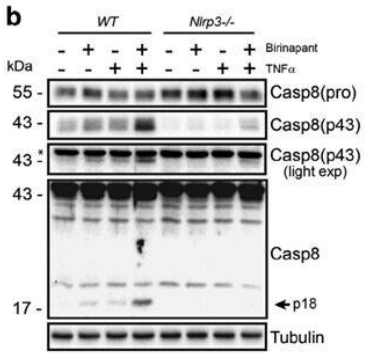
***Reference**:*

1. Allensworth JL, Sauer SJ, Lyerly HK et al. Smac mimetic Birinapant induces apoptosis and enhances TRAIL potency in inflammatory breast cancer cells in an IAP-dependent and TNF-α-independent mechanism. Breast Cancer Res Treat. 2013 Jan;137(2):359-71.
2. Krepler C, Chunduru SK, Halloran MB et al. The novel SMAC mimetic birinapant exhibits potent activity against human melanoma cells. Clin Cancer Res. 2013 Apr 1;19(7):1784-94.

Product Citations

1. Chung H, Vilaysane A, et al. "NLRP3 regulates a non-canonical platform for caspase-8 activation during epithelial cell apoptosis." Cell Death Differ. 2016 Feb 19. PMID:26891693

Product Validation



Nlrp3-dependent regulation of death receptor-mediated apoptosis. Immunoblotting for caspase-8 in WTand Nlrp3− /− TECs treated for the indicated times with TNFα (10 ng/ml) and the SMAC-mimetic birinapant (10 μM). Cell Death Differ. 2016 Feb 19.

Caution

FOR RESEARCH PURPOSES ONLY.

NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE.

Specific storage and handling information for each product is indicated on the product datasheet. Most ApexBio products are stable under the recommended conditions. Products are sometimes shipped at a temperature that differs from the recommended storage temperature. Shortterm storage of many products are stable in the short-term at temperatures that differ from that required for long-term storage. We ensure that the product is shipped under conditions that will maintain the quality of the reagents. Upon receipt of the product, follow the storage recommendations on the product data sheet.

ApexBio Technology

www.apexbt.com

7505 Fannin street, Suite 410, Houston, TX 77054.

Tel: +1-832-696-8203 | Fax: +1-832-641-3177 | Email: info@apexbt.com