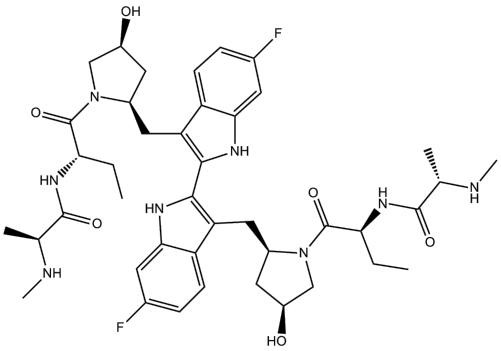
Product Data Sheet

Product Name: Birinapant (TL32711)
Cat. No.: GC12426

Chemical Properties

Cas. No.	1260251-31-7		
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)		
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		
Formula	$C_{42}H_{56}F_2N_8O_6$	M.Wt	806.94
Solubility	≥ 40.35 mg/mL in DMSO, ≥ 46.9 mg/mL in EtOH	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

IAP binding affinity of Birinapant (TL32711)[1]:

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Preparation Method	A fluorescence polarization assay was used to determine the dissociation constants (K d) of Smac mimetics Birinapant (TL32711) and GT13402 for XIAP and cIAP1 by monitoring the decrease in fluorescence polarization signal due to competitive displacement of an FP peptide from the BIR3/FP peptide binary complex.
Applications	The binding constants (K d) of Birinapant (TL32711) for XIAP and cIAP1 were determined to be 45 and

Cell experiment [2]:

Cell lines	451Lu and WM1366 melanoma cells
Preparation Method	Cells were treated with Birinapant (TL32711) 1 μmol/L in combination with TNF-α 1 ng/mL. Cells were then incubated for 72 hours in the presence or absence of Necrostatin-1 a RIP1 kinase inhibitor. Proliferation was assessed using the MTS assay.
Reaction Conditions	1 μmol/L Birinapant (TL32711) for 72 hours
Applications	The majority of cell lines exhibited strong combination activity of Birinapant (TL32711) and TNF-α.

Animal experiment [3]:

Animal models	Male C57BL/6J mice aged 8 week old, weighing 21 ± 1.3g

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Preparation Method	Before the LPS administration, mice were injected intraperitoneally with Birinapant (TL32711) (30 mg/kg body weight, Birinapant (TL32711) group) either vehicle control (vehicle group) for 24 h. Birinapant (TL32711) was dissolved in 12.5% Captisol in distilled water. Twenty-four mice in each group were euthanized and the samples of the liver and blood were harvested at 0, 6, 12 and 24 h after LPS challleage.
Dosage form	30 mg/kg Birinapant (TL32711) ip. for 24 h.
Applications	Birinapant (TL32711) pretreatment significantly improved mice survival.

References:

[1]. Allensworth JL, Sauer SJ, 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. doi: 10.1007/s10549-012-2352-6. Epub 2012 Dec 7. PMID: 23225169.

[2]. Krepler C, Chunduru SK, et,al. The novel SMAC mimetic birinapant exhibits potent activity against human melanoma cells. Clin Cancer Res. 2013 Apr 1;19(7):1784-94. doi: 10.1158/1078-0432.CCR-12-2518. Epub 2013 Feb 12. PMID: 23403634; PMCID: PMC3618495.

[3]. Liu H, Liao R, et,al. The SMAC mimetic birinapant attenuates lipopolysaccharide-induced liver injury by inhibiting the tumor necrosis factor receptor-associated factor 3 degradation in Kupffer cells. Immunol Lett. 2017 May;185:79-83. doi: 10.1016/j.imlet.2017.02.016. Epub 2017 Mar 9. PMID: 28286228.

Background

Birinapant (TL32711) is a SMAC mimetic designed to specifically target cIAP1 and cIAP2 for degradation[1]. Birinapant rapidly degrades cIAPs and enables cytokines (TNFα, TRAIL) to activate the extrinsic apoptosis pathway, while Birinapant rapidly turns off the canonical NF-κB survival

pathway, causing cancer cell death[2]. Birinapant has been widely used to inhibit the growth of various cancer cells and to increase the production of TNF[3].

In vitro, Birinapant treatment for 72 hours significantly inhibited the viability of MDA-MB-231 and A875 cells, with IC_{50} values of 10nM and 40nM, respectively [4]. Treatment with 1μM Birinapant for 24 hours significantly induced apoptosis in SUM190 cells, resulting in activation of caspase and NF-κB, as well as cleavage of PARP[5].

In vivo, Birinapant treatment via intraperitoneal injection at a dose of 30mg/kg, once a week for 2 weeks, significantly promoted apoptosis and inhibited the growth of subcutaneous hepatocellular carcinoma tumors in nude mice[6]. A single intraperitoneal injection of a 30mg/kg dose of Birinapant alleviated liver injury induced by lipopolysaccharide (LPS) in mice and increased the survival rate of mice within 72 hours[7]. A single intravenous injection of Birinapant at 30mg/kg for 24h alleviated lung injury induced by LPS in mice and reduced the production of pro-inflammatory cytokines[8].

References:
[1] Condon S M, Mitsuuchi Y, Deng Y, et al. Birinapant, a smac-mimetic with improved tolerability for the treatment of solid tumors and hematological malignancies[J]. 2014.
[2] Benetatos C A, Mitsuuchi Y, Burns J M, et al. Birinapant (TL32711), a bivalent SMAC mimetic, targets TRAF2-associated cIAPs, abrogates TNF-induced NF-κB activation, and is active in patient-derived xenograft models[J]. Molecular cancer therapeutics, 2014, 13(4): 867-879.
[3] Chang Y C, Cheung C H A. An updated review of smac mimetics, LCL161, birinapant, and GDC-0152 in cancer treatment[J]. Applied Sciences, 2020, 11(1): 335.
[4] Perez H L, Chaudhry C, Emanuel S L, et al. Discovery of potent heterodimeric antagonists of inhibitor of apoptosis proteins (IAPs) with sustained antitumor activity[J]. Journal of medicinal chemistry, 2015, 58(3): 1556-1562.
[5] Allensworth J L, Sauer S J, Lyerly H K, 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[J]. Breast cancer research and treatment, 2013, 137(2): 359-371.
[6] Ding J, Qin D, Zhang Y, et al. SMAC mimetic birinapant inhibits hepatocellular carcinoma growth by activating the cIAP1/TRAF3 signaling pathway[J]. Molecular medicine reports, 2020, 21(3): 1251-1257.
[7] Liu H, Liao R, He K, et al. The smac mimetic birinapant attenuates lipopolysaccharide-induced

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liver injury by inhibiting the tumor necrosis factor receptor–associated factor 3 degradation in kupffer cells[J]. Immunology Letters, 2017, 185: 79-83.
[8] Hu H, Ma M, Li T, et al. The SMAC mimetic birinapant alleviates lipopolysaccharide-induced acute lung injury by inhibiting MAPK signaling[J]. Immunology Letters, 2023, 264: 31-35.