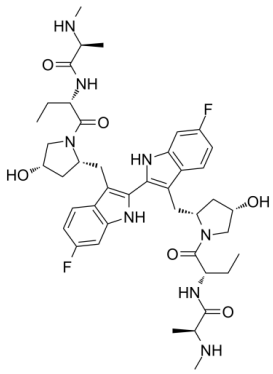
Data Sheet

Product Name:	Birinapant
Cat. No.:	CS-1719
CAS No.:	1260251-31-7
Molecular Formula:	C42H56F2N8O6
Molecular Weight:	806.94
Target:	Apoptosis; HIV; IAP
Pathway:	Anti-infection; Apoptosis
Solubility:	DMSO : ≥ 40 mg/mL (49.57 mM); Ethanol : 25 mg/mL (30.98 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

Birinapant (TL32711), a bivalent Smac mimetic, is a potent antagonist for **XIAP** and **cIAP1** with K_ds of 45 nM and less than 1 nM, respectively. Birinapant (TL32711) induces the autoubiquitylation and proteasomal degradation of cIAP1 and cIAP2 in intact cells, which results in formation of a RIPK1: caspase-8 complex, caspase-8 activation, and induction of tumor cell death. Birinapant (TL32711) targets TRAF2-associated cIAPs and abrogates TNF-induced NF-κB activation. IC50 & Target: Kd: 45 nM (XIAP), <1 nM (cIAP1)[1] **In Vitro:** Birinapant (TL32711) (30-10000 nM; 24 hours) significantly decreases the viability of SUM190 cells in a dose-dependent manner[1].

Birinapant (TL32711) (30-1000 nM; 4 hours) shows a significant decrease in cIAP1 levels and enhanced PARP cleavage, and induces apoptosis[1].

Birinapant (TL32711) binds with high affinity to the isolated BIR3 domains of cIAP1, cIAP2, and XIAP and the single BIR domain of ML-IAP and rapidly degrades TRAF2-bound cIAP1 and cIAP2 thereby inhibiting TNF-mediated NF-κB activation[1]. **In Vivo:** Birinapant (TL32711) (30 mg/kg; i.p.; every third day (*5)) shows antitumor efficacy and are devoid of overt toxicity in preclinical models[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]Trypan blue exclusion assay is performed as described. Cells are seeded in 6 well plates at 7.5×10^4 (SUM149) or 1.5×10^5 (SUM190) cells per well and allowed to adhere overnight. Cells are treated with TRAIL (0-100 ng/mL), Birinapant (0-10,000 nM), GT13402 (0-10,000 nM), TNF-α (50 ng/mL), TNF-α neutralizing antibody (10 μg/mL), pan-caspase inhibitor Q-VD-OPh (20 μM), or a combination as indicated. All treatments are applied for 24 h, and then the cells are trypsinized and resuspended in PBS. Next, 10 μL of cell suspension is added to 10 μL 0.4 % trypan blue, and 10 μL of the mixture is loaded onto a hemocytometer; cells are counted, and live and dead cell numbers are recorded. **Animal Administration:** Birinapant is dissolved in 12.5% Captisol in distilled water.[2]Ten animals each are inoculated s.c. with 1×10^6 451Lu or 1205Lu human melanoma cells in a suspension of matrigel/complete media at a ratio of 1:1. After formation of palpable tumors, mice from both tumor models are randomized into two groups. Both groups are treated intraperitoneal three times/week with either vehicle control or birinapant 30 mg/kg for 21 days. Birinapant is dissolved in 12.5% Captisol in distilled water. Tumor size is assessed twice weekly by caliper measurement. Subsequently, satellite groups of ten and fifteen mice are inoculated in the same fashion with 451Lu and 1205Lu tumor cells respectively. After tumors have reached a mean volume of 200 mm^3 animals are dosed with either birinapant or vehicle control as described above. After 48 hours and two doses, animals are sacrificed and tumors are harvested at four time points after the last treatment. Tumor samples are snap frozen in liquid nitrogen for subsequent protein analysis and preserved as FFPE blocks for immune-histochemistry.

References:

[1]. Allensworth JL, 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, et al. The novel SMAC mimetic birinapant exhibits potent activity against human melanoma cells. Clin Cancer Res. 2013 Apr 1;19(7):1784-94.

[3]. Nguyen QD, et al. Temporal and spatial evolution of therapy-induced tumor apoptosis detected by caspase-3-selective molecular imaging. Clin Cancer Res. 2013 Jul 15;19(14):3914-24.

[4]. Benetatos CA, 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. Mol Cancer Ther. 2014 Apr;13(4):867-79.

CAIndexNames:

Propanamide, N,N'-[(6,6'-difluoro[2,2'-bi-1H-indole]-3,3'-diyl)bis[methylene[(2R,4S)-4-hydroxy-2,1-pyrrolidinediyl][(1S)-1-ethyl-2-oxo-2,1-ethanediyl]]]bis[2-(methylamino)-, (2S,2'S)-

SMILES:

FC1=CC2=C(C=C1)C(C[C@H]3N(C([C@@H](NC([C@@H](NC)C)=O)CC)=O)C[C@@H](O)C3)=C(C(N4)=C(C[C@H]5N(C([C@@H](NC([C@@H](NC)C)=O)CC)=O)C[C@@H](O)C5)C6=C4C=C(F)C=C6)N2

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