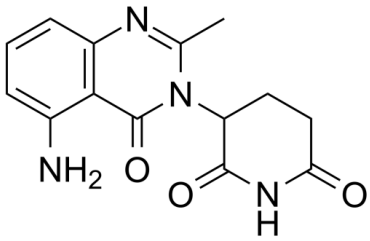
Data Sheet

Product Name:	Avadomide
Cat. No.:	CS-5995
CAS No.:	1015474-32-4
Molecular Formula:	C14H14N4O3
Molecular Weight:	286.29
Target:	Apoptosis; E1/E2/E3 Enzyme
Pathway:	Apoptosis; Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 33 mg/mL (115.27 mM)



BIOLOGICAL ACTIVITY:

Avadomide (CC 122) is an orally available **cereblon** modulator. Avadomide modulates cereblon E3 ligase activity and exhibits potent antitumor and immunomodulatory activities[1]. **In Vitro:** Avadomide inhibits proliferation and induces apoptosis in ABC and GCB DLBCL. In DLBCL cell lines, Avadomide-induced degradation or short hairpin RNA-mediated knockdown of Aiolos and Ikaros correlates with increased transcription of IFN-stimulated genes independent of IFN-α, -β, and -γ production and/or secretion and results in apoptosis in both activated B-cell (ABC) and germinal center B-cell DLBCL.[1] **In Vivo:** Treatment of female CB-17 SCID mice with Avadomide (CC122) at 3 or 30 mg/kg once daily significantly decreased tumor growth in OCI-LY10 ABC-DLBCL ($P = .028$ and $P < .001$, respectively) and WSU-DLCL2 GCB-DLBCL derived xenograft models ($P < .01$) compared with the vehicle control. In a separate study, we assessed the ability of Avadomide (CC122) to promote degradation of Ikaros and Aiolos in vivo. In the 21-day efficacy study of WSU-DLCL2 xenograft transplanted mice, tumors were excised 1, 6, or 24 hours post final dosing. Aiolos and Ikaros expression was interrogated through immunohistochemistry (IHC) and was found to be decreased 64% and 30%, respectively, compared with vehicle within 1 hour of treatment, with a maximal reduction of 94% and 69%, respectively, observed at 6 hours. Aiolos and Ikaros levels partially recovered 24 hours postdosing with protein level within 20% and 34% of vehicle, respectively. The 24-hour postdose Aiolos and Ikaros expression represents the trough compound level following multiple doses of Avadomide (CC122). When the 1-hour time point is compared with the 24-hour postdose time point, there is a significant reduction in Aiolos but not Ikaros expression; however, at the 6-hour time point, both transcription factors are significantly different from the 24-hour time point. Taken together, these data reveal that Avadomide (CC122) inhibited DLBCL tumor growth in vivo and that this activity was associated with the degradation of Aiolos and Ikaros in both ABC- and GCB-DLBCL xenograft models.[1]

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: Female SCID mice (CB17/Icr-Prkdcscid, Charles River) were 8 weeks old, with body weights ranging from 15.0 to 23.2 g, on day 1 of these studies. Each SCID mouse was injected subcutaneously in the right flank with 5x106 OCI-LY10 cells (0.2 ml cell suspension). Tumors were calipered in two dimensions to monitor growth as their mean volume approached 100–150 mm3 . Fourteen days (WSU-DLCL2) or twenty-one days (OCI-LY10) after tumor cell implantation, mice were sorted into treatment groups (n=10/group). Tumors were callipered twice weekly during the study. Avadomide (CC122) was suspended in 0.5% carboxymethyl cellulose: 0.25% Tween-80 in de-ionized water. Vehicle and Avadomide (CC122) were each administered via oral gavage (p.o.) once daily for twenty-eight days (qd x28). [1]

References:

[1]. Hagner, P.R.et al.CC-122, a pleiotropic pathway modifier, mimics an IFN response and has antitumor activity in DLBCL.Blood.Aug 6;126(6):779-89.

[2]. Rasco DW, et al. A First-in-Human Study of Novel Cereblon Modulator Avadomide (CC-122) in Advanced Malignancies. Clin Cancer Res. 2019 Jan 1;25(1):90-98.

CAIndexNames:

2,6-Piperidinedione, 3-(5-amino-2-methyl-4-oxo-3(4H)-quinazolinyl)-

SMILES:

O=C(C(N1C(C)=NC2=C(C(N)=CC=C2)C1=O)CC3)NC3=O

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