Product Data Sheet

Product Name: CRA-026440
Cat. No.: GC32565

Chemical Properties

Cas. No.	847460-34-8		
SMILES	O=C(C(N1)=CC2=C1C=CC(OCCN(C)C)=C2)NCC#CC3=CC=C(C(NO)=O)C=C3		
Formula	$C_{23}H_{24}N_4O_4$	M.Wt	420.46
Solubility	DMSO : 100 mg/mL (237.83 mM; Need ultrasonic)	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	CRA-026440		

Protocol

Cell experiment: Ten tumor cell lines and HUVECs are cultured for at least two doubling times, and growth is monitored at the end of compound exposure using an Alamar Blue fluorometric cell proliferation assay. CRA-026440 is assayed in triplicate wells at nine concentrations in half-log intervals from 0.0015 to 10 μM. The concentration required to inhibit cell growth by 50% (GI50) and 95% confidence intervals are estimated from nonlinear regression using a four-variable logistic equation[1].

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Animal experiment:

Mice[1] Female BALB/c nu/nu mice are used. HCT116 at 3×106 and U937 at 4×106 are implanted s.c. Tumor-bearing mice are randomized based on tumor volume before the initiation of treatment. The treatment duration is 2 and 3 weeks for the U937 and the HCT 116 xenograft models, respectively. For combination studies, Avastin is given i.p. once a week, a day before the i.v. administration of CRA-026440. Tumor volume is calculated. Inhibition of tumor growth is calculated. HCT 116 tumor-bearing nude mice are treated with CRA-026440 at 100 mg/kg daily for three consecutive days. Tumor xenograft samples are fixed overnight in 10% zinc-buffered formalin and embedded in paraffin. Immunohistochemical staining on Ki-67 is done at BioPathology Sciences Medical Corp.

References:

[1]. Cao ZA, et al. CRA-026440: a potent, broad-spectrum, hydroxamic histone deacetylase inhibitor with antiproliferative and antiangiogenic activity in vitro and in vivo. Mol Cancer Ther. 2006 Jul;5(7):1693-701.

Background

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CRA-026440 is a potent, broad-spectrum HDAC inhibitor. The Ki values against recombinant HDAC isoenzymes HDAC1, HDAC2, HDAC3, HDAC6, HDAC8, and HDAC10 are 4, 14, 11, 15, 7, and 20 nM respectively.

CRA-026440 inhibits pure recombinant isozymes HDAC1, HDAC2, HDAC3/SMRT, HDAC6, HDAC8, and HDAC10 in the nanomolar range. Treatment of cultured tumor cell lines grown in vitro with CRA-026440 results in the accumulation of acetylated histone and acetylated tubulin, leading to an inhibition of tumor cell growth and the induction of apoptosis. To determine if HDAC inhibition by CRA-026440 affects the proliferation of tumor cells, a panel of human tumor cell lines is treated in vitro at various concentrations of inhibitor. Antitumor activity is observed in all 10 tumor cell lines tested, with GI50 values ranging from 0.12 to 9.95 μM. In addition, CRA-026440 has antiproliferative effect on HUVEC endothelial cells with a GI50 value of 1.41 μM[1].

CRA-026440 parenterally given to mice harboring HCT116 or U937 human tumor xenografts results in a statistically significant reduction in tumor growth. CRA-026440 is delivered i.v. to mice, and plasma concentrations are monitored over time. Based on these data, the clearance is calculated to be 38 mL/min/kg; the volume of distribution in the central compartment is 67 mL/kg. The steady-state volume of distribution is 454 mL/kg. The predominant plasma half-life is 7 minutes (44% of area under the curve); and the mean residence time is 12 minutes. One notable finding is that CRA-026440 has a different pharmacokinetic profile in tumor. It has a lower Cmax, but the compound concentration is maintained more steadily over time, probably due to the compound's large volume of distribution. CRA-026440 at 25 and 50 mg/kg given qdx3 per week significantly inhibits tumor growth at 40% ($P<0.01$) and 58% ($P<0.01$), respectively. The combination of Avastin at 25 mg/kg once a week and CRA-026440 at 25 and 50 mg/kg for three consecutive days per week lead to more profound tumor growth inhibition of 84% ($P< 0.01$) and 85% ($P<0.01$), respectively. Compared with Avastin alone, the combination yields a marginally better result ($P<0.1$). The combination of Avastin and CRA-026440 at 50 mg/kg is significantly better than CRA-026440 alone at 50 mg/kg ($P<0.05$). Both combination treatments are well tolerated with maximal weight loss <3% [1].

[1]. Cao ZA, et al. CRA-026440: a potent, broad-spectrum, hydroxamic histone deacetylase inhibitor with antiproliferative and antiangiogenic activity in vitro and in vivo. Mol Cancer Ther. 2006 Jul;5(7):1693-701.

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