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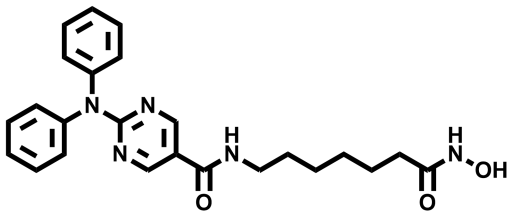
HDAC6 inhibitor– ACY-1215 (Rocilinostat)

Chemical Name: 2-(diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)pyrimidine-5-carboxamide



Molecular Weight:	433.50
Formula:	$C_{24}H_{27}N_5O_3$
Purity:	≥ 98%
CAS#:	1316214-52-4
Solubility:	DMSO up to 100 mM
Storage	Powder: 4ºC 1 year DMSO: 4ºC 3 month -20ºC 1 year

Biological Activity:

ACY-1215 (Rocilinostat) is a highly potent, selective, and orally bioavailable inhibitor of histone deacetylase 6 (HDAC6). It inhibits HDAC6 with an enzymatic IC_{50} ~ 5nM, and has about 10 fold selectivity against HDAC1, HDAC2, and HDAC3 (58 nM, 48 nM, 51 nM). It has minimal activity (IC_{50} >1 μM) against HDAC4, HDAC5, HDAC7, HDAC9, HDAC11, Sirtuin1, and Sirtuin2, and has slight activity against HDAC8 (IC_{50} ~0.1 μM). ACY-1215 selectively targets and binds to HDAC6, thereby disrupting the Hsp90 protein chaperone system through hyperacetylation of Hsp90 and preventing the subsequent aggresome protein degradation. This leads to an accumulation of unfolded and misfolded ubiquitinated proteins and may eventually induce cancer cell apoptosis, and inhibition of cancer cell growth. Low doses of ACY-1215 combined with bortezomib triggered synergistic anti- multiple myeloma (anti-MM) activity, resulting in protracted endoplasmic reticulum stress and apoptosis via activation of caspase-3, caspase-8, and caspase-9 and poly (ADP) ribosome polymerase. In vivo, the anti-MM activity of ACY-1215 in combination with bortezomib was confirmed using 2 different xenograft SCID mouse models. Currently ACY-1215 is in phase I clinical trials in combination with Lenalidomide and Dexamethasone for patients with multiple myeloma.

How to Use:

In vitro: ACY-1215 was used at 1 μM final concentration in vitro and in cellular assays.

In vivo: ACY-1215 was intraperitoneally dosed to mice consecutively for 5 days a week at 50 mg/kg dissolved in 5% dextrose in water with 10% DMSO or in combination with bortezomib (biweekly IV) 0.5 mg/kg dissolved in 0.9% saline solution.

Reference:

1. Santo L, et al. Preclinical activity, pharmacodynamic, and pharmacokinetic properties of a selective HDAC6 inhibitor, ACY-1215, in combination with bortezomib in multiple myeloma. (2012) Blood. 119(11):2579-89.
2. https://ash.confex.com/ash/2012/webprogram/Paper52013.html