

Product Data Sheet

Product Name: ACY-957

Cat. No.: GC30526

Chemical Properties

Cas. No. 1609389-52-7

SMILES O=C(C1=CC=C2N=C(N3CCNCC3)C=CC2=C1)NC4=CC(C5=CC=CS5)=CC=C4N

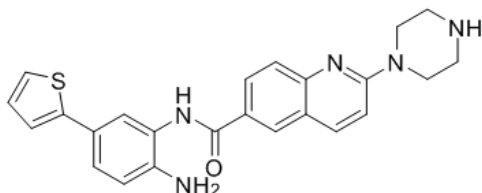
Formula $C_{24}H_{23}N_5OS$ M.Wt 429.54

Solubility DMSO : 83.33 mg/mL (194.00 mM) 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

Cell experiment [1]:

Cell lines Karpas-422 cells

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Karpas-422 cells were grown in RPMI 1640 medium supplemented with, 1% penicillin/streptomycin, and 10% heat-inactivated fetal bovine serum (FBS) in 384-well plates at a density of 2.5×10^5 cells/ml at 37°C in an incubator with 5% CO₂. Different concentrations of ACY-957 (2μM) were added and incubated at 37°C with 5% CO₂ for 48h. Cell viability was measured.

Reaction Conditions 2μM; 48h

Applications ACY-957 treatment significantly reduced cell viability of Karpas-422 cells.

Animal experiment [2]:

Animal models Female Crl:NU(NCr)-Foxn1^{nu} mice

Female Crl:NU(NCr)-Foxn1^{nu} mice were injected subcutaneously with 1×10^7 MOLM-13 cells in 50% Matrigel in the right flank. When tumors reached an average size of 100-150mm³, mice (n=10/group) were randomized into 3 treatment groups: Azacitidine, ACY-957, and vehicle control. Azacitidine was administered intravenously (i.v.) twice weekly at 5.5mg/kg in saline while ACY-957 was administered orally (p.o.) daily at 125mg/kg in 0.5% hydroxypropyl methylcellulose in deionized water. Mice were treated for 28 days. Tumors were measured twice weekly in two dimensions using calipers and volume was calculated by width²×length/2.

Dosage form 125mg/kg/day for 28 days; p.o.

Applications ACY-957 treatment significantly inhibited tumor growth in the MOLM-13 xenograft mouse model.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

References:

- [1] Johnson D P, Spitz G S, Tharkar S, et al. HDAC1, 2 inhibition impairs EZH2-and BBAP-mediated DNA repair to overcome chemoresistance in EZH2 gain-of-function mutant diffuse large B-cell lymphoma[J]. Oncotarget, 2014, 6(7): 4863.
- [2] Min C, Moore N, Shearstone J R, et al. Selective inhibitors of histone deacetylases 1 and 2 synergize with azacitidine in acute myeloid leukemia[J]. PloS one, 2017, 12(1): e0169128.

Background

ACY-957 is an orally active and selective chemical inhibitor of HDAC1 and HDAC2 with IC₅₀ values of 7nM and 18nM, respectively [1]. ACY-957 inhibits the expression levels of HbG mRNA and HbF protein and suppressed Bcl11A and Sox6 mRNA levels through the induction of Gata2 [2]. ACY-957 has been widely used to regulate the numbers of red blood cells, platelets and total cells in the bone marrow of Mx-Cre mouse models[3].

In vitro, ACY-957 treatment for 72h significantly inhibited the cell viability of MV-4-11, Kasumi-1 and HL-60 cells, with IC₅₀ values of 0.8μM, 1.6μM and 2.2μM, respectively[4]. Treatment with 2μM ACY-957 for 72 hours significantly induced cell cycle arrest and apoptosis in SUDHL4 cells, and led to a significant increase in H3K27ac levels[5].

In vivo, ACY-957 treatment via oral administration at a dose of 75mg/kg, five times a week for 3 weeks, significantly increased HbG mRNA expression in the blood of non-anemic cynomolgus monkeys and led to the accumulation of HbG protein[6]. Oral administration of ACY-957 at a dose of 30mg/kg daily for 6 days led to elevated HbE expression in the blood of rats and a slight decrease in body weight[7].

References:

- [1] Shearstone J R, Golonzhka O, Chonkar A, et al. Chemical inhibition of histone deacetylases 1 and 2 induces fetal hemoglobin through activation of GATA2[J]. PloS one, 2016, 11(4): e0153767.
- [2] Shearstone J R, van Duzer J H, Jones S S, et al. Mechanistic insights into fetal hemoglobin (HbF) induction through chemical inhibition of histone deacetylase 1 and 2 (HDAC1/2)[J]. Blood, 2013, 122(21): 2253.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

- [3] Shearstone J R, van Duzer J H, Jones S S, et al. Pharmacological Inhibition Of Histone Deacetylase (HDAC) 1, 2 Or 3 Have Distinct Effects On Cellular Viability, Erythroid Differentiation, and Fetal Globin (HbG) Induction[J]. Blood, 2013, 122(21): 564.
- [4] Min C, Moore N, Shearstone J R, et al. Selective inhibitors of histone deacetylases 1 and 2 synergize with azacitidine in acute myeloid leukemia[J]. PloS one, 2017, 12(1): e0169128.
- [5] Johnson D P, Spitz G S, Tharkar S, et al. HDAC1, 2 inhibition impairs EZH2-and BBAP-mediated DNA repair to overcome chemoresistance in EZH2 gain-of-function mutant diffuse large B-cell lymphoma[J]. Oncotarget, 2014, 6(7): 4863.
- [6] Chonkar A, Jarpe M, Bhol K, et al. The histone deacetylase 1 and 2 (HDAC1/2) inhibitor ACY-957: impact of dosing schedule on pharmacokinetics (PK), pharmacodynamics (PD), hematopoietic toxicity, and gamma globin (HBG, γ) expression in monkey[J]. Blood, 2016, 128(22): 323.
- [7] Shearstone J R, Chonkar A, Bhol K, et al. The histone deacetylase 1 and 2 (HDAC1/2) Inhibitor ACY-957 Increases Epsilon (HbE) and Gamma (HbG) Globin mRNA in the peripheral blood of non-anemic rats and monkeys[J]. Blood, 2015, 126(23): 3378.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA