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Givinostat hydrochloride monohydrate

Cat. No.: HY-14842B

CAS No.: 732302-99-7

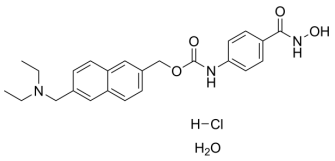
Molecular Formula: $C_{24}H_{30}ClN_3O_5$

Molecular Weight: 475.97

Target: HDAC

Pathway: Cell Cycle/DNA Damage; Epigenetics

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (210.10 mM)

H_2O : 2.94 mg/mL (6.18 mM; ultrasonic and warming and heat to 60°C)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1010 mL	10.5049 mL	21.0097 mL
5 mM	0.4202 mL	2.1010 mL	4.2019 mL
10 mM	0.2101 mL	1.0505 mL	2.1010 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.17 mg/mL (4.56 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.17 mg/mL (4.56 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.17 mg/mL (4.56 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Givinostat hydrochloride monohydrate (ITF-2357 hydrochloride monohydrate) is a HDAC inhibitor with an IC_{50} of 198 and 157 nM for HDAC1 and HDAC3, respectively.

IC_{50} & Target

hHDAC3 157 nM (IC_{50})	hHDAC1 198 nM (IC_{50})	hHDAC11 292 nM (IC_{50})	hHDAC6 315 nM (IC_{50})
hHDAC2	hHDAC10	hHDAC7	hHDAC5

	325 nM (IC_{50})	340 nM (IC_{50})	524 nM (IC_{50})	532 nM (IC_{50})
	hHDAC9 541 nM (IC_{50})	hHDAC8 854 nM (IC_{50})	hHDAC4 1059 nM (IC_{50})	HD1-B 7.5 nM (IC_{50})
	HD1-A 16 nM (IC_{50})	HD2 10 nM (IC_{50})		

In Vitro

Givinostat (ITF2357) suppresses total LPS-induced IL-1β production robustly compared with the reduction by ITF3056. At 25, 50, and 100 nM, Givinostat reduced IL-1β secretion more than 70%. Givinostat (ITF2357) suppresses the production of IL-6 in PBMCs stimulated with TLR agonists as well as the combination of IL-12 plus IL-18. IL-6 secretion decreases to 50% at 50 nM Givinostat (ITF2357), but at 100 and 200 nM, there is no reduction[1]. As shown by the CCK-8 assay, Givinostat (ITF2357) inhibits JS-1 cell proliferation in a concentration-dependent manner. Treatment with Givinostat (ITF2357) ≥500 nM is associated with significant inhibition of JS-1 cell proliferation ($P<0.01$). Also, the cell inhibition rate significantly differs between the group cotreated with Givinostat ≥250 nM plus LPS and the group without LPS treatment (same Givinostat concentration) ($P<0.05$)[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Givinostat (ITF2357) at 10 mg/kg is used as a positive control and, as expected, reduced serum TNFα by 60%. Strikingly, pretreatment of ITF3056 starting at 0.1 mg/kg significantly reduces the circulating TNFα by nearly 90%. To achieve a significant increase in serum IL-1β production, a higher dose of LPS is injected (10 mg/kg), and blood is collected after 4 h. Similarly, when pretreated with lower doses of Givinostat (ITF2357) (1 or 5 mg/kg), there is a 22% reduction for 1 mg/kg and 40% for 5 mg/kg[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]

After the JS-1 cell line is cultured in DMEM with 10% fetal bovine serum for 24 h, 30 wells of JS-1 cells are divided into two groups. In the first group, the culture medium is replaced by complete medium with final Givinostat concentrations of 0 nM, 125 nM, 250 nM, 500 nM, and 1000 nM. In the second group, Givinostat of relevant concentrations is added concomitantly with 100 nM of LPS solution. Three replicates are performed for each group. After inoculation at 37°C and 5% CO_2 for 24 h, each well (100 μL) is incubated with 10 μL of CCK-8 solution. The plates are incubated at 37 °C for 1 h and the absorbance is measured at 450 nm using a microplate reader[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration [1]

Mice[1]

C57BL/6 mice are housed in the animal facility for at least 5 days before use. For the comparison study, Givinostat (ITF2357) at 10 mg/kg is administered orally, and Givinostat (ITF2357) is injected intraperitoneally. One hour after administration of the compounds, the animals are treated intraperitoneally with LPS from Salmonella typhimurium at a dose of 2.5 mg/kg. 90 min after the LPS treatment, mice are sacrificed, and sera are collected and stored at -80°C until further analysis of cytokine productions.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Dis. 2020 Sep 15;11(9):753.
- Cell Prolif. 2021 May 24;e13072.
- Acta Pharmacol Sin. 2021 Apr 13.

- J Mol Med (Berl). 2019 Aug;97(8):1183-1193.
- Commun Biol. 2021 Oct 29;4(1):1235.

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REFERENCES

[1]. Li S, et al. Specific inhibition of histone deacetylase 8 reduces gene expression and production of proinflammatory cytokines in vitro and in vivo. J Biol Chem. 2015 Jan 23;290(4):2368-78.

[2]. Wang YG, et al. Givinostat inhibition of hepatic stellate cell proliferation and protein acetylation. World J Gastroenterol. 2015 Jul 21;21(27):8326-39.

[3]. Leoni F, et al. The histone deacetylase inhibitor ITF2357 reduces production of pro-inflammatory cytokines in vitro and systemic inflammation in vivo. Mol Med. 2005 Jan-Dec;11(1-12):1-15.

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