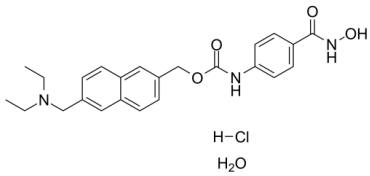
Data Sheet

Product Name:	Givinostat (hydrochloride monohydrate)
Cat. No.:	CS-7576
CAS No.:	732302-99-7
Molecular Formula:	C24H30ClN3O5
Molecular Weight:	475.97
Target:	HDAC
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Solubility:	DMSO : ≥ 100 mg/mL (210.10 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 198 nM (HDAC1), 157 nM (HDAC3)[1], 10 nM (HD2), 7.5 nM (HD1-B), 16 nM (HD1-A)[3] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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].

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.

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.

CAIndexNames:

Carbamic acid, N-[4-[(hydroxyamino)carbonyl]phenyl]-, [6-[(diethylamino)methyl]-2-naphthalenyl]methyl ester, hydrochloride, hydrate (1:1:1)

SMILES:

O=C(OCC1=CC=C2C=C(CN(CC)CC)C=CC2=C1)NC3=CC=C(C(NO)=O)C=C3.[H]Cl.O

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