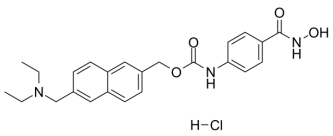
Givinostat hydrochloride

Cat. No.:	HY-14842A
CAS No.:	199657-29-9
Molecular Formula:	$C_{24}H_{28}ClN_3O_4$
Molecular Weight:	457.95
Target:	HDAC
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Givinostat (ITF-2357) hydrochloride is a HDAC inhibitor with an IC_{50} of 198 and 157 nM for HDAC1 and HDAC3, respectively[1][2][3].

IC_{50} & Target

hHDAC3 157 nM (IC_{50})	hHDAC1 198 nM (IC_{50})	hHDAC11 292 nM (IC_{50})	hHDAC6 315 nM (IC_{50})
hHDAC2 325 nM (IC_{50})	hHDAC10 340 nM (IC_{50})	hHDAC7 524 nM (IC_{50})	hHDAC5 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 reduces IL-1β secretion more than 70%. Givinostat 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, but at 100 and 200 nM, there is no reduction[1]. Givinostat (ITF-2357) inhibits JS-1 cell proliferation in a concentration-dependent manner in the CCK-8 assay. Treatment with Givinostat (ITF-2357) ≥500 nM is associated with significant inhibition of JS-1 cell proliferation. Also, the cell inhibition rate significantly differs between the group cotreated with Givinostat (ITF-2357) ≥250 nM plus LPS and the group without LPS treatment[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 reduces serum TNFα by 60%. Pretreatment of Givinostat (ITF-2357) 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[1].

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

PROTOCOL

Kinase Assay [1]	Recombinant human HDAC enzymes (HDAC1- HDAC11) are used. Activity of HDAC1, HDAC2, HDAC3, HDAC6, HDAC10 and HDAC11 is assayed using the Fluor de Lys deacetylase substrate. HDAC8 activity is assayed using Fluor de Lys Green deacetylase substrate. N-Trifluoroacetyl-L-lysine is used to assay activity of HDAC4, HDAC5, HDAC7 and HDAC9. Recombinant enzymes are preincubated with Givinostat (ITF2357) or ITF3056 at 30°C in a volume of 25 µL in wells of a microtiter plate. After a brief incubation, 25 µL of substrate is added, and the fluorescent signal is generated by the addition of 50 µL of developer containing 2 µM Trichostatin A. For each assay, the amount of enzyme, incubation times, assay buffer, and concentration of the substrates are optimized. Positive control for enzyme activity consisted of enzyme plus substrate without Givinostat or ITF3056. The fluorescence signal is detected using a Victor multilabel plate reader[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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 (ITF-2357) 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 (ITF-2357) 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.

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

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