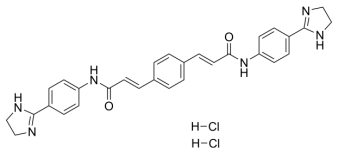
GW4869

Cat. No.:	HY-19363
CAS No.:	6823-69-4
Molecular Formula:	$C_{30}H_{30}Cl_2N_6O_2$
Molecular Weight:	577.5
Target:	Phospholipase
Pathway:	Metabolic Enzyme/Protease
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 : 0.1 mg/mL (0.17 mM; Need ultrasonic) H_2O : < 0.1 mg/mL (ultrasonic) (insoluble)

BIOLOGICAL ACTIVITY

Description	GW4869 is a noncompetitive neutral sphingomyelinase (N-SMase) inhibitor with an IC_{50} of 1 μM. GW4869 is an inhibitor of exosome biogenesis/release[1][2][3][4].
IC_{50} & Target	IC50: 1 μM (neutral sphingomyelinase)[1]
In Vitro	GW4869 (10 μM) partially inhibits TNF-induced sphingomyelin (SM) hydrolysis, and 20 μM of the compound is protected completely from the loss of SM. The addition of 10-20 μM GW4869 completely inhibits the initial accumulation of ceramide, whereas this effect is partially lost at later time points (24 h). The action of GW4869 occurs downstream of the drop in glutathione. GW4869 is able, in a dose-dependent manner, to significantly protect from cell death[1]. GW4869 (10 or 20 μM) inhibits both exosome release and pro-inflammatory cytokine production in macrophages. GW4869 inhibits the ceramide-mediated inward budding of multivesicular bodies (MVBs) and release of mature exosomes from MVBs [2]. GW4869 also could reverse the inhibition of CCN2 3'-UTR activity by miR-214-enriched exosomes in hepatic stellate cells[3]. Solution Attention: GW4869 is routinely stored at 80 °C as a stock suspension in DMSO. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	MCF7 human breast cancer cells.
Concentration:	10-20 μM.
Incubation Time:	30 min (then treated with TNF (3 nM) followed).
Result:	Significantly inhibited TNF-induced SM hydrolysis, whereas 20 μM of the compound protected completely from the loss of SM.

Cell Viability Assay[2]

Cell Line:	Fresh RAW264.7 macrophages.
Concentration:	10 or 20 μM.
Incubation Time:	2 hours (then treated with 1 μg/mL LPS incubation).
Result:	LPS-triggered exosome generation was remarkably attenuated in macrophages upon pre-treatment of macrophages with 10 μM GW4869, as evidenced by a 22% reduction in the activity of AChE. Such attenuation was further enhanced by treatment with the dose of 20 μM.

In Vivo

GW4869 (2.5 μg/g, i.p.) causes inhibition of exosome release blocks LPS-stimulated pro-inflammatory cytokine production and cardiac inflammation in mice. GW4869 mitigates LPS-caused myocardial dysfunction and improves survival in mice[2]. GW4869 (2.5 μg/g, i.p.) blocks the production of pro-inflammatory cytokines and cardiac inflammation in CLP mice[2].

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

Animal Model:	10-12 weeks old Male wild-type C57BL/6 mice (Endotoxin-Challenged Mice)[2].
Dosage:	2.5 μg/g.
Administration:	I.P. once (1 h later, followed by an i.p. injection of LPS (2.5 μg/g, 100 μL)).
Result:	Significantly decreased exosome levels by 37% in sera, compared to levels collected from control mice. At 12 h after LPS injection, the levels of circulating exosomeswere increased significantly compared to PBS-controls, as evidenced by a 1.7-fold elevation in the AChE activity.

Animal Model:	10-12 weeks old Male wild-type C57BL/6 mice (CLP Polymicrobial Sepsis Model)[2].
Dosage:	2.5 μg/g.
Administration:	I.P. once (before sham or CLP surgery).
Result:	Decreased exosome concentration by 33% compared to mice injected with PBS in sham-surgery controls. CLP-stimulated exosome release was significantly inhibited by pre-treatment of CLP mice compared to CLP mice pre-treated with PBS.

CUSTOMER VALIDATION

- Adv Mater. 2021 Dec;33(49):e2103471.
- Protein Cell. 21 September 2022.
- Bioact Mater. 2024 Mar, 33, 85-99.
- Bioact Mater. 2023 Sep, 377-393.
- Nat Commun. 2022 Aug 1;13(1):4461.

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REFERENCES

[1]. Luberto C, et al. Inhibition of tumor necrosis factor-induced cell death in MCF7 by a novel inhibitor of neutralsphingomyelinase. J Biol Chem. 2002 Oct 25;277(43):41128-39.

[2]. Essandoh K, et al. Blockade of exosome generation with GW4869 dampens the sepsis-induced inflammation and cardiac dysfunction. Biochim Biophys Acta. 2015 Nov;1852(11):2362-71.

[3]. Chen L, et al. Integrins and heparan sulfate proteoglycans on hepatic stellate cells (HSC) are novel receptors for HSC-derived exosomes. FEBS Lett. 2016 Dec;590(23):4263-4274.

[4]. Nakamura H, et al. Sphingomyelin Regulates the Activity of Secretory Phospholipase A2 in the Plasma Membrane. J Cell Biochem. 2015 Sep;116(9):1898-907.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA