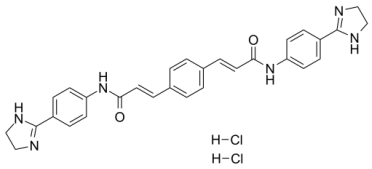
Data Sheet

Product Name:	GW4869
Cat. No.:	CS-6865
CAS No.:	6823-69-4
Molecular Formula:	C30H30Cl2N6O2
Molecular Weight:	577.50
Target:	Others
Pathway:	Others
Solubility:	DMSO : 0.044 mg/mL (0.08 mM; Need ultrasonic and warming); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GW4869 is a noncompetitive **neutral sphingomyelinase (N-SMase)** inhibitor (exosome inhibitor) with an **IC_{50}** of 1 μM. IC50 & 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[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 1.5 mM stock suspension in DMSO (Me_2SO). Right before use, the suspension is solubilized by the addition of 5% methane sulfonic acid (MSA) (2.5 μl of 5% MSA in sterile double-distilled H_2O are added to 50 μL of GW4869 stock suspension)[1]. GW4869 is routinely stored at -30 °C as a 1.5 mM stock suspension in DMSO. Immediately before use, this suspension is solubilized by the addition of 0.25% methane sulfonic acid (2.5 mL of 5% methane sulfonic acid in sterile distilled H_2O is added to 47.5 mL of GW4869 stock solution). The suspension is mixed and heated at 37 °C until clear[4].
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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: GW4869 is routinely stored at −80 °C as a 1.5 mM stock suspension in Me_2SO. Right before use, the suspension is solubilized by the addition of 5% methane sulfonic acid (MSA) (2.5 μl of 5% MSA in sterile double-distilled H_2O are added to 50 μL of GW4869 stock suspension)[1]. GW4869 is routinely stored at -30 °C as a 1.5 mM stock suspension in DMSO. Immediately before use, this suspension is solubilized by the addition of 0.25% methane sulfonic acid (2.5 mL of 5% methane sulfonic acid in sterile distilled H_2O is added to 47.5 mL of GW4869 stock solution). The suspension is mixed and heated at 37 °C until clear[3].[1]Cells are treated with GW4869 for 30 min and then TNF is added in 10 μL/well. At the indicated time points, 25 μL of MTT stock solution are added to each well and incubated at 37 °C in 5% CO_2 for 3 h. The cell viability is using the MTT assay[1]. **Animal Administration:** GW4869 is dissolved in DMSO (0.005%).[2]Mice: The mice are randomly assigned to four groups: PBS, GW4869, PBS+LPS and GW4869+LPS (n=5 per group). GW4869 is intraperitoneally (i.p.) injected at one dose of 2.5μg/g. Mice in the PBS+LPS group are pre-injected i.p. with PBS 1 h prior to an i.p. injection of LPS (25 μg/g). Mice in the group of GW4869+LPS are pre-injected i.p. with GW4869 (2.5μg/g) for 1 h, followed by an i.p. injection of LPS (25 μg/g, 100μl). Mice receive injections of PBS to a comparable volume (100μl) as controls. The survival rate of the PBS+LPS and GW4869+LPS groups are monitored every 6 h for a 36 h period[2].

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.

CAIndexNames:

2-Propenamide, 3,3'-(1,4-phenylene)bis[N-[4-(4,5-dihydro-1H-imidazol-2-yl)phenyl]-, hydrochloride (1:2)

SMILES:

O=C(NC1=CC=C(C2=NCCN2)C=C1)/C=C/C3=CC=C(/C=C/C(NC4=CC=C(C5=NCCN5)C=C4)=O)C=C3.[H]Cl.[H]Cl

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