上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：GW4869
产品别名：GW4869

生物活性：		
Description	GW4869 is a noncompetitive neutral sphingomyelinase (N-SMase) inhibitor (exosome inhibitor) with an IC50 of 1 μM.	
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[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 H2O is added to 47.5 mL of GW4869 stock solution). The suspension is mixed and heated at 37 °C until clear[4].	
	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].	
	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 (25 μg/g, 100μL)).
	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 exosomes were increased significantly compared to PBS-controls, as evidenced by a 1.7-fold elevation in the AChE activity.
Solvent&Solubility	***In Vitro:*** **H_2O : < 0.1 mg/mL** (insoluble) **DMSO : 0.044 mg/mL** (**0.08 mM;** Need ultrasonic and warming)	
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.	