Product Data Sheet

Product Name: GW3965
Cat. No.: GC16964

Chemical Properties

Cas. No.	405911-09-3		
Chemical Name	2-[3-[3-[[2-chloro-3-(trifluoromethyl)phenyl]methyl-(2,2-diphenylethyl)amino]propoxy]phenyl]acetic acid		
SMILES	C1=CC=C(C=C1)C(CN(CCCOC2=CC=CC(=C2)CC(=O)O)CC3=C(C(=CC=C3)C(F)(F)F)Cl)C4=CC=CC=C4		
Formula	$C_{33}H_{31}ClF_3NO_3$	M.Wt	582.05
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	GW3965		

Protocol

Cell experiment [1,2]:

Cell lines	U87 and U87-EGFRvIII GBM cells,
Preparation method	Soluble in DMSO. General tips for obtaining a higher concentration: Please warm the tube at 37 ℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months.
Reacting condition	2-5 μM, 4 days

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Applications	In U87 and U87-EGFRvIII GBM cells, treatment with GW3965 (2-5 μM) for 4 days dose-dependently inhibited growth and promoted tumor cell death. Low-dose GW3965 (1 or 2 μM) induced ABCA1. In U87 and U87-EGFRvIII GBM cells, GW3965 (5 μM, 24h) upregulated expression of the cholesterol transporter gene ABCA1 and the E3 ubiquitin ligase IDOL and reduced LDLR levels. GW3965 (1 or 5 μM) displayed a minor inhibitory effect on fibrinogen binding and P-selectin exposure. GW3965 (10 μM) reduced the levels of fibrinogen and P-selectin on the platelet surface.

Animal experiment [1,2]:

Animal models	SCID/Beige mice xenografted with isogenic human malignant glioma cells (U87, U87-EGFRvIII); C57BL/6 mice
Dosage form	Oral gavage, 40 mg/kg, daily for 12 days
Application	In mice bearing U87/EGFRvIII cells, GW3965 (40 mg/kg daily by oral gavage) for 12 days potently inhibited GBM growth, promoted tumor cell death and inhibited tumor growth. In C57BL/6 mice, GW3965 (2 mg/kg, i.v.) increased bleeding time and modulated platelet thrombus formation.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

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References:

[1]. Guo D, Reinitz F, Youssef M, et al. An LXR agonist promotes glioblastoma cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR–dependent pathway[J]. Cancer discovery, 2011.

[2]. Spyridon M, Moraes L A, Jones C I, et al. LXR as a novel antithrombotic target[J]. Blood, 2011, 117(21): 5751-5761.

Background

GW3965 is a potent and selective activitor of liver X receptors (LXRs) with EC50 value of 190 and 30 nM respectively to hLXRαand hLXRβ.[1]
Liver X receptors belong to the nuclear receptor family. They are classified into subfamily 1 of the nuclear receptor superfamily. There are two isforms of LXRs and they are LXRαand LXRβ. LXRs play an important role in regulating glucose, fatty acid, and cholesterol homeostasis. Crystal analysis show that human LXRβ (liver X receptor β) forms heterodimer with retinoid X receptor α(RXRα) which is the partner on its cognate element. Before activation, LXRα and LXRβ can form heterodimers with the partner 9-cis RXR (retinoic acid receptor). The heterodimer will be activated by an LXR agonist or a RXR agonist. After activation, LXR will binds to LXR response element and regulated related gene expression.[2]
GW3965 can result in promotion of tumor cell death and inhibition of cell growth in GBM

cells at 2μM. GW3965 treatment at 2μM can significantly promote increases in mRNA levels of ABCA1 and IDOL, then induced cell death.[3]
GW3965 significantly reduced LDLR expression and induced ABCA1 expression in mice which was implanted U87/EGFRvIII cells at 40 mg/kg. GW3965 also blocked tumor growth at this dose.[3] GW3965 increased the expression of ABCA1and apoE at 30 mg/kg/d in APP/PS1 mice.[4]

References:

[1]. Zhang Y, Ge C, Wang L, Liu X, Chen Y, Li M, Zhang M: Induction of DKK1 by ox-LDL negatively regulates intracellular lipid accumulation in macrophages. FEBS Lett, 589(1):52-58.

[2]. Spyridon M, Moraes LA, Jones CI, Sage T, Sasikumar P, Bucci G, Gibbins JM: LXR as a novel antithrombotic target. Blood, 117(21):5751-5761.

[3]. Guo D, Reinitz F, Youssef M, Hong C, Nathanson D, Akhavan D, Kuga D, Amzajerdi AN, Soto H, Zhu S et al: An LXR agonist promotes glioblastoma cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR-dependent pathway. Cancer Discov, 1(5):442-456.

[4]. Donkin JJ, Stukas S, Hirsch-Reinshagen V, Namjoshi D, Wilkinson A, May S, Chan J, Fan J, Collins J, Wellington CL: ATP-binding cassette transporter A1 mediates the beneficial effects of the liver X receptor agonist GW3965 on object recognition memory and amyloid burden in amyloid precursor protein/presenilin 1 mice. J Biol Chem, 285(44):34144-34154.