

Product Data Sheet

Product Name: Tideglusib

Cat. No.: GC14465

Chemical Properties

Cas. No. 865854-05-3

Chemical Name 4-benzyl-2-naphthalen-1-yl-1,2,4-thiadiazolidine-3,5-dione

SMILES C1=CC=C(C=C1)CN2C(=O)N(SC2=O)C3=CC=CC4=CC=CC=C43

Formula C₁₉H₁₄N₂O₂S M.Wt 334.39

Solubility ≥ 16.7 mg/mL in DMSO with gentle warming Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.

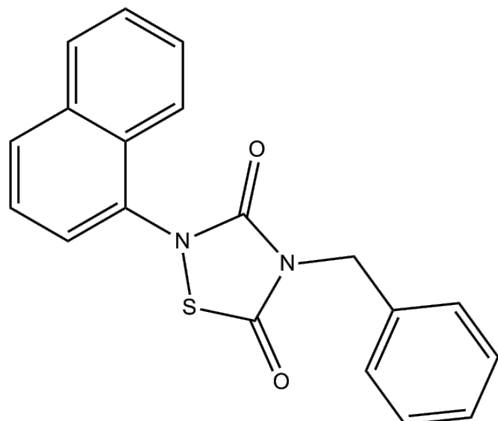
Caution: Product has not been fully validated for medical applications. For research use only.

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Structure



Protocol

Kinase experiment [1]:

Kinase assay was carried out at 25°C in a final volume of 10µl in 384-well low volume round bottom black plates with 50mM Hepes, pH 7.5, 10mM MgCl₂, 1mM EGTA, and 0.01% Brij-35 as assay buffer. Enzyme concentration ranged from 2 to 5nM. ATP and peptide concentrations were 12.5 and 2µM, respectively. The assays were run for 1h in the presence or absence of

Preparation Method compounds in a final DMSO concentration of 1%, and samples were processed. When double titrations of ATP and Tideglusib were performed, varying both ATP and Tideglusib concentrations while keeping the concentration of peptide substrate fixed. Data analysis was performed by fitting the experimental data to the appropriate equations for competitive, uncompetitive, and non-competitive inhibition.

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Reaction
Conditions 0.1nM-1μM; 1h

Applications The IC₅₀ value of Tideglusib in inhibiting GSK-3β is 5nm in the pre-incubation condition and 105nm in the non-pre-incubation condition.

Cell experiment [2]:

Cell lines Rat primary astrocytes, microglia, and neurons

Preparation Method Tideglusib (2.5μm) was added to the culture medium of astrocytes and microglia 1 h before exposure to glutamate (500μm), cells were incubated for 24 h before tissue culture medium was collected, and the cells were evaluated for tumor necrosis factor-α (TNF-α) and cyclooxygenase type 2 (COX-2) expression.

Reaction
Conditions 2.5μM; 24h

Applications Tideglusib completely abolished the expression of TNF-α and COX-2 in the astrocyte and microglial cell cultures induced by glutamate.

Animal experiment [2]:

Animal models Wistar rats (focal excitotoxic model)

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Each group of rats ($n \geq 5$) was anesthetized by intraperitoneal injection of ketamine (60mg/kg) and Domtor (5 μ g/kg), and then placed in a stereotactic apparatus. kainic acid (KA) (1 μ g dissolved in 2.5 μ L PBS) or in combination with Tideglusib (2ng dissolved in 2.5 μ L PBS) was injected separately into the hippocampus. The control animals were injected with solvent. Each injection was administered using a micro-pump and lasted for more than 2.5 minutes.

Afterward, these rats were housed individually for recovery care. Behavioral

Preparation Method analysis was conducted. After stereotactic injection, the animals were anesthetized at different times and perfused with 4% paraformaldehyde solution via the heart. The brain was removed and placed in the same solution overnight at 4°C, subjected to cryoprotection in a 30% sucrose polyformaldehyde solution, frozen, and obtained 30 μ m coronal sections under a cryostat. The floating sections were processed with the diaminobenzidine method or double immunofluorescence analysis for Nissl staining or immunohistochemical treatment.

Dosage form 2ng/2.5 μ L PBS; stereotactic injection

Applications Tideglusib treatment significantly improved brain damage in rats, reduced the loss of hippocampal cells, and significantly decreased the TNF- α positive staining in astrocytes and microglia.

References:

- [1] Domínguez, Juan Manuel et al. "Evidence for irreversible inhibition of glycogen synthase kinase-3 β by tideglusib." The Journal of biological chemistry vol. 287,2 (2012): 893-904.
- [2] Luna-Medina R, Cortes-Canteli M, Sanchez-Galiano S, et al. NP031112, a thiadiazolidinone compound, prevents inflammation and neurodegeneration under excitotoxic conditions: potential therapeutic role in brain disorders[J]. Journal of Neuroscience, 2007, 27(21): 5766-5776.

Background

Tideglusib is a potent, selective, and irreversible non-ATP competitive glycogen synthase kinase-3 (GSK-3) inhibitor. The IC₅₀ values for GSK-3 β WT and GSK-3 β C199A are 5nM and 60nM,

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respectively [1]. GSK-3 is a serine/threonine kinase that is associated with glucose regulation, apoptosis, protein synthesis, cell signaling, cell transport, gene transcription, and cell proliferation [2]. Tideglusib can inhibit inflammation and neurodegenerative diseases and can be used to treat Alzheimer's disease [3-4].

In vitro, Tideglusib (2.5µM; 24h) completely eliminated the expression of TNF-α and COX-2 in glutamate-induced astrocyte and microglial cell cultures, and significantly reduced the number of laminin-V positive cells, exerting anti-inflammatory and neuroprotective effects on cortical neurons [5]. Different concentrations of Tideglusib (5-120µM; 48h) dose-dependently reduced the cell viability of human neuroblastoma (IMR32) cells [6].

In vivo, Tideglusib (2ng/2.5µl PBS; stereotactic injection) treatment significantly improved brain injury in kainic acid (KA) induced focal excitotoxicity model rats and reduced TNF-α positive staining in astrocytes and microglia [5]. Tideglusib (200mg/kg/day; 3 months) oral treatment reduced tau protein phosphorylation levels in APP/tau double transgenic mice, decreased amyloid protein deposition and plaque-related astrocyte proliferation, and protected the entorhinal cortex and prevented hippocampal CA1 zone neuron death [7].

References:

- [1] Domínguez JM, Fuertes A, Orozco L, et al. Evidence for irreversible inhibition of glycogen synthase kinase-3β by tideglusib. *J Biol Chem*. 2012;287(2):893-904.
- [2] Pandey M K, DeGrado T R. Glycogen synthase kinase-3 (GSK-3)-targeted therapy and imaging[J]. *Theranostics*, 2016, 6(4): 571.
- [3] Serenóa L, Coma M, Rodríguez M, et al. A novel GSK-3β inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. *Neurobiol Dis*. 2009 Sep; 35(3): 359-67.
- [4] Lovestone S, Boada M, Dubois B, et al. A phase II trial of tideglusib in Alzheimer's disease[J]. *Journal of Alzheimer's Disease*, 2015, 45(1): 75-88.
- [5] Luna-Medina R, Cortes-Canteli M, Sanchez-Galiano S, et al. NP031112, a thiadiazolidinone compound, prevents inflammation and neurodegeneration under excitotoxic conditions: potential therapeutic role in brain disorders[J]. *Journal of Neuroscience*, 2007, 27(21): 5766-5776.
- [6] Mathuram, Theodore Lemuel et al. "Tideglusib induces apoptosis in human neuroblastoma IMR32 cells, provoking sub-G0/G1 accumulation and ROS generation." *Environmental toxicology and pharmacology* vol. 46 (2016): 194-205.

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[7] Serenó, L et al. "A novel GSK-3beta inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo." *Neurobiology of disease* vol. 35,3 (2009): 359-67.

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