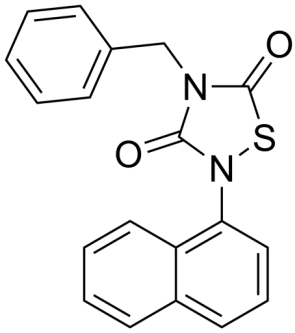
Data Sheet

Product Name:	Tideglusib
Cat. No.:	CS-0613
CAS No.:	865854-05-3
Molecular Formula:	$C_{19}H_{14}N_2O_2S$
Molecular Weight:	334.39
Target:	GSK-3
Pathway:	PI3K/Akt/mTOR; Stem Cell/Wnt
Solubility:	DMSO: 12.5 mg/mL



BIOLOGICAL ACTIVITY:

Tideglusib is an irreversible **GSK-3** inhibitor with **IC_{50}** of 5 nM and 60 nM for **GSK-3β^{WT}** (1 h preincubation) and **GSK-3β^{C199A}** (1 h preincubation), respectively.

IC50 & Target: IC50: 5 nM (GSK-3β^{WT}), 60 nM (GSK-3β^{C199A})[1]

In Vitro: Tideglusib (NP12) is a small heterocyclic thiadiazolidinone (TDZD) derivative, which is an ATP-non competitive inhibitor of GSK-3β with an IC_{50} value in the micromolar range[2]. Incubation of both astrocyte and microglial cultures with Tideglusib (NP031112) completely abrogates the induction of TNF-α and COX-2 expression after glutamate treatment. These effects of NP031112 are not caused by a loss of cell viability, because the 24 h exposure of astrocyte and microglial cells to this TDZD does not modify cell viability[3].

In Vivo: Tideglusib (NP12) treatment correlates with an increase of 46% as an average in the inhibitory phosphorylation of GSK-3β at Ser-9 in the brains of APP^{sw}-tau^{vlw} mice, and the levels of the inactive from of the enzyme in NP12 treated mice are comparable to those found in wild-type littermate controls (p=0.893) (n=6-8 for each treatment). NP12 treatment results in significantly decreased phosphorylation at the putative GSK-3β-directed sites Ser-202 (CP13) and Ser-396/404 (PHF-1) in 15-month-old mice by more than 60% (p=0.023 and p=0.024, respectively)[2]. Injection of Tideglusib (NP031112) (50 mg/kg) into the rat hippocampus dramatically reduces kainic acid-induced inflammation, as measured by edema formation using T2-weighted magnetic resonance imaging and glial activation and has a neuroprotective effect in the damaged areas of the hippocampus[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1][^{35}S]Tideglusib (207 Bq/nmol) at 55 μM is incubated with 5 μM GSK-3β for 1 h at 25°C in 315 μL of 50 mM Tris-HCl, pH 7.5, containing 150 mM NaCl and 0.1 mM EGTA. The incubation is extended for another 30 min after having added 35 μL of the same buffer with or without 100 mM DTE. Samples are then processed in three different ways. First, an aliquot of 125 μL of each sample is mixed with 375 μL of 8 M GdnHCl in H_2O and heated at 80°C for 5 min. A second aliquot of 125 μL is diluted up to 500 μL with H_2O and left at room temperature for 5 min. In both cases, the free drug is removed afterwards by gel filtration through Sephadex G-25, and the amount of bound drug is determined by liquid scintillation counting on a 1450-MicroBeta TriLux counter. Finally, a third 40 μL aliquot of each original sample is mixed with 10 μL of denaturing electrophoresis sample buffer without reducing agents, and 35 μL of this mixture is loaded onto a 10% polyacrylamide gel and subjected to SDS-PAGE (again in the absence of reducing agents except for the DTE already included in the corresponding sample), followed by fluorography of the dried gel[1]. **Animal Administration:** Tideglusib (NP12) is reconstituted in 26% peg400 (Polyethylene Glycol 400), 15% Chremophor EL and water (Mice)[2].[2][3]Mice[2]

Groups of APP^{sw}-tau^{vlw} mice are administered Tideglusib (n=10-11 for each age) or vehicle (n=10-11 for each age) starting at 9

months and 12 months of age during consecutive 3 months and used for subsequent clinicopathological analyses. Tideglusib is administered at a daily dose of 200 mg/kg. Groups of age and gender-matched wild-type littermate controls (n=10 for each age) receive vehicle alone on a similar timetable schedule. Rat[3]

Adult male Wistar rats (8-12 weeks old) are used in this study. Rats (n≥5 per group) are anesthetized by intraperitoneal injection of ketamine (60 mg/kg) and Domtor (5 μg/kg) and placed into a stereotaxic apparatus. KA (1 μg in 2.5 μL PBS) alone or in combination with Tideglusib (2 ng in 2.5 μL PBS) is injected into the hippocampus. Control animals of the same age are injected with vehicle.

References:

[1]. Domínguez JM, et al. Evidence for irreversible inhibition of glycogen synthase kinase-3β by tideglusib. J Biol Chem, 2012, 287(2), 893-90

[2]. Sereno L, et al. A novel GSK-3beta inhibitor reduces Alzheimer's pathology and rescues neuronal loss in vivo. Neurobiol Dis. 2009 Sep;35(3):359-67.

[3]. Luna-Medina R, et al. NP031112, a thiadiazolidinone compound, prevents inflammation and neurodegeneration under excitotoxic conditions: potential therapeutic role in brain disorders. J Neurosci, 2007, 27(21), 5766-5776.

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