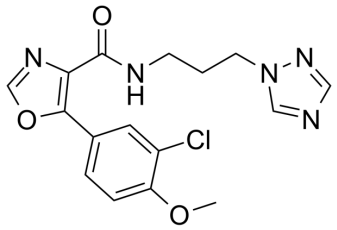
PF-04802367

Cat. No.:	HY-122026
CAS No.:	1962178-27-3
Molecular Formula:	$C_{16}H_{16}ClN_5O_3$
Molecular Weight:	361.78
Target:	GSK-3
Pathway:	PI3K/Akt/mTOR; Stem Cell/Wnt
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (276.41 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.7641 mL	13.8206 mL	27.6411 mL
5 mM	0.5528 mL	2.7641 mL	5.5282 mL
10 mM	0.2764 mL	1.3821 mL	2.7641 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.91 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.91 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.91 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-04802367 (PF-367) is a highly selective GSK-3 inhibitor with an IC_{50} of 2.1 nM based on a recombinant human GSK-3β enzyme assay and 1.1 nM based on ADP-Glo assay. PF-04802367 shows desirable central nervous system (CNS) properties and potency. PF-04802367 is equally effective at inhibition of the two known GSK-3 isoforms (GSK-3α and GSK-3β) with IC_{50} values of 10.0 and 9.0 nM in mobility shift assays, respectively[1].

IC_{50} & Target	GSK-3α	GSK-3β
	10 nM (IC_{50})	9 nM (IC_{50})

In Vitro

PF-04802367 (PF-367) is efficient at inhibiting GSK-3β enzymatic activity in vitro with ligand and lipophilic efficiency scores of 0.46 and 7.0, respectively[1].

PF-367 has reasonable in vitro stability in human hepatic microsomes ($t_{1/2}$=78.7 min), has excellent passive permeability[1].

In a stable inducible CHO cell line over-expressing GSK-3β and its substrate tau, PF-367 inhibited phosphorylation of tau with an IC_{50} of 466 nM[1].

PF-367 has good cell viability (IC_{50} of 117 μM in THLE cytotoxicity assays) and an IC_{50} >100 μM in a hERG screening assay[1].

PF-367 shows significant right shifts against β-catenin translocation in HeLa cells with EC_{50} of 6.2 μM, gene transcription in U20S cells with EC_{50} of 20.6 μM, and cell proliferation in HeLa cells as evaluated by Ki-67 incorporation with EC_{50} of 9.0 μM[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

PF-04802367 (PF-367) a potent GSK-3 inhibitor with exceptional kinome selectivity that modulates phosphorylated tau levels in vivo. Inhibition of phosphorylation of tau in brain by PF-367 (A single subcutaneous of 1, 3.2, 10, 32 or 50 mg/kg) is dose-dependent[1].

PF-04802367 (PF-367), a potent type-I dual GSK-3α/β inhibitor, showing promising absorption; distribution, metabolism and elimination (ADME) properties combined with robust CNS/peripheral p-Tau and muscle phosphorylated glycogen synthase (pGS) inhibition in vivo[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Sprague-Dawley rats[1]
Dosage:	1, 3.2, 10, 32 or 50 mg/kg
Administration:	A single subcutaneous
Result:	Inhibition of phosphorylation of tau in brain is dose-dependent.

REFERENCES

[1]. Steven H Liang, et al. Discovery of a Highly Selective Glycogen Synthase Kinase-3 Inhibitor (PF-04802367) That Modulates Tau Phosphorylation in the Brain: Translation for PET Neuroimaging. Angew Chem Int Ed Engl. 2016 Aug 8;55(33):9601-5.

[2]. Vadim Bernard-Gauthier, et al. Structural Basis for Achieving GSK-3β Inhibition with High Potency, Selectivity, and Brain Exposure for Positron Emission Tomography Imaging and Drug Discovery. J Med Chem. 2019 Nov 14;62(21):9600-9617.

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