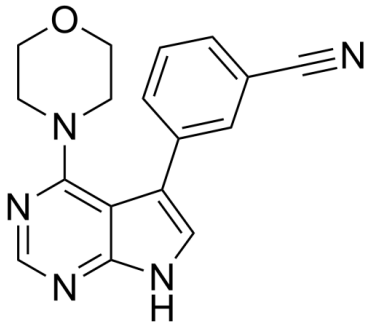
Data Sheet

Product Name:	PF-06447475
Cat. No.:	CS-3553
CAS No.:	1527473-33-1
Molecular Formula:	$C_{17}H_{15}N_5O$
Molecular Weight:	305.33
Target:	LRRK2
Pathway:	Autophagy
Solubility:	DMSO : 60 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

PF-06447475 is a highly potent, selective and brain penetrant **LRRK2** inhibitor with an **IC_{50}** of 3 nM. IC50 & Target: IC50: 3 nM (LRRK2)[1]. ***In Vitro:*** PF-06447475 inhibits LRRK2 enzyme and LRRK2 in the whole cell assay with IC_{50}s of 3 and 25 nM, respectively [1]. Cells incubated with PF-06447475 alone (0.5, 1, 3 μM) or in the presence of ROT significantly reduces (S935)-LRRK2 kinase phosphorylation to control. PF-06447475 significantly preserves the nucleus morphology and ΔΨm of NLCs exposed to ROT compared to untreated and control. PF-475 significantly diminishes ROT-induced ROS generation to a similar extent to cells exposed to PF-475 alone[2]. ***In Vivo:*** In G2019S+ rats treated with PF-06447475, a significant reduction in microgliosis to levels found in wild-type rats could be observed. The proinflammatory marker MHC-II expressed on myeloid cells but not neurons also appears to be less abundant in confocal sections in G2019S+ rats treated with PF-06447475. PF-06447475 treatment in G2019S+ rats significantly lowers the number of CD68 cells recruited to the SNpc. PF-06447475 successfully blocks the enhanced neuroinflammation associated with G2019S-LRRK2 expression. Treatment of G2019S+ rats with PF-06447475 preserves TH expression in the dorsal striatum, consistent with drug attenuating neurodegeneration in the SNpc[3]. PF-06447475 is well tolerated in rats[1].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: [3]Rats: PF-06447475 are administered to the desired amount in a suspension solution consisting of 10% propylene glycol, 20% PEG-400, and 70% 0.5% methylcellulose. To determine the potency of PF-06447475 in blocking brain LRRK2 kinase activity, wild-type Sprague-Dawley rats are treated at 3 and 30 mg/kg PF-06447475 (p.o. b.i.d.) for 14 days, and total and phospho-LRRK2 are subsequently measured from brain tissue lysates[3].

References:

[1]. Henderson JL, et al. Discovery and preclinical profiling of 3-[4-(morpholin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]benzonitrile (PF-06447475), a highly potent, selective, brain penetrant, and in vivo active LRRK2 kinase inhibitor. J Med Chem. 2015 Jan 8;58(1):419-32.

[2]. Mendivil-Perez M, et al. Neuroprotective Effect of the LRRK2 Kinase Inhibitor PF-06447475 in Human Nerve-Like Differentiated Cells Exposed to Oxidative Stress Stimuli: Implications for Parkinson's Disease. Neurochem Res. 2016 Oct;41(10):2675-2692.

[3]. Daher JP, et al. Leucine-rich Repeat Kinase 2 (LRRK2) Pharmacological Inhibition Abates α-Synuclein Gene-induced Neurodegeneration. J Biol Chem. 2015 Aug 7;290(32):19433-44.

CAIndexNames:

Benzonitrile, 3-[4-(4-morpholinyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]-

SMILES:

N#CC1=CC=CC(C2=CNC3=NC=NC(N4CCOCC4)=C32)=C1

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