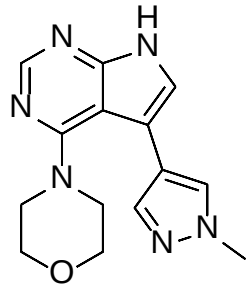
Product data sheet

MedKoo Cat#: 532463 Name: PF-06454589 CAS: 1527473-30-8 Chemical Formula: $C_{14}H_{16}N_6O$ Exact Mass: 284.1386 Molecular Weight: 284.323	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
PF-06454589 is a potent and selective LRRK2 inhibitor.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	60.5	212.79

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.28 mL	16.38 mL	32.75 mL
5 mM	0.66 mL	3.28 mL	6.55 mL
10 mM	0.33 mL	1.64 mL	3.28 mL
50 mM	0.07 mL	0.33 mL	0.66 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Volpicelli-Daley LA, Abdelmotilib H, Liu Z, Stoyka L, Daher JP, Milnerwood AJ, Unni VK, Hirst WD, Yue Z, Zhao HT, Fraser K, Kennedy RE, West AB. G2019S-LRRK2 Expression Augments α-Synuclein Sequestration into Inclusions in Neurons. J Neurosci. 2016 Jul 13;36(28):7415-27. doi: 10.1523/JNEUROSCI.3642-15.2016. Erratum in: J Neurosci. 2022 Jan 26;42(4):718. PMID: 27413152; PMCID: PMC4945663.

In vivo study

1. Filippone A, Cucinotta L, Bova V, Lanza M, Casili G, Paterniti I, Campolo M, Cuzzocrea S, Esposito E. Inhibition of LRRK2 Attenuates Depression-Related Symptoms in Mice with Moderate Traumatic Brain Injury. Cells. 2023 Mar 29;12(7):1040. doi: 10.3390/cells12071040. PMID: 37048114; PMCID: PMC10093681.
2. Daher JP, Abdelmotilib HA, Hu X, Volpicelli-Daley LA, Moehle MS, Fraser KB, Needle E, Chen Y, Steyn SJ, Galatsis P, Hirst WD, West AB. Leucine-rich Repeat Kinase 2 (LRRK2) Pharmacological Inhibition Abates α-Synuclein Gene-induced Neurodegeneration. J Biol Chem. 2015 Aug 7;290(32):19433-44. doi: 10.1074/jbc.M115.660001. Epub 2015 Jun 15. PMID: 26078453; PMCID: PMC4528108.

7. Bioactivity
Biological target:

PF-06447475 is a highly potent, selective and brain penetrant LRRK2 inhibitor with an IC50 of 3 nM.

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In vitro activity

To compare these molecules directly, this study found that both MLi-2 and PF-06447475 inhibited LRRK2 peptide phosphorylation with similar IC_{50} values of 1.1 ± 0.2 and 3.5 ± 1.1 nm, respectively (Fig. 5*B*), demonstrating exceptional potency for both molecules. A LRRK2 peptide phosphorylation assay in the presence of 1.1 nm of MLi-2 or 3.5 nm of PF-06447475 demonstrated that both inhibitors increased the K_m-ATP (149.9 ± 9.7, 421.4 ± 18.7, and 272.3 ± 14.3 μm in the presence of DMSO, MLi-2, or PF-06447475, respectively) while leaving the V_{max} unchanged (1.97 ± 0.03 min), suggesting a near-perfect ATP-competitive inhibitory profile that is comparable between the two molecules (Fig. 5*C*). These results show that MLi-2 and PF-06447475 inhibit LRRK2 in a similar, ATP-competitive manner and with similar potencies and have nanomolar inhibition profiles at physiological ATP concentrations.

Reference: J Neurosci. 2016 Jul 13;36(28):7415-27. https://pubmed.ncbi.nlm.nih.gov/27413152/

In vivo activity

To better understand the therapeutic potential of LRRK2 kinase inhibition in PD, this study evaluated the tolerability and efficacy of a LRRK2 kinase inhibitor, PF-06447475, in preventing α-synuclein-induced neurodegeneration in rats. Rats were treated with PF-06447475 or a control compound for 4 weeks post-viral transduction. This study found that rats expressing G2019S-LRRK2 have exacerbated dopaminergic neurodegeneration and inflammation in response to the overexpression of α-synuclein. Both neurodegeneration and neuroinflammation associated with G2019S-LRRK2 expression were mitigated by LRRK2 kinase inhibition. Furthermore, PF-06447475 provided neuroprotection in wild-type rats. This study could not detect adverse pathological indications in the lung, kidney, or liver of rats treated with PF-06447475.

Reference: J Biol Chem. 2015 Aug 7;290(32):19433-44. https://pubmed.ncbi.nlm.nih.gov/26078453/