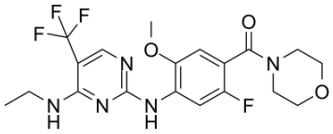
GNE-7915

Cat. No.:	HY-18163
CAS No.:	1351761-44-8
Molecular Formula:	$C_{19}H_{21}F_4N_5O_3$
Molecular Weight:	443.4
Target:	LRRK2
Pathway:	Autophagy

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 : 14.33 mg/mL (**32.32 mM;** Need ultrasonic and warming)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2553 mL	11.2765 mL	22.5530 mL
	5 mM	0.4511 mL	2.2553 mL	4.5106 mL
	10 mM	0.2255 mL	1.1277 mL	2.2553 mL

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

In Vivo

1. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: 2.5 mg/mL (5.64 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.5 mg/mL (5.64 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GNE-7915 is a potent, selective and brain-penetrant inhibitor of **LRRK2** with an **IC_{50}** of 9 nM.

IC_{50} & Target

IC50: 9 nM[1] (LRRK2)

In Vitro

Maintaining the methoxy/fluoro arrangement at C-2′/C-5′ and varying aminoalkyl R1 substitution resultes in single-digit nanomolar LRRK2 cellular activities for GNE-7915 and compound 19. Expanded Invitrogen kinase profiling (187 kinases) at 0.1 μM for both GNE-7915 (100-fold over LRRK2 Ki) and 19 (250-fold over LRRK2 Ki) resultes in only TTK showing greater than 50% inhibition. Selectivity profiling using the DiscoverX KinomeScan55 competitive binding

assay panel, which includes 392 unique kinases, is also performed for GNE-7915 at 0.1 μM. Binding of >50% probe displacement is detected for 10 kinases and of >65% for only LRRK2, TTK, and ALK, further supporting the excellent LRRK2 selectivity for GNE-7915. Cerep receptor profiling, including expanded brain panels, suggestes that GNE-7915 and 19 only inhibite 5-HT_{2B} with >70% inhibition at 10 μM. GNE-7915 and 19 are confirmed to be moderately potent 5-HT_{2B} antagonists in vitro functional assays[2].

CUSTOMER VALIDATION

- **Hum Mol Genet**. 2017 Jul 15;26(14):2747-2767.
- **bioRxiv**. 2020 Apr.
- **Programa Oficial de Doctorado en Biomedicina**. Universidad de Granada. 5-Jul-2017.
- **Harvard Medical School LINCS LIBRARY**

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REFERENCES

[1]. Kavanagh ME, et al. The development of CNS-active LRRK2 inhibitors using property-directed optimisation. Bioorg Med Chem Lett.?2013 Jul 1;23(13):3690-6.

[2]. Estrada AA, et al. Discovery of highly potent, selective, and brain-penetrable leucine-rich repeat kinase 2 (LRRK2) small molecule inhibitors. J Med Chem. 2012 Nov 26;55(22):9416-33.

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