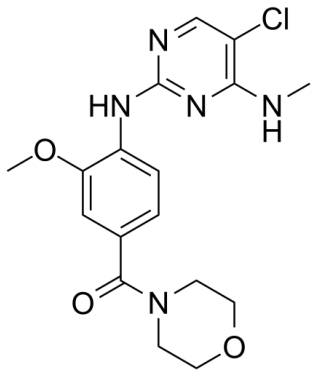
Data Sheet

Product Name:	HG-10-102-01
Cat. No.:	CS-1803
CAS No.:	1351758-81-0
Molecular Formula:	C17H20ClN5O3
Molecular Weight:	377.83
Target:	LRRK2
Pathway:	Autophagy
Solubility:	DMSO : ≥ 50 mg/mL (132.33 mM)



BIOLOGICAL ACTIVITY:

HG-10-102-01 is a potent and selective inhibitor of wild-type LRRK2(IC50=23.3 nM) and the G2019S mutant(IC50=3.2 nM) IC50 Value: 23.3 nM (WT LRRK2); 3.2 nM (LRRK2 G2019S) [1] Target: LRRK2 HG-10-102-01 maintains the ability to potently inhibit the biochemical activity of wild-type and G2019S mutant LRRK2. HG-10-102-01 exhibited biochemical IC50s of 20.3 and 3.2 nM against wild-type LRRK2 and LRRK2[G2019S], respectively. At a concentration of 10 μM, HG-10-102-01 only inhibited the kinase activities of MLK1 and MNK2 to greater than 80% of the DMSO control. Dose-response analysis revealed inhibition of MLK1 with an IC50 2.1 μM and MNK2 with an IC50 0.6 μM. KinomeScan analysis against a near comprehensive panel of 451 kinases at a concentration of 1 μM resulted in no interactions detected with kinases other than G2019S LRRK2 with the exception of one mutant form of c-Kit (L576P) demonstrating the outstanding selectivity of this inhibitor. HG-10-102-01 significantly inhibited phosphorylation of wildtype LRRK2 and LRRK2[G2019S] mutant at Ser910 and Ser935 at 0.3-1.0 μM in cell culture, which is approximately the same potency as LRRK2-IN-1 (1). HG-10-102-01 is relatively insensitive to the A2016T mutation which suggests that this mutant will not be useful to validate whether the pharmacological effects of the compound are LRRK2-dependent. HG-10-102-01 can inhibit phosphorylation of Ser910 and Ser935 of LRRK2 in brain and peripheral tissues following intraperitoneal doses of 50 mg/kg. Further optimization of this chemo-type especially in regards to in vivo half-life will be reported in due course [1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] HEK293 and Swiss 3T3 cells were cultured in DMEM supplemented with 10% FBS, 2 mM glutamine and 1× penicillin/streptomycin solution. For inhibitor experiments, HG-10-102-01 and/or LRRK2-IN-1 was dissolved in DMSO and utilised at the indicated concentrations. The concentration of DMSO in the culture media did not exceed 1%. Following treatment, cells were washed once with PBS and lysed with buffer containing 50 mM Tris/HCl, pH 7.5, 1 mM EGTA, 1 mM EDTA, 1 mM sodium orthovanadate, 10 mM sodium β-glycerophosphate, 50 mM NaF, 5 mM sodium pyrophosphate, 0.27 M sucrose, 1 mM benzamidine, 2 mM phenylmethanesulphonylfluoride (PMSF) and 1% Triton X-100. When not used immediately, all lysate supernatants were snap-frozen in liquid nitrogen and stored at -80°C until use. Protein concentrations were determined following centrifugation of the lysate at 16,000 x g at 4°C for 20 minutes using the Bradford method with BSA as the standard. Transient transfection of HEK293 cells was performed using the polyethylenimine (PEI). Animal administration [1] HG-10-102-01 was dissolved in 5% 1-methyl-2-pyrrolidinone (NMP) /95% PEG 300 solution and administered by intraperitoneal injection into wild type male C57BL/6 mice at doses of 0, 3, 10, 30, 50 and 100 mg/kg, and 100 mg/kg of LRRK2-IN-1 as a comparative control. Control mice were treated with an equal volume of NMP/PEG solution. One hour after administration, mice were sacrificed by cervical dislocation and, kidney, spleen and brain tissues were rapidly dissected and snap-frozen in liquid nitrogen.

References:

[1]. Choi HG, et al. Brain Penetrant LRRK2 Inhibitor. ACS Med Chem Lett. 2012 Aug 9;3(8):658-662.

CAIndexNames:

Methanone, [4-[[5-chloro-4-(methylamino)-2-pyrimidinyl]amino]-3-methoxyphenyl]-4-morpholinyl-

SMILES:

COC1=CC(C(N2CCOCC2)=O)=CC=C1NC3=NC(NC)=C(Cl)C=N3

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