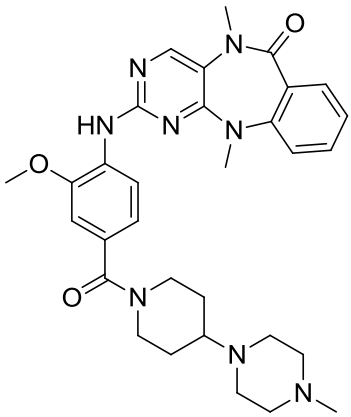
LRRK2-IN-1



Chemical Formula: $C_{31}H_{38}N_8O_3$
Molecular Weight: 570.69

Category	Parameter	Description
Compound	Name	LRRK2-IN-1
	Citation	*Nat. Chem. Biol.* **2011**, *7*, 203-205.
	Chemical descriptors	O=C1C2=C(C=CC=C2)N(C)C3=NC(NC4=C(OC)C=C(C(N5CCC(N6CCN(C)CC6)CC5)=O)C=C4)=NC=C3N1C
	Chemical name	2-((2-methoxy-4-(4-(4-methylpiperazin-1-yl)piperidine-1-carbonyl)phenyl)amino)-5,11-dimethyl-5H-benzo[e]pyrimido[5,4-b][1,4]diazepin-6(11H)-one
	Availability	MERCK4Biosciences http://www.merck-chemicals.com/life-science-research/lrrk2-in-1/EMD_BIO-438193/p_uuid?WT_oss=438193&WT_oss_r=1
In vitro profiling	Target (potency)	**LRRK2** (20 nM K_d in Ambit binding assay, 3 nM IC_{50} in Invitrogen biochemical assay, 13 nM IC_{50} in Dundee biochemical assay) **LRRK2(G2019S)** (11 nM K_d in Ambit binding assay, 4 nM IC_{50} in Invitrogen biochemical assay, 6 nM IC_{50} in Dundee biochemical assay)
	Additional Target (potency)	**MAPK7** (28 nM K_d in Ambit binding assay) **DCLK2** (16 nM K_d in Ambit binding assay, 45 nM IC_{50} in Invitrogen biochemical assay, 210 nM IC_{50} in Dundee biochemical assay)
	Selectivity	
	Potential reactivity	None to our knowledge
	SAR	
	Mechanism of inhibition	ATP-competitive
	Structure of target-probe complex	

Cellular profiling	Validation of cellular target	LRRK2-IN-1 dose-dependently inhibited LRRK2, LRRK2(G2019S) at 1-3 μM in HEK293 cells. LRRK2-IN-1 dose-dependently inhibited LRRK2 at 1-3 μM in human lymphoblastoid cells derived from a control individual. LRRK2-IN-1 dose-dependently inhibited LRRK2(G2019S) at 1-3 μM in a Parkinson's disease patient homozygous. LRRK2-IN-1 dose-dependently inhibited LRRK2 at 1-3 μM in human derived neuroblastoma SHSY5Y cells and mouse Swiss 3T3 cells. LRRK2-IN-1 dose-dependently inhibited MAPK7 autophosphorylation induced by EGF in HeLa cells with IC50 of 160 nM. Compound phenotypes were compared to literature. The cellular effects were correlated with *in vitro* biochemical activities.
	Validation of cellular specificity	
Pharmacodynamics		Poor BBB property.
Pharmacokinetics		$T_{1/2}$ = 4.47 hours, CL = 5.6 (mL/min/Kg), Vss = 1.7 (L/Kg), F = 49.3%
Synthetic scheme