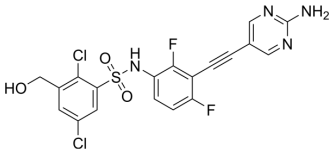
GCN2-IN-6

Cat. No.:	HY-130240
CAS No.:	2183470-09-7
Molecular Formula:	$C_{19}H_{12}Cl_2F_2N_4O_3S$
Molecular Weight:	485.29
Target:	Eukaryotic Initiation Factor (eIF)
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 250 mg/mL (515.16 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0606 mL	10.3031 mL	20.6062 mL
	5 mM	0.4121 mL	2.0606 mL	4.1212 mL
	10 mM	0.2061 mL	1.0303 mL	2.0606 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (4.29 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.29 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GCN2-IN-6 (Compound 6d) is a potent, and orally available GCN2 inhibitor confirmed by in-house enzymatic (IC_{50} of 1.8 nM) and cellular assays (IC_{50} of 9.3 nM). GCN2-IN-6 is also a eIF2α kinase PERK inhibitor with an IC_{50} of 0.26 nM (in enzymatic assay) and 230 nM (in cells)[1]. GCN2-IN-6 is a click chemistry reagent, it contains an Alkyne group and can undergo copper-catalyzed azide-alkyne cycloaddition (CuAAc) with molecules containing Azide groups.

IC_{50} & Target

GCN2

In Vitro

To examine the impact of GCN2 inhibition on cancer cell proliferation, acute lymphoblastic leukemia (ALL) CCRFCEM cells are treated with GCN2-IN-6 (Compound 6d) in the presence of asparaginedepleting agent asparaginase. Treatment with GCN2-IN-6 greatly sensitizes CCRF-CEM cells to asparaginase. The moderate antiproliferative effects achieved by combining

asparaginase and GCN2-IN-6 treatment are observed in GCN2-wildtype (WT) mouse embryonic fibroblast (MEF) cells but not in GCN2-knockout (KO) MEF. GCN2-IN-6 demonstrates suppression on p-GCN2, p-eIF2α, and ATF4 activated by asparaginase [1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

GCN2-IN-6 (Compound 6d; 0.3-3 mg/kg; oral administration; for 8 hours; mice) treatment at 3 mg/kg suppresses both self-phosphorylation of GCN2 and the downstream effector ATF4 to the basal level following pretreatment with asparaginase[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Mice bearing CCRF-CEM cells xenografts[1]
Dosage:	0.3 mg/kg, 1 mg/kg, and 3 mg/kg
Administration:	Oral administration; for 8 hours
Result:	Suppressed both self-phosphorylation of GCN2 and the downstream effector ATF4 to the basal level following pretreatment with asparaginase.

CUSTOMER VALIDATION

- Mol Cell. 2022 Mar 3;82(5):920-932.e7.
- Blood Cancer Discov. December 13, 2021.

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REFERENCES

[1]. Fujimoto J, et al. Identification of Novel, Potent, and Orally Available GCN2 Inhibitors with Type I Half Binding Mode. ACS Med Chem Lett. 2019 Sep 19;10(10):1498-1503.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA