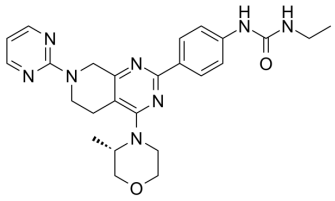
mTOR inhibitor-3

Cat. No.:	HY-18353
CAS No.:	1207358-59-5
Molecular Formula:	$C_{25}H_{30}N_8O_2$
Molecular Weight:	474.56
Target:	mTOR
Pathway:	PI3K/Akt/mTOR

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 : 50 mg/mL (105.36 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1072 mL	10.5361 mL	21.0722 mL
	5 mM	0.4214 mL	2.1072 mL	4.2144 mL
	10 mM	0.2107 mL	1.0536 mL	2.1072 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 (5.27 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

mTOR inhibitor-3 is a remarkably selective mTOR inhibitor with a K_i of 1.5 nM. mTOR inhibitor-3 suppresses mTORC1 and mTORC2 in cellular and in vivo pharmacokinetic (PK)/pharmacodynamic (PD) experiments.

IC_{50} & Target

mTOR	mTORC1	mTORC2
1.5 nM (Ki)		

In Vitro

mTOR inhibitor-3 (Compound 12i) inhibits mTOR with a K_i of 1.5 nM, 500-fold selectivity over closely related PI3 kinases. mTOR inhibitor-3 inhibits NCI-PC3 and MCF7neo/Her2 cells proliferation with IC_{50}s of 150 nM and 57 nM, respectively[2].

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

In Vivo	mTOR inhibitor-3 (Compound 8h) has high free plasma clearance in both mice (1818 mL/min/kg) and rats (1538 mL/min/kg in rat) [1]. mTOR inhibitor-3 (Compounds 12i) is selected for this study due to its potency, selectivity, and favorable mouse PK profile. Plasma levels of mTOR inhibitor-3 6 h following oral administration in PC3 tumor-bearing mice along with the fold decreases of phosphorylated mTORC1 and -2 substrates relative to time-matched vehicle controls. mTOR inhibitor-3 has moderate terminal elimination half-life ($t_{1/2}$=1.7 h for mouse(1 mg/kg, iv)). mTOR inhibitor-3 achieves tumor stasis at the highest 200 mg/kg/day dose examined, which appears to also be approaching the limit of tolerability for this molecule[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [2]	Mice[2] Human prostate cancer NCI-PC3 cells are implanted subcutaneously into the right hind flanks of female NCR nude mice (5×10^6 cells in 100 µL of Hank's balanced salt solution). Tumors are monitored until they reach a mean tumor volume of approximately 500 mm^3. Then similarly sized tumors are randomly assigned to groups (n=4). Compounds are formulated as suspensions in 0.5% methylcellulose/0.2% Tween 80 (MCT) and dosed orally at 25, 50, and 100 mg/kg (100 µL dose/25 g animal). Tumor and plasma samples are harvested at 1, 6, and 10 h postdose. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Mol Pain. Jan-Dec 2021;17:17448069211041847.
- Biomed Res Int. 2021 Oct 19;2021:7329072.

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REFERENCES

[1]. Pei Z, et al. Discovery and Biological Profiling of Potent and Selective mTOR Inhibitor GDC-0349. ACS Med Chem Lett. 2012 Nov 29;4(1):103-7.

[2]. Koehler MF, et al. Potent, selective, and orally bioavailable inhibitors of the mammalian target of rapamycin kinase domain exhibiting single agent antiproliferative activity. J Med Chem. 2012 Dec 27;55(24):10958-71.

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