RapaLink-1

Cat. No.: HY-111373

CAS No.: 1887095-82-0

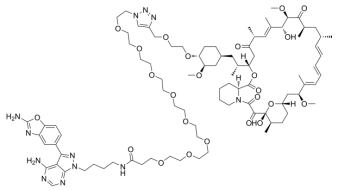
Molecular Formula: $C_{91}H_{138}N_{12}O_{24}$

Molecular Weight: 1784.14

Target: mTOR; Autophagy

Pathway: PI3K/Akt/mTOR; Autophagy

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 178 mg/mL (99.77 mM; Need ultrasonic and warming)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	0.5605 mL	2.8025 mL	5.6049 mL
5 mM	0.1121 mL	0.5605 mL	1.1210 mL
10 mM	0.0560 mL	0.2802 mL	0.5605 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 5 mg/mL (2.80 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

RapaLink-1, the third-generation bivalent mTOR inhibitor, combines Rapamycin (HY-10219) with MLN0128 (HY-13328, a second-generation mTOR kinase inhibitor) by an inert chemical linker. RapaLink-1 shows better efficacy than Rapamycin or mTOR kinase inhibitors (TORKi), potently blocking cancer-derived, activating mutants of mTOR. RapaLink-1 can cross the blood-brain barrier. RapaLink-1 binding to FKBP12 results in targeted and durable inhibition of mTORC1. RapaLink-1 plays an antithrombotic role in antiphospholipid syndrome by improving autophagy. Anticancer activity[1][2].

IC_{50} & Target

mTOR

In Vitro

RapaLink-1 (0-200 nM; 3 days) shows U87MG cells growth inhibition[1].
RapaLink-1 (0-12.5 nM; 48 hours) arrests U87MG cells at G0/G1[1].
RapaLink-1 selectively inhibits p-RPS6$^{S235/236}$ and p-4EBP1$^{T37/46}$ at doses as low as 1.56 nM[1].
Rapalink-1 (100 nM; 24 to 96 hours) suppressed renal cell carcinoma (RCC) cell proliferation by inducing apoptosis and cell cycle arrest[2].

?RapaLink-1 exploits the unique juxtaposition of two drug-binding pockets to create a bivalent interaction. RapaLink-1 overcomes resistance to existing first- and second-generation inhibitors[3].

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

Cell Proliferation Assay[1]

Cell Line:	U87MG cells
Concentration:	0-200 nM
Incubation Time:	3 days
Result:	Showed growth inhibition.

Cell Cycle Analysis[1]

Cell Line:	U87MG cells
Concentration:	0-12.5 nM
Incubation Time:	48 hours
Result:	Arrested cells at G0/G1.

Western Blot Analysis[1]

Cell Line:	U87MG cells
Concentration:	0.39-12.5 nM
Incubation Time:	3 hours
Result:	Selectively inhibited p-RPS6$^{S235/236}$ and p-4EBP1$^{T37/46}$ at doses as low as 1.56 nM. The mTORC2 targets p-AKT^{S473}, p-SGK1^{S78}, and p-NDRG1^{T346}, and the p-AKT^{S473} target p-GSK3β^{S9} was inhibited only at high doses.

In Vivo

RapaLink-1 (i.p.; every 5 days for 25 days, then once a week for 11 week) shows potent anti-tumor efficacy[1].

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

Animal Model:	BALB/ Cnu/nu mice bearing U87MG intracranial xenografts[1]
Dosage:	1.5 mg/kg
Administration:	I.p.; every 5 days for 25 days, then once a week for 11 week
Result:	Led to initial regression and subsequent stabilization of tumor size.

CUSTOMER VALIDATION

- Nutrients. 2022 Jul 22;14(15):3022.
- iScience. 28 October 2022, 105458.
- Int J Mol Sci. 2023, 24(3), 2055.
- SLAS Technol. 2023 Feb 17;S2472-6303(23)00011-0.
- bioRxiv. 2023 Aug 4.

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REFERENCES

[1]. Fan Q, et al. A Kinase Inhibitor Targeted to mTORC1 Drives Regression in Glioblastoma. Cancer Cell. 2017 Mar 13;31(3):424-435.

[2]. Kuroshima K, et al. Potential new therapy of Rapalink-1, a new generation mammalian target of rapamycin inhibitor, against SU 11248-resistant renal cell carcinoma. Cancer Sci. 2020 May;111(5):1607-1618.

[3]. Mu F, et al. RapaLink-1 plays an antithrombotic role in antiphospholipid syndrome by improving autophagy both in vivo and vitro. Biochem Biophys Res Commun. 2020 Apr 30;525(2):384-391.

[4]. Rodrik-Outmezguine VS, et al. Overcoming mTOR resistance mutations with a new-generation mTOR inhibitor. Nature. 2016 Jun 9;534(7606):272-6.

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