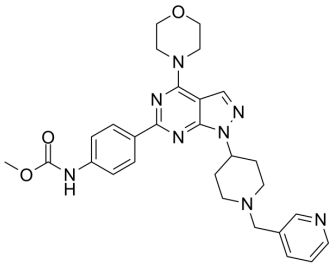
WYE-687

Cat. No.:	HY-15271
CAS No.:	1062161-90-3
Molecular Formula:	$C_{28}H_{32}N_8O_3$
Molecular Weight:	528.61
Target:	mTOR; PI3K
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (47.29 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8918 mL	9.4588 mL	18.9175 mL
	5 mM	0.3784 mL	1.8918 mL	3.7835 mL
	10 mM	0.1892 mL	0.9459 mL	1.8918 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: ≥ 2.5 mg/mL (4.73 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.73 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

WYE-687 is an ATP-competitive mTOR inhibitor with an IC_{50} of 7 nM. WYE-687 concurrently inhibits activation of mTORC1 and mTORC2. WYE-687 also inhibits PI3Kα and PI3Kγ with IC_{50}s of 81 nM and 3.11 μM, respectively.

IC_{50} & Target

mTOR 7 nM (IC_{50})	mTORC1	mTORC2	PI3K alpha 81 nM (IC_{50})
PI3K gamma 3.11 μM (IC_{50})	CK1 gamma1 17.8 μM (IC_{50})	p38 alpha 28.9 μM (IC_{50})	

In Vitro	In the DELFIA measuring His6-S6K1 T389 phosphorylation, WYE-687 inhibits recombinant mTOR enzyme with an IC_{50} of 7 nM [1]. HL-60 AML cells are treated with applied concentrations of WYE-687 (33-1000 nM), MTT cell survival assay results demonstrate that WYE-687 potently inhibits HL-60 cell survival in a dose-dependent manner. A time dependent response by WYE-687 is also noticed. The number of dead ("trypan blue" positive) HL-60 cells is significantly increased following applied WYE-687 (100-1000 nM) treatment. At the meantime, HL-60 cell proliferation, tested by [H^3] Thymidine integration assay, is also inhibited by the WYE-687. Results show that WYE-687 is also antisurvival ("cytotoxic") to the other AML cell lines: U937, THP-1 and AML-193[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	U937 cells are inoculated into the flanks of SCID/beige mice. When xenografted tumors reach a volume around 100 mm^3, mice are orally administrated with either vehicle control (5% ethanol, 2% Tween 80, and 5% polyethylene glycol-400) or WYE-687 (5 or 25 mg/kg) daily for a total of 7 days. The WYE-687 regimen utilized in this study is based on preexperimental results and related studies. WYE-687 administration (5 or 25 mg/kg, daily) significantly inhibits U937 xenograft tumor growth in SCID mice, and the in vivo activity by WYE-687 is dose-dependent. At day 15, the 5 mg/kg WYE-687-treated tumors and 25 mg/kg WYE-687-treated tumors are 50% and 75% smaller than the vehicle control tumors, respectively. Tumor weights of WYE-687-treated mice are also significantly lower than that of vehicle group. Oral administration of WYE-687 potently inhibits U937 leukemic xenograft tumor growth in SCID mice, without causing significant toxicities[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The routine inhibitor assays are performed in 96-well plates for 2 h at room temperature in 25 μL containing 6 nM Flag-TOR(3.5) (estimated 5-10% purity), 1 μM His6-S6K and 100 μM ATP. The assays are performed and detected by DELFIA employing the Euphospho-p70S6K T389 antibody. Some assays employ a commercially purchased batch of mTOR. For inhibitor versus ATP matrix competition, mTOR kinase reactions are carried out with varying concentrations of ATP (0, 25, 50 100, 200, 400 and 800 μM) in combination with varying concentrations of inhibitor. The assays contain 12 nM Flag-TOR(3.5), 1 μM His-S6K and are incubated for 30 min. The assay results are similarly detected by DELFIA and processed for generation of double-reciprocal plots[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Acute myeloid leukemia (AML) cells/progenitor cells are seeded at a density of 1×10^5 cells/well in 0.5 mL DMEM containing 10% FBS onto the 48-well tissue culture plates, cells are treated with indicated concentrations of WYE-687 (33-1000 nM) with the presence of 1 mCi/mL of tritiated thymidine. To determine [H^3] thymidine incorporation, cells are washed, the DNA is precipitated with cold 10% trichloroacetic acid (TCA), solubilized with 1.0 M sodium hydroxide, and aliquots are counted by liquid-scintillation spectrometry. The value of treatment group is normalized to that of untreated control group[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] U937 cells (2×10^6 cells/mice, suspended in 100 mL of culture medium) are injected into the right flanks of 6-week-old male CB17 severe combined immunodeficient (SCID)/beige mice, and cells are allowed to grow to palpable tumors. When tumors reach a volume around 100 mm^3, animals are randomly assigned to three groups: WYE-687 (5 mg/kg body weight), WYE- 687 (25 mg/kg body weight) or the vehicle control (5% ethanol, 2% Tween 80, and 5% polyethylene glycol-400). WYE-687 and vehicle control are freshly prepared, and given by oral gavage daily for 7 consecutive days. Tumor sizes are measured. At the end of experiment, the animals are killed, and the tumors are removed and weighted. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Rep. 2022 Apr 12;12(1):6090.

- Molecules. 2020 Apr 23;25(8):1980.
- Biosci Rep. 2019 Dec 20;39(12):BSR20191041.

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REFERENCES

[1]. Yu K, et al. Biochemical, cellular, and in vivo activity of novel ATP-competitive and selective inhibitors of the mammalian target of rapamycin. Cancer Res. 2009 Aug 1;69(15):6232-40.

[2]. Cheng F, et al. Preclinical evaluation of WYE-687, a mTOR kinase inhibitor, as a potential anti-acute myeloid leukemia agent. Biochem Biophys Res Commun. 2016 Feb 5;470(2):324-330.

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