Product Data Sheet

Product Name: WYE-687
Cat. No.: GC13321

Chemical Properties

Cas. No.	1062161-90-3		
Chemical Name	methyl N-[4-[4-morpholin-4-yl-1-[1-(pyridin-3-ylmethyl)piperidin-4-yl]pyrazolo[3,4-d]pyrimidin-6-yl]phenyl]carbamate		
SMILES	COC(=O)NC1=CC=C(C=C1)C2=NC3=C(C=NN3C4CCN(CC4)CC5=CN=CC=C5)C(=N2)N6CCOCC6		
Formula	$C_{28}H_{32}N_8O_3$	M.Wt	528.61
Solubility	Limited solubility, soluble in DMSO or Water	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	WYE-687		

Protocol

Kinase experiment:	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].
Cell experiment:	Acute myeloid leukemia (AML) cells/progenitor cells are seeded at a density of 1 ×105 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 [H3] 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].

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Animal experiment:

Mice[2]U937 cells (2×106 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 mm3, 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.

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.

Background

WYE-687 is an ATP-competitive inhibitor of mTOR with IC50 value of 7nM [1].

WYE-687 is a small-molecule pyrazolopyrimidine inhibitor of mTOR1 and mTOR2. In the immune-complex kinase assay using His6-AKT and His6-S6K as the specific substrates of mTOR1 and mTOR2, WYE-687 prevents mTOR from phosphorylating the substrates dose-dependently. Besides that, WYE-687 is found to

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highly selective against PI3Kα (>100-fold) and PI3Kγ (>500-fold) as well as 24 other protein kinases. It is found that WYE-687 can suppress cell growth via causing a strong G1 arrest in cell cycle in tumor cell lines including MDA361 and HCT116. WYE-687 also affects the angiogenic factor of cancer cells. It reduces the expression of HIF-1α in U87MG, MDA361 and LNCap cells [1].

References:
[1] Yu K, Toral-Barza L, Shi C, et al. Biochemical, cellular, and in vivo activity of novel ATP-competitive and selective inhibitors of the mammalian target of rapamycin. Cancer research, 2009, 69(15): 6232-6240.

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