Torkinib

Cat. No.: HY-10474

CAS No.: 1092351-67-1

Molecular Formula: $C_{16}H_{16}N_6O$

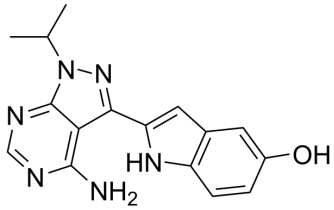
Molecular Weight: 308.34

Target: mTOR; Autophagy; Mitophagy; Apoptosis

Pathway: PI3K/Akt/mTOR; Autophagy; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (162.16 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2432 mL	16.2159 mL	32.4317 mL
	5 mM	0.6486 mL	3.2432 mL	6.4863 mL
	10 mM	0.3243 mL	1.6216 mL	3.2432 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 (8.11 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (8.11 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Torkinib (PP 242) is a selective and ATP-competitive mTOR inhibitor with an IC_{50} of 8 nM[1]. PP242 inhibits both mTORC1 and mTORC2 with IC_{50}s of 30 nM and 58 nM, respectively[2].

IC_{50} & Target

mTOR 8 nM (IC_{50})	mTORC1 30 nM (IC_{50})	mTORC2 58 nM (IC_{50})	p110δ 100 nM (IC_{50})
PDGFR 410 nM (IC_{50})	DNA-PK 410 nM (IC_{50})	p110γ 1.3 μM (IC_{50})	p110α 2 μM (IC_{50})

	p110β 2.2 μM (IC_{50})	Hck 1.2 μM (IC_{50})	Scr 1.4 μM (IC_{50})	VEGFR2 1.5 μM (IC_{50})
	Abl 3.6 μM (IC_{50})	EphB4 3.4 μM (IC_{50})	EGFR 4.4 μM (IC_{50})	Scr(T338I) 5.1 μM (IC_{50})
	Autophagy	Mitophagy		

In Vitro

Torkinib (PP 242) potently inhibits mTOR (IC_{50}=8 nM) but is much less active against other PI3K family members. Testing of Torkinib (PP 242) against 219 protein kinases reveals remarkable selectivity relative to the protein kinome: at a concentration 100-fold above its IC_{50} for mTOR, Torkinib (PP 242) inhibits only one kinase by more than 90% (Ret) and only three by more than 75% (PKCα, PKCβII and $JAK2^{V617F}$)[1]. Torkinib (PP 242) has a dose-dependent effect on proliferation and at higher doses is much more effective than Rapamycin at blocking cell proliferation. The ability of Torkinib (PP 242) to block cell proliferation more efficiently than Rapamycin could be a result of its ability to inhibit mTORC1 and mTORC2, because Rapamycin can only inhibit mTORC1. In $SIN1^{-/-}$ mouse embryonic fibroblasts (MEFs), Rapamycin is also less effective at blocking cell proliferation than Torkinib. That Torkinib (PP 242) and Rapamycin exhibit very different anti-proliferative effects in $SIN1^{-/-}$ MEFs suggests that the two compounds differentially affect mTORC1[2].

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

In Vivo

In fat and liver, Torkinib (PP 242) is able to completely inhibit the phosphorylation of Akt at S473 and T308, consistent with its effect on these phosphorylation sites observed in cell culture. Surprisingly, Torkinib (PP 242) is only partially able to inhibit the phosphorylation of Akt in skeletal muscle and is more effective at inhibiting the phosphorylation of T308 than S473, despite it's ability to fully inhibit the phosphorylation of 4EBP1 and S6. These results will be confirmed by in vivo dose-response experiments, but, consistent with the partial effect of Torkinib (PP 242) on pAkt in skeletal muscle, a muscle-specific knockout of the integral mTORC2 component rictor resulted in only a partial loss of Akt phosphorylation at S473. These results suggest that a kinase other than mTOR, such as DNA-PK, may contribute to phosphorylation of Akt in muscle[2].

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PROTOCOL

Cell Assay [2]

Wild-type and $SIN1^{-/-}$ MEFs are plated in 96-well plates at approximately 30% confluence and left overnight to adhere. The following day cells are treated with Torkinib (PP 242) (1 nM, 10 nM, 100 nM, 1 μM, and 10 μM), Rapamycin, or vehicle (0.1% DMSO). After 72 h of treatment, 10 μL of 440 μM resazurin sodium salt is added to each well, and after 18 h, the florescence intensity in each well is measured using a top-reading florescent plate reader with excitation at 530 nm and emission at 590 nm[2].

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Animal Administration [2]

Mice[2]

Six-wk-old male C57BL/6 mice are fasted overnight prior to drug treatment. Torkinib (PP 242) (0.4 mg), Rapamycin (0.1 mg), or vehicle alone is injected IP. After 30 min for the Rapamycin-treated mouse or 10 min for the Torkinib (PP 242) and vehicle-treated mice, 250 mU of insulin in 100 μL of saline is injected IP. 15 min after the insulin injection, the mice are killed by CO_2 asphyxiation followed by cervical dislocation. Tissues are harvested and frozen on liquid nitrogen in 200 μL of cap lysis buffer. The frozen tissue is thawed on ice, manually disrupted with a mortar and pestle, and then further processed with a micro tissue-homogenizer. Protein concentration of the cleared lysate is measured by Bradford assay and 5-10 μg of protein is analyzed by Western blot[2].

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

CUSTOMER VALIDATION

- Acta Pharm Sin B. 2020 Jun;10(6):1004-1019.
- Theranostics. 2022 Jan 1;12(2):675-688.
- J Exp Clin Cancer Res. 2021 Jan 9;40(1):25.
- Cancer Res. 2013 Apr 15;73(8):2574-86.
- Curr Biol. 2023 Apr 14;S0960-9822(23)00391-3.

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REFERENCES

[1]. Apsel B, et al. Targeted polypharmacology: discovery of dual inhibitors of tyrosine and phosphoinositide kinases. Nat Chem Biol. 2008 Nov;4(11):691-9.

[2]. Feldman ME, et al. Active-site inhibitors of mTOR target rapamycin-resistant outputs of mTORC1 and mTORC2. PLoS Biol. 2009 Feb 10;7(2):e38.

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