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Torin 2

Cat. No.: HY-13002

CAS No.: 1223001-51-1

Molecular Formula: $C_{24}H_{15}F_3N_4O$

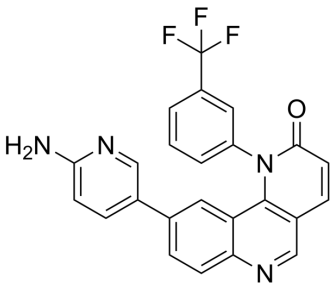
Molecular Weight: 432.4

Target: mTOR; DNA-PK; Autophagy; Apoptosis

Pathway: PI3K/Akt/mTOR; Cell Cycle/DNA Damage; 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 : 15.62 mg/mL (36.12 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3127 mL	11.5634 mL	23.1267 mL
	5 mM	0.4625 mL	2.3127 mL	4.6253 mL
	10 mM	0.2313 mL	1.1563 mL	2.3127 mL

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

In Vivo

1. Add each solvent one by one: 10% 1-Methyl-2-pyrrolidinone >> 90% PEG300
   Solubility: ≥ 2 mg/mL (4.63 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.56 mg/mL (3.61 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Torin 2 is an mTOR inhibitor with EC_{50} of 0.25 nM for inhibiting cellular mTOR activity, and exhibits 800-fold selectivity over PI3K (EC_{50}: 200 nM). Torin 2 also inhibits DNA-PK with an IC_{50} of 0.5 nM in the cell free assay. Torin 2 can suppress both mTORC1 and mTORC2.

IC_{50} & Target

mTOR 2.81 nM (IC_{50})	mTOR 0.25 nM (EC50, Cell Assay)	mTORC1	mTORC2
DNA-PK 0.5 nM (IC_{50})	p110γ 5.67 nM (IC_{50})	PI3K-C2β 24.5 nM (IC_{50})	PI3K-C2α 28.1 nM (IC_{50})

	hVps34 8.58 nM (IC_{50})	PI3K 200 nM (EC50, Cell Assay)	PI4Kβ 18.3 nM (IC_{50})	Autophagy

In Vitro

Torin 2 is subject to further profiling against a panel of lipid kinases with IC_{50}s of 2.81 nM, 0.5 nM, 5.67 nM, 8.58 nM, 18.3 nM, 24.5 nM and 28.1 nM for mTOR, DNA-pK, p110γ, hVPS34, PI4Kβ, PI3K-C2β and PI3K-C2α, respectively. Torin 2 (Torin2) possesses a 250 pM EC_{50} for inhibiting mTOR in cells while maintaining 800-fold cellular selectivity relative to inhibition of PI3K and most other protein kinases[1]. Torin 2 (Torin2) exhibits potent biochemical and cellular activity against PIKK family kinases including ATM (EC_{50} 28 nM), ATR (EC_{50} 35 nM) and DNA-PK (EC_{50} 118 nM). Torin 2 potently inhibits T308 of Akt, a direct substrate of PDK1 and an indirect substrate of PI3Ks, with an EC_{50} of less than 10 nM[2]. Torin-2 can suppress both?mTORC1 and mTORC2[4].

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

In Vivo

Torin 2 exhibits good bioavailability and exposure and can maintain strong inhibition of mTOR activity in lung and liver to at least six hours after a single dose of 20 mg/kg. Torin 2 is easier to produce on scale and exhibits improved pharmacokinetic properties which should enable it use in vivo experiments[1]. Torin 2 strongly suppresses pS6K(T389) and p4EBP1(T37/46) and partly suppresses pAkt(T308). Treatment of mice with AZD6244 at 25 mg/kg results in a profound inhibition of pERK. Combined administration of Torin 2 (40 mg/kg) and AZD6244 (25 mg/kg) demonstrates strong inhibition of all pharmacodynamics markers[2]. Treatment with Torin 2 and Rapamycin induces IL-6 secretion by astrocytes and may contribute to the reduction of mechanical hypersensitivity after SCI. Torin1 and Torin 2 treatment increases IL-6 mRNA, suggesting that the PI3K-mTOR pathway is a negative regulator of IL-6 expression in astrocytes. Importantly, Torin 2 treatment does not show any cell toxicity, as no signs of cell death are observed by TUNEL assay or by detection of cleaved-caspase 3 by western blotting[3].

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

PROTOCOL

Cell Assay [2]

HCT116 cells are treated with 100 nM Torin 2 or AZD8055 for 1 hour before they are thoroughly washed out by 3×PBS and 1×DMEM medium. Then cells are incubated in DMEM medium for indicated time before they are lysed and collected using M-PER. Protein concentrations are measured and equal amount of proteins are loaded. Experiments are repeated three times and one set of results[2].

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

Animal Administration [1][3]

Mice[1]

Six-week old male C57BL/6 mice are fasted overnight prior to Torin 2 treatment. The mice are treated with vehicle (for 10 h) or Torin 2 (20 mg/kg for 6h) via oral gavage and then re-fed 1 h prior to sacrifice (CO_2 asphyxiation). Liver and lung are collected and frozen on dry ice. The frozen tissue is thawed on ice and lysed by sonication in tissue lysis buffer (50 mM HEPES, pH 7.4, 40 mM NaCl, 2 mM EDTA, 1.5 mM sodium orthovanadate, 50 mM sodium fluoride, 10 mM sodium pyrophosphate, 10 mM sodium β-glycerophosphate, 0.1% SDS, 1.0% sodium deoxycholate, and 1.0% Triton, supplemented with protease inhibitor cocktail tablets). The concentration of clear lysate is measured using the Bradford assay and samples are subsequently normalized by protein content and analyzed by SDS-PAGE and immunoblotting.

Rats[3]

Female rats (220 g) are group-housed 4 animals per cage, and kept on a 12-hour light/dark cycle with food and water ad libitum. Spinal cord injury is done with the Keck Center for Neurosciences impactor using a 10 g weight dropped from a height of 25 mm onto the dorsal surface of the exposed spinal cord. After recording BBB scores, withdrawal thresholds evoked by touch stimulus, and body weights for the first week post-injury, animals are divided into 5 treatment groups: naïve (N=4), sham (N=6), vehicle (N=6), Torin 2 (N=6), and Torin 2+Rapamycin (N=8). Torin 2 alone (4 mg/kg) or in combination with Rapamycin (1.5 mg/kg) is administered orally by gavage once a day starting at day 15 after injury and ending at day 29. In sham operated rats only the laminectomy is performed.

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

CUSTOMER VALIDATION

- Genes Dev. 2021 Oct 1;35(19-20):1327-1332.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.
- Cell Death Dis. 2022 Jul 15;13(7):615.
- Cell Chem Biol. 2020 Nov 19;27(11):1359-1370.e8.

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REFERENCES

[1]. Liu Q, et al. Discovery of 9-(6-aminopyridin-3-yl)-1-(3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (Torin2) as a potent, selective, and orally available mammalian target of rapamycin (mTOR) inhibitor for treatment of cancer. J Med Chem. 2011 Mar 10;54(5):1473-80.

[2]. Liu Q, et al. Characterization of Torin2, an ATP-competitive inhibitor of mTOR, ATM, and ATR. Cancer Res. 2013 Apr 15;73(8):2574-86.

[3]. Codeluppi S, et al. Interleukin-6 secretion by astrocytes is dynamically regulated by PI3K-mTOR-calcium signaling. PLoS One. 2014 Mar 25;9(3):e92649.

[4]. Wang X, et al. mTORC signaling in hematopoiesis. Int J Hematol. 2016 May;103(5):510-8.

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