Dactolisib

Cat. No.: HY-50673

CAS No.: 915019-65-7

Molecular Formula: $C_{30}H_{23}N_5O$

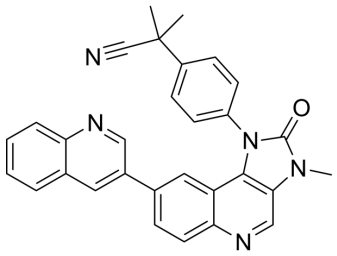
Molecular Weight: 469.54

Target: PI3K; mTOR; Autophagy

Pathway: PI3K/Akt/mTOR; Autophagy

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

5% TFA : 8.33 mg/mL (17.74 mM; ultrasonic and warming and heat to 60°C)
DMSO : 7.81 mg/mL (16.63 mM; ultrasonic and warming and heat to 60°C)
DMF : 2 mg/mL (4.26 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1297 mL	10.6487 mL	21.2974 mL
	5 mM	0.4259 mL	2.1297 mL	4.2595 mL
	10 mM	0.2130 mL	1.0649 mL	2.1297 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 12.5 mg/mL (26.62 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% 1-Methyl-2-pyrrolidinone >> 90% PEG300
   Solubility: ≥ 1.1 mg/mL (2.34 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 0.52 mg/mL (1.11 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.52 mg/mL (1.11 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Dactolisib (BEZ235) is an orally active and dual pan-class I PI3K and mTOR kinase inhibitor with IC_{50}s of 4 nM/5 nM/7 nM/75 nM, and 20.7 nM for p110α/p110γ/p110δ/p110β and mTOR, respectively. Dactolisib (BEZ235) inhibits both mTORC1 and mTORC2.

IC_{50} & Target	p110α 4 nM (IC_{50})	p110α-H1047R 4.6 nM (IC_{50})	p110α-E545K 5.7 nM (IC_{50})	p110γ 5 nM (IC_{50})
	p110δ 7 nM (IC_{50})	p110β 75 nM (IC_{50})	mTOR 20.7 nM (IC_{50})	mTORC1
	mTORC2	Autophagy		

In Vitro

Dactolisib (BEZ235) potently inhibits PI3K in an ATP Competitive Manner. Dactolisib (BEZ235) (250 nM) significantly reduced the phosphorylation levels of the mTOR activated kinase p70S6K. Dactolisib (BEZ235) also leads to a reduction of S235/S236P-RPS6 levels with an IC_{50} of 6.5 nM, suggesting that Dactolisib (BEZ235) can directly inhibit the mTOR kinase, as the kinase domain of mTOR is highly homologous to the one of class IA PI3K. The activity of Dactolisib (BEZ235) against mTOR is confirmed using a biochemical mTOR K-LISA assay (IC_{50}, 20.7 nM)[1].

The IC_{50}s of Dactolisib (BEZ235) for HCT116, DLD-1, and SW480 cell lines are 14.3±6.4, 9.0±1.5, and 12.0±1.6 nM, respectively [2].

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

In Vivo

Dactolisib (BEZ235) (45 mg/kg, p.o.) treatment induces colonic tumor regression in a GEM model for sporadic PIK3CA wild-type CRC[2]. Dactolisib (BEZ235) (45 mg/kg) is administered to MENX rats (n=2 each group) by oral gavage and animals are sacrificed 1 or 6 hours after treatment. Immunostains for P-AKT and P-S6 show considerable reduction of the two proteins, and particularly of P-S6, 6 hours after administration of Dactolisib (BEZ235) when compares with PEG-treated rats. At 6 hours after treatment, the pituitary adenomas of Dactolisib (BEZ235)-treated rats has a proteomic profile significantly different from the tumors of placebo-treated rats[3].

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

PROTOCOL

Cell Assay [2]

HCT116 (PIK3CA mutant; kinase domain at H1047R), DLD-1 (PIK3CA mutant; helical domain at E545K), and SW480 (PIK3CA wild-type) human CRC cell lines (ATCC) and isogenic DLD-1 PIK3CA mutant and wild-type cells are maintained in DMEM. Cells are plated at different initial densities (HCT116: 3,000 cells/well, DLD-1: 5,500 cells/well, SW480: 4,500 cells/well, DLD-1 PIK3CA mutant: 7,000 cells/well, and DLD-1 PIK3CA wild-type: 9,000 cells/well) to account for differential growth kinetics. After 16 hours, cells are incubated with increasing concentrations of BEZ235 (10, 100, 1000 nM), and drug-containing growth medium is changed every 24 hours. Cell viability is assessed 16 hours after the initial plating and 48 hours after initiation of drug treatment using the colorimetric MTS assay CellTiter 96 AQueous One Solution Cell Proliferation Assay. Cell viability after drug treatment is normalized to that of untreated cells also grown for 48 hours. IC_{50} values are calculated using 4 parameter nonlinear regression in GraphPad Prism 5[2].

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Animal Administration [2][3]

Mice[2]

Tumor-bearing Apc CKO mice are randomly assigned to treatment with either control vehicle alone (n=8) or 45 mg/kg body weight BEZ235 in 10% 1-methyl-2-pyrrolidone/90% PEG 300 (n=8) by daily oral gavage for 28 days. The treatment dose is chosen based on literature indicating that 40-50 mg/kg body weight BEZ235 effectively treats murine tumor models without adverse effects. Base on pharmacokinetic studies demonstrating maximal tissue concentration one hour after NVP-BEZ235 administration, tumor-bearing mice are sacrificed one hour after final treatment dose. Colonic tumor volume is assessed using calipers (width×length×height) and tumors are harvested for both western blot analysis and immunohistochemistry.

Rats[3]

MENX-affected rats used. Three doses of BEZ235 are tested in MENX rats: 20, 30, and 45 mg/kg. As the two higher doses causes a weight loss >10% after 10 days of treatment, the dose of 20 mg/kg is used for further studies. For MRI studies, MENX-affected rats at 7 to 8 months of age (with sizeable adenomas but still in good general health) are treated for 14 days with BEZ235 (20 mg/kg) or placebo (PEG) administered daily per oral gavage.

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

CUSTOMER VALIDATION

- Nature. 2018 Aug;560(7719):499-503.
- Cell Res. 2019 Nov;29(11):895-910.
- Blood. 2019 Oct 17;134(16):1323-1336.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2017 Jun 8;8:15617.

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REFERENCES

[1]. Maira SM, et al. Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther, 2008, 7(7), 1851-1863.

[2]. Roper J, et al. The dual PI3K/mTOR inhibitor NVP-BEZ235 induces tumor regression in a genetically engineered mouse model of PIK3CA wild-type colorectal cancer. PLoS One, 2011, 6(9), e25132.

[3]. Lee M, et al. Targeting PI3K/mTOR Signaling Displays Potent Antitumor Efficacy against Nonfunctioning Pituitary Adenomas. Clin Cancer Res. 2015 Jul 15;21(14):3204-15.

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