Rabusertib

Cat. No.: HY-14720

CAS No.: 911222-45-2

Molecular Formula: $C_{18}H_{22}BrN_5O_3$

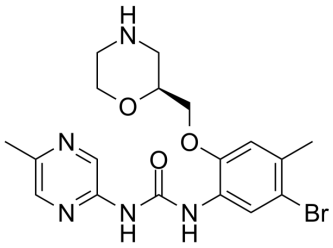
Molecular Weight: 436

Target: Checkpoint Kinase (Chk); Autophagy

Pathway: Cell Cycle/DNA Damage; Autophagy

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 : 31.25 mg/mL (71.67 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2936 mL	11.4679 mL	22.9358 mL
5 mM	0.4587 mL	2.2936 mL	4.5872 mL
10 mM	0.2294 mL	1.1468 mL	2.2936 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 (5.73 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.73 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Rabusertib (LY2603618) is a potent and selective inhibitor of Chk1 with an IC_{50} of 7 nM.

IC_{50} & Target

Chk1 7 nM (IC_{50})	Chk2 12000 nM (IC_{50})	PDK1 893 nM (IC_{50})	CAMK2 1550 nM (IC_{50})
VEGFR3 2128 nM (IC_{50})	MET 2200 nM (IC_{50})	JNK1 4930 nM (IC_{50})	RSK2 5700 nM (IC_{50})

	NTRK1 12000 nM (IC_{50})
In Vitro	Rabusertib (LY2603618) is a highly effective inhibitor of multiple aspects of Chk1 biology. Rabusertib (LY2603618) is tested against a panel of 51 diverse protein kinases in vitro. With an IC_{50} of 7 nM for Chk1, Rabusertib (LY2603618) is approximately 100-fold more potent against Chk1 than against any of the other protein kinases evaluated (PDK1, IC_{50}=893 nM, others >1000 nM). Rabusertib (LY2603618) effectively reduced Chk1 autophosphorylation with an EC_{50} of 430 nM. Inhibition of Chk1 by Rabusertib (LY2603618) also effectively abrogated the G_2/M DNA damage checkpoint in cells treated with DNA damaging agents. Treatment of cells with Rabusertib (LY2603618) produced a cellular phenotype similar to that reported for depletion of Chk1 by RNAi. Inhibition of intracellular Chk1 by Rabusertib (LY2603618) results in impaired DNA synthesis, elevated H2A.X phosphorylation indicative of DNA damage and premature entry into mitosis[1]. Treatments of the SK-N-BE(2) cells with variable concentrations of Rabusertib (LY2603618) results in dose-dependent inhibition of cell growth determined by MTT assays with an IC_{50} of 10.81 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Mice bearing Calu-6 xenografts are treated with 150 mg/kg (IP) Gemcitabine and a single simultaneous 200 mg/kg oral dose of Rabusertib (LY2603618). 200 mg/kg of Rabusertib (LY2603618) is sufficient to inhibit 85 % of Chk1 autophosphorylation in vivo at 2 h. Rabusertib (LY2603618) effectively reduces Gemcitabine-induced phosphorylation on Tlk serine 695 as well, supporting the cited report with a selective chemical inhibitor of Chk1[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are plated at 2.5×10^3 per well, on 96-well tissue culture plates and incubated for one cell doubling (18-24 h). Gemcitabine dilutions are set up by half-log steps across a final concentration range of 1-1000 nM. Rabusertib (LY2603618) is prepared by dilutions in DMSO to 5000× final concentration, and then diluted 1000-fold into medium to generate 5× stocks for addition to wells. Approximately 24 h after Gemcitabine addition, Rabusertib (LY2603618) is added. Each combination is done in triplicate. After a period of two cell doublings following Rabusertib (LY2603618) addition, MTS/PMS reagent is added to each well according to the manufacturer's instructions. Absorbance is read on a Spectra Max 250 spectrophotometer at 490 nm and the data analyzed with GraphPad Prism 4.0. Dose-response curves are fit by non-linear regression, with bottom fits constrained to 0 % inhibition[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female Harlan athymic nude mice (26-28 g) are used for these studies. Tumor growth is initiated by subcutaneous injection of 1×10^6 Calu-6 cells in a 1:1 mixture of serum-free growth medium and Matrigel in the rear flank of each subject animal. When tumor volumes reach approximately 150 mm^3 in size, the animals are randomized by tumor size and body weight, and placed into their respective treatment groups. Each animal receives 2 injections, one of either saline vehicle or 150 mg/kg Gemcitabine administered by intraperitoneal injection in a volume of 200 μL, and the other being the Captisol vehicle or LY2603618 administered orally in a volume of 200 μL. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2021 Jan 20;13(577):eaba7401.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nucleic Acids Res. 2021 Apr 6;49(6):3322-3337.
- Dev Cell. 2022 Feb 23;S1534-5807(22)00079-X.

- Cell Syst. 2020 Jan 22;10(1):66-81.e11.

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REFERENCES

[1]. King C, et al. Characterization and preclinical development of LY2603618: a selective and potent Chk1 inhibitor. Invest New Drugs. 2014 Apr;32(2):213-26.

[2]. Wang G, et al. Panobinostat synergistically enhances the cytotoxic effects of cisplatin, doxorubicin or etoposide on high-risk neuroblastoma cells. PLoS One. 2013 Sep 30;8(9):e76662.

Caution: Product has not been fully validated for medical applications. For research use only.

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