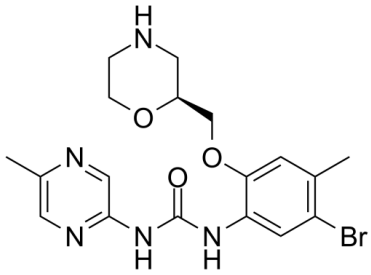
Data Sheet

Product Name:	Rabusertib
Cat. No.:	CS-0472
CAS No.:	911222-45-2
Molecular Formula:	C18H22BrN5O3
Molecular Weight:	436.30
Target:	Autophagy; Checkpoint Kinase (Chk)
Pathway:	Autophagy; Cell Cycle/DNA Damage
Solubility:	DMSO : 50 mg/mL (114.60 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Rabusertib (LY2603618) is a potent and selective inhibitor of **Chk1** with an **IC_{50}** of 7 nM. IC50 & Target: IC50: 7 nM (Chk1)[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: LY2603618 is prepared in DMSO (10 mM) and stock, and then diluted 1000-fold into medium[1].[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]. **Animal Administration:** LY2603618 is prepared in DMSO and diluted with saline or PBS (Mice)[1].[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.

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.

CAIndexNames:

Urea, N-[5-bromo-4-methyl-2-[(2S)-2-morpholinylmethoxy]phenyl]-N'-(5-methyl-2-pyrazinyl)-

SMILES:

BrC(C=C1NC(NC2=NC=C(N=C2)C)=O)=C(C=C1OC[C@H]3OCCNC3)C

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