

Product Data Sheet

Product Name: SB1317
Cat. No.: GC12064

Chemical Properties

Cas. No. 937270-47-8

SMILES CN(C/C=C/CCOC1=CC=CC2=C1)CC3=CC(NC4=NC=CC2=N4)=CC=C3

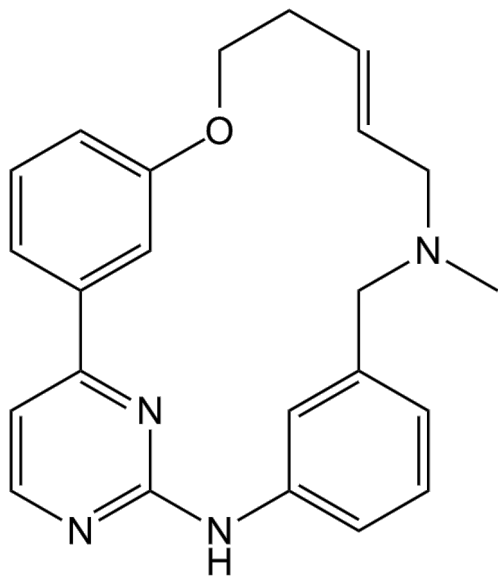
Formula $C_{23}H_{24}N_4O$ M.Wt 372.46

Solubility ≥ 44.87 mg/mL in DMSO, ≥ 3.98 mg/mL in EtOH with ultrasonic and warming
Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



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

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Protocol

Kinase experiment:

The recombinant enzymes (CDK2/cyclin A, JAK2, and FLT3) are used. All assays are carried out in 384-well white microtiter plates using the PKLight assay system. This assay platform is a luminometric assay for the detection of ATP in the reaction using a luciferase-coupled reaction. The compounds are tested at eight concentrations prepared from 3- or 4-fold serial dilution starting at 10 μ M. For CDK2/cyclin A assay, the reaction mixture consisted of the following components in 25 μ L of assay buffer (50 mM Hepes, pH 7.5, 10 mM MgCl₂, 5 mM MnCl₂, 5 mM BGP, 1 mM DTT, 0.1 mM sodium orthovanadate), 1.4 μ g/mL of CDK2/cyclin A complex, 0.5 μ M RbING substrate, and 0.5 μ M ATP. The mixture is incubated at room temperature for 2 h. Then 13 μ L of PKLight ATP detection reagent is added and the mixture is incubated for 10 min. Luminescence signals are detected on a multilabel plate reader. The analytical software Prism 5.0 is used to generate IC₅₀ values from the data[1].

Cell experiment:

All cell lines are obtained from the American Type Culture Collection and cultured. For proliferation assays in 96-well plates, 20 000 cells are seeded in 100 μ L of medium and treated the following day with compounds (e.g., SB1317) (in triplicate) at concentrations up to 10 μ M for 48 h. Cell viability is monitored using the CellTiter-96 Aqueous One solution cell proliferation assay. Dose-response curves are plotted to determine IC₅₀ values for the compounds using the XL-fit software[1].

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Animal experiment: Mice and Rats[1] Male BALB/c mice (aged ~10-12 weeks and weighing 17-22 g), male Beagle dogs (~6-7 months of age, weighing 10-14 kg), and male Wistar rats (aged 6-8 weeks, weighing 239-249 g) are used in this study. The oral doses for mice, dogs, and rats are 75, 10, and 10 mg/kg, respectively. The doses are administered by gavage as suspensions (0.5% methylcellulose and 0.1% Tween 80) to mice and rats, and as gelatin capsules (12 Torpac) to dogs. Following oral dosing serial blood samples are collected (cardiac puncture in mice, jugular vein in dogs, and superior vena cava in rats) at different time points (0-24 h) in tubes containing K3EDTA as anticoagulant, centrifuged, and plasma is separated and stored at -70°C until analysis. Plasma samples are processed and analyzed by LC-MS/MS. Pharmacokinetic parameters are estimated by noncompartmental methods using WinNonlin.

References:

- [1]. William AD, et al. Discovery of kinase spectrum selective macrocycle (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a potent inhibitor of cyclin dependent kina
- [2]. Pasha MK, et al. Preclinical metabolism and pharmacokinetics of SB1317 (TG02), a potent CDK/JAK2/FLT3 inhibitor. Drug Metab Lett. 2012 Mar;6(1):33-42.

Background

SB1317 is a potent inhibitor of Cyclin dependent kinases (CDKs), FMS-like tyrosine kinase-3 (FLT3) and Janus kinase 2 (JAK2) with IC₅₀ values of 13nM, 56nM and 73nM for CDK2, JAK2 and FLT3, respectively [1].

CDKs are serine-threonine kinases that regulating the cell cycle. JAK2 is a nonreciprocal intracellular tyrosine kinase that transduces cytokine-mediated signals via the JAK-STAT pathway. FLT3 is a cytokine receptor and plays an important role in the normal development of haematopoietic stem cells [1].

In luciferase-expressing MM1S cells, SB1317 overcame the proliferative/protective advantage conferred by IL-6. In MM1S cells, SB1317 increased the percentage of cells in G2/M phases and decreased cells in the S phase. Also, SB1317 increased the amount of cells in the subG0 region [2].

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In CB17-SCID mice bearing human multiple myeloma plasmacytoma xenograft models (the bortezomib-sensitive MM1S model and the more bortezomib-resistant OPM2 model), SB1317 significantly inhibited tumor growth [2]. In a subcutaneous AML model, treatment mice with SB1317 dosed 10, 20 or 40 mg/kg daily for 21 days reduced the average tumor volume by 53%, 61% and 113%, respectively [3].

References:

- [1]. William AD, Lee AC, Goh KC, et al. Discovery of kinase spectrum selective macrocycle (16E)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a potent inhibitor of cyclin dependent kinases (CDKs), Janus kinase 2 (JAK2), and fms-like tyrosine kinase-3 (FLT3) for the treatment of cancer. *J Med Chem*, 2012, 55(1): 169-196.
- [2]. Álvarez-Fernández S, Ortiz-Ruiz MJ, Parrott T, et al. Potent antimyeloma activity of a novel ERK5/CDK inhibitor. *Clin Cancer Res*, 2013, 19(10): 2677-2687.
- [3]. Goh KC, Novotny-Diermayr V, Hart S, et al. TG02, a novel oral multi-kinase inhibitor of CDKs, JAK2 and FLT3 with potent anti-leukemic properties. *Leukemia*, 2012, 26(2): 236-243.

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