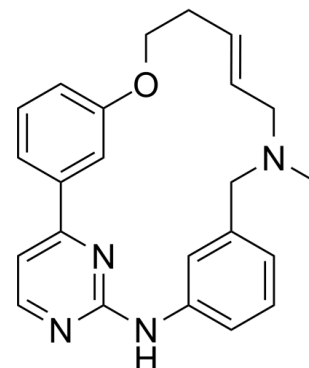


Data Sheet

Product Name:	SB1317
Cat. No.:	CS-0884
CAS No.:	937270-47-8
Molecular Formula:	C ₂₃ H ₂₄ N ₄ O
Molecular Weight:	372.46
Target:	CDK; FLT3; JAK
Pathway:	Cell Cycle/DNA Damage; Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt
Solubility:	DMSO : 26.5 mg/mL (71.15 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

SB1317 is a potent inhibitor of **CDK2**, **JAK2**, and **FLT3** for the treatment of cancer, with IC_{50} of 13, 73, and 56 nM for CDK2, JAK2 and FLT3, respectively. IC_{50} & Target: IC_{50} : 13 nM (CDK2), 73 nM (JAK2), 56 nM (FLT3)^[1] **In Vitro:** SB1317 has a highly novel kinase inhibitory spectrum inhibiting 17 kinases from a panel of 63, 11 of which are CDK/JAK/FLT family members. The others, Lck, Fyn, Fms, TYRO3, ERK5, and p38 δ , are implicated in inflammatory and proliferative processes. Human CYP1A2, 3A4, 2C9, and 2C19 isoforms are not inhibited by SB1317 at the highest tested concentration of 25 μ M, but SB1317 inhibits CYP2D6 with IC_{50} =0.95 μ M, approximately at the plasma C_{max} observed at the maximum tolerated dose. SB1317 inhibits cell proliferation concentrations in HCT-116 (IC_{50} =0.079 μ M) and HL-60 (IC_{50} =0.059 μ M)^[1]. SB1317 is a novel small molecule potent CDK/JAK2/FLT3 inhibitor. SB1317 is mainly metabolized by CYP3A4 and CY1A2 in vitro. SB1317 does not inhibit any of the major human CYPs in vitro except CYP2D6 (IC_{50} =1 μ M). SB1317 does not significantly induce CYP1A and CYP3A4 in human hepatocytes in vitro^[2]. **In Vivo:** Treatment with SB1317 at 75 mg/kg po q.d. 3 \times /week significantly inhibits the growth of tumors with a mean TGI of 82%, while the lower dose of 50 mg/kg po 3 \times /week is marginally effective. Treatment with SB1317 using either regime significantly inhibits the growth of tumors with mean TGIs of 42% and 63% for the oral and ip delivery methods, respectively^[1]. In pharmacokinetic studies SB1317 shows moderate to high systemic clearance (relative to liver blood flow), high volume of distribution (>0.6 L/kg), oral bioavailability of 24%, ~4 and 37% in mice, rats and dogs, respectively; and extensive tissue distribution in mice^[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: ^[1]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 IC_{50} values from the data^[1]. **Cell Assay:** SB1317 is prepared in DMSO and stored, and then diluted with appropriate medium before use^[1].^[1]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 IC_{50} values for the compounds using the XL-fit software^[1]. **Animal Administration:** SB1317 hydrochloride is dissolved in 0.5% methyl cellulose/0.1% Tween 80 (MC/Tween) for oral (po) dosing or in 10% dimethylacetamide (DMA) and 10% Cremophor (DMA/CRE) for ip dosing. Dosing solutions are prepared weekly in a feeding volume of 10 mL per kilogram body weight and stored at 4°C^[1].^[1]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.

CAIndexNames:

20-Oxa-5,7,14,27-tetraazatetracyclo[19.3.1.12,6.18,12]heptacos-1(25),2,4,6(27),8,10,12(26),16,21,23-decaene, 14-methyl-

SMILES:

CN1CC2=CC(NC3=NC(C4=CC(OCC/C=C/C1)=CC=C4)=CC=N3)=CC=C2

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

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