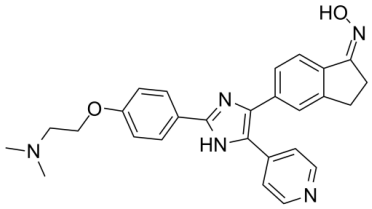
Data Sheet

Product Name:	SB-590885
Cat. No.:	CS-0093
CAS No.:	405554-55-4
Molecular Formula:	C27H27N5O2
Molecular Weight:	453.54
Target:	Raf
Pathway:	MAPK/ERK Pathway
Solubility:	DMSO : 33.33 mg/mL (73.49 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

SB-590885 is a potent **B-Raf** inhibitor with **K_i** of 0.16 nM, and has 11-fold greater selectivity for B-Raf over c-Raf, without inhibition to other human kinases. IC50 & Target: IC50: 0.16 nM (B-Raf) **In Vitro:** SB-590885 displays significant selectivity for B-Raf over c-Raf with K_i of 0.16 nM over 1.72 nM. SB-590885 is a more potent inhibitor than the previously described Raf/VEGFR kinase inhibitor BAY 439006 (K_i=38 nM for mutant B-Raf, 6 nM for c-Raf). SB-590885 displays potent selectivity over 46 other kinases. Unlike the multi-kinase inhibitor BAY43-9006, SB-590885 stabilizes the oncogenic B-Raf kinase domain in an active configuration. In Colo205, HT29, A375P, SKMEL28, and MALME-3M cells expressing oncogenic B-Raf^{V600E}, SB-590885 treatment potently inhibits ERK phosphorylation with EC_{50} of 28 nM, 58 nM, 290 nM, 58 nM, and 190 nM, respectively, and consistently, inhibits the proliferation with EC_{50} of 0.1 μM, 0.87 μM, 0.37 μM, 0.12 μM, and 0.15 μM, respectively. SB-590885 decreases anchorage-independent growth of melanoma cell lines in a BRAF mutant-selective manner[1]. SB-590885 displays high affinity for B-Raf with K_d of 0.3 nM[2]. Most of the melanoma cell lines that harbor the BRAF V600E mutation and lack CDK4 mutations (451Lu, WM35, and WM983) are highly sensitive to SB-590885 with IC_{50} of <1 μM. Increased levels of cyclin D1 resulting from genomic amplification mediate SB-590885 resistance in B-Raf V600E-mutated melanomas[3]. **In Vivo:** Administration of SB-590885 potently decreases tumorigenesis in murine xenografts established from mutant B-Raf-expressing A375P melanoma cells, and modestly inhibits tumor growth[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: SB-590885 is dissolved in DMSO.[1]For proliferation assays, cells are treated with compounds in 0.1% DMSO and incubated for 72 hours at 37°C, 5% CO_2. Viable cells are quantified using CellTiter-Glo reagent and luminescence detection on a Victor 2V plate reader. Cells are prepared for cell cycle analysis on a Becton Dickinson FACScan, according to the manufacturer's instructions. Data is acquired and analyzed using CellQuest v3.3 software. Anchorage-independent growth assays are done as described elsewhere, with inhibitors or DMSO vehicle included in the agar layer. Cultures are re-fed with media and inhibitor or DMSO every 5 to 7 days for a total of 28 days. Colonies are visualized and photographed by conventional light microscopy and quantified by counting on a grid in triplicate. **Animal Administration:** SB-590885 is formulated in 2% N,N-dimethylacetamide, 2% Cremophor EL, and 96% acidified water. [1]The pharmacokinetic properties and safety of SB-590885, following i.p. injection, are determined and 50 mg/kg daily injections are found to give therapeutic levels with minimal body weight changes. Tumors are initiated in 8- to 12-week-old female nude mice by s.c. injection of 5×10^6 A375P cells in Matrigel suspension, and 3 weeks after tumor induction when the tumors had reached a volume of 150 to 250 mm^3, mice are randomized into groups of eight prior to treatment. Animals are treated with vehicle [2% N,N-dimethylacetamide, 2% Cremophor EL, and 96% acidified water (pH 4-5)], or vehicle containing 50 mg/kg of SB-590885 daily for 21 days. A cohort of mice treated with SB-590885 are then observed an additional 14 days following cessation of treatment. Tumor volume is measured for 55 days by calipers twice weekly.

References:

[1]. King AJ, et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. Cancer Res, 2006, 66(23), 11100-11105.

[2]. Takle AK, et al. The identification of potent and selective imidazole-based inhibitors of B-Raf kinase. Bioorg Med Chem Lett, 2006, 16(2), 378-381.

[3]. Smalley KS, et al. Increased cyclin D1 expression can mediate BRAF inhibitor resistance in BRAF V600E-mutated melanomas. Mol Cancer Ther, 2008, 7(9), 2876-2883.

CAIndexNames:

1H-Inden-1-one, 5-[2-[4-[2-(dimethylamino)ethoxy]phenyl]-5-(4-pyridinyl)-1H-imidazol-4-yl]-2,3-dihydro-, oxime

SMILES:

O/N=C1CCC2=CC(C3=C(NC(C4=CC=C(C=C4)OCCN(C)C)=N3)C5=CC=NC=C5)=CC=C/12

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