

Product Data Sheet

Product Name: Bosutinib (SKI-606)

Cat. No.: GC13343

Chemical Properties

Cas. No. 380843-75-4

Chemical Name 4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile

SMILES CN1CCN(CC1)CCCOCC2=C(C=C3C(=C2)N=CC(=C3NC4=CC(=C(C=C4Cl)Cl)OC)C#N)OC

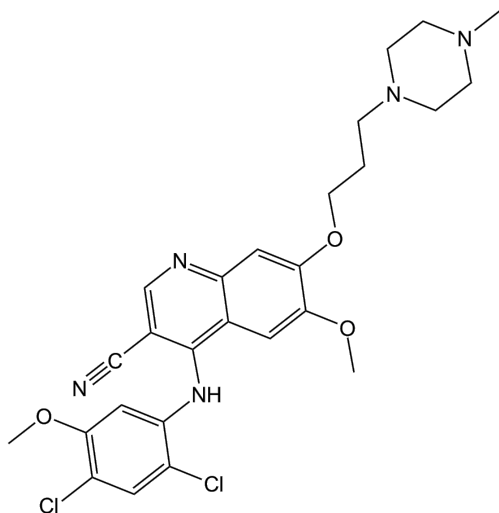
Formula $C_{26}H_{29}Cl_2N_5O_3$ M.Wt 530.45

Solubility $\geq 26.5\text{mg/mL}$ in DMSO Storage 4°C , protect from light

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



Protocol

Cell experiment: [1]

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

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Cell lines MDA-MB-468, MDA-MB-231, MCF-7 and MDA-MB-435 cells

Preparation method The solubility of this compound in DMSO is >10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reaction Conditions 1 µM, 48 hours

Applications Effects on cell morphology were observed at a concentration of 1 µM SKI-606 for all cell lines examined, and morphological changes were apparent at concentrations as low as 0.25 µM. SKI-606 caused the cells to adhere to each other, forming dense clusters as compared to vehicle control (DMSO) treated cells, which showed spreading over larger areas.

Animal experiment: [2]

Animal models Female athymic nude mice bearing human pancreas xenografts (P281 or P420)

Dosage form Oral administration, 100 mg/Kg/d, for 28 days

Applications Two xenografts, one sensitive (P281) and one resistant (P420), were chosen to assess pharmacodynamic changes by Western blot after treatment with bosutinib. Four different samples were analyzed from P281 and P420, and optical scanning was done. The sensitive xenograft P281 showed decreased posttreatment Src, STAT-5, p-STAT-5, p-Akt, MAPK, and EGFR. Bosutinib-treated P281 showed a marked increase in cleaved PARP.

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Other notes

Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1] Vultur A, Buettner R, Kowolik C, et al. SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. *Molecular cancer therapeutics*, 2008, 7(5): 1185-1194.

[2] Messersmith W A, Rajeshkumar N V, Tan A C, et al. Efficacy and pharmacodynamic effects of bosutinib (SKI-606), a Src/Abl inhibitor, in freshly generated human pancreas cancer xenografts. *Molecular cancer therapeutics*, 2009, 8(6): 1484-1493.

Background

Bosutinib (SKI-606) is a potent inhibitor of Src and Abl kinases with IC₅₀ of 1.2 nM and 1 nM [1].

In chronic myelogenous leukemia (CML) cells, SKI-606 inhibited phosphorylation of Bcr-Abl, Src and Stat5. It also ablated the expression of v-Abl in fibroblasts and blocked proliferation of CML cells [2]. In colorectal cancer cells, SKI-606 inhibited Src autophosphorylation with an IC₅₀ of ~ 0.25 µM, and simultaneity suppressed Tyr (925) phosphorylation of a Src substrate [3]. SKI-606 blocked beta-catenin function by inhibiting its binding to the TCF4 transcription factor and dose-dependently suppressed cyclin D1. SKI-606 increased its binding affinity of beta-catenin to E-cadherin and adhesion, with ensuing reduced motility in a wound healing assay [4].

Oral administration of SKI-606 at 100 mg/kg for 5 days causes complete regression of large K562 xenografts in nude mice [2].

[1]. Boschelli DH, Ye F, Wang YD, Dutia M, Johnson SL, Wu B, Miller K, Powell DW, Yaczko D, Young M, Tischler M, Arndt K, Discafani C, Etienne C, Gibbons J, Grod J, Lucas J, Weber JM, Boschelli F. Optimization of 4-phenylamino-3-quinolinecarbonitriles as potent inhibitors of Src kinase activity. *J Med Chem*. 2001 Nov 8;44(23):3965-77.

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- [2]. Golas JM, Arndt K, Etienne C, Lucas J, Nardin D, Gibbons J, Frost P, Ye F, Boschelli DH, Boschelli F. SKI-606, a 4-anilino-3-quinolinecarbonitrile dual inhibitor of Src and Abl kinases, is a potent antiproliferative agent against chronic myelogenous leukemia cells in culture and causes regression of K562 xenografts in nude mice. *Cancer Res.* 2003 Jan 15;63(2):375-81.
- [3]. Golas JM, Lucas J, Etienne C, Golas J, Discafani C, Sridharan L, Boghaert E, Arndt K, Ye F, Boschelli DH, Li F, Titsch C, Huselton C, Chaudhary I, Boschelli F. SKI-606, a Src/Abl inhibitor with in vivo activity in colon tumor xenograft models. *Cancer Res.* 2005 Jun 15;65(12):5358-64.
- [4]. Coluccia AM, Benati D, Dekhil H, De Filippo A, Lan C, Gambacorti-Passerini C. SKI-606 decreases growth and motility of colorectal cancer cells by preventing pp60(c-Src)-dependent tyrosine phosphorylation of beta-catenin and its nuclear signaling. *Cancer Res.* 2006 Feb 15;66(4):2279-86.

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