Bosutinib (SKI-606) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>530.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{26}H_{26}Cl_{2}N_{3}O_{3}</td>
</tr>
<tr>
<td>CAS No.</td>
<td>380843-75-4, 918639-08-4 (H2O), 918639-09-5 (2-propanol)</td>
</tr>
<tr>
<td>Synonyms</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Solubility (25°C)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>DMSO 110 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Water &lt;1 mg/mL</td>
</tr>
<tr>
<td></td>
<td>Ethanol 54 mg/mL</td>
</tr>
</tbody>
</table>

Storage

<table>
<thead>
<tr>
<th>Storage Condition</th>
<th>Powder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 years -20°C</td>
</tr>
<tr>
<td></td>
<td>2 weeks 4°C in DMSO</td>
</tr>
<tr>
<td></td>
<td>6 months -80°C in DMSO</td>
</tr>
</tbody>
</table>

Biological Activity

<table>
<thead>
<tr>
<th>Description</th>
<th>Bosutinib (SKI-606) is a novel, dual Src/Abl inhibitor with IC50 of 1.2 nM and 1 nM, respectively.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets</td>
<td>Src, Abl</td>
</tr>
<tr>
<td>IC50</td>
<td>1.2 nM[1]</td>
</tr>
</tbody>
</table>

**In vitro**

Bosutinib is selective for Src over non-Src family kinases with an IC50 of 1.2 nM, and potently inhibits Src-dependent cell proliferation with an IC50 of 100 nM.[1] Bosutinib significantly inhibits the proliferation of Bcr-Abl-positive leukemia cell lines KU812, K562, and MEG-01 but not Molt-4, HL-60, Ramos, and other leukemia cell lines, with IC50 of 5 nM, 20 nM and 20 nM, respectively, more potently than that of STI-571. Similar to STI-571, Bosutinib displays antiproliferative activity against the Abl-MLV-transformed fibroblasts with IC50 of 90 nM. Bosutinib ablates tyrosine phosphorylation of Bcr-Abl and STAT5 in CML cells and of v-Abl expressed in fibroblasts at the concentration of ~50 nM, 10-25 nM and 200 nM, respectively, leading to the Bcr-Abl downstream signaling inhibition of Lyn/Hck phosphorylation.[2] Although unable to inhibit the proliferation and survival of breast cancer cells, Bosutinib significantly decreases the motility and invasion of breast cancer cells with IC50 of ~250 nM, involved in an increase in cell-to-cell adhesion and membrane localization of β-catenin.[3]

**In vivo**

Bosutinib (60 mg/kg/day) is active against Src-transformed fibroblasts xenografts and HT29 xenografts in nude mice with T/C of 18% and 30%, respectively.[1] Oral administration of Bosutinib for 5 days significantly suppresses K562 tumor growth in mice in a dose-dependent manner, with the large tumors eradicated at dose of 100 mg/kg and tumor in mice at 150 mg/kg without overt toxicity.[2] As being inactive against Colo205 xenografts in nude mice at 50 mg/kg twice daily, Bosutinib dosing at 75 mg/kg twice daily is necessary against Colo205 xenografts, and increasing the dose of Bosutinib has no additional benefit, in contrast to the significant dose-dependent ability against HT29 xenografts.[3]

**Clinical Trials**

A Phase I study to compare the Bosutinib clinical tablet and clinical capsule and to investigate food effect on Bosutinib commercial formulation in healthy subjects has been completed.

**Features**

**Protocol (Only for Reference)**

**Kinase Assay**[1]

**The Src and Abl kinase assays**

The Src kinase activity is measured in an ELISA format. Src (3 units/reaction), reaction buffer (50 mM Tris-HCl pH 7.5, 10 mM MgCl₂, 0.1 mM EGTA, 0.5 mM Na₃VO₄) and ccd2 substrate peptide are added to various concentrations of Bosutinib and incubated at 30 °C for 10 minutes. The reaction is started by the addition of ATP to a final concentration of 100 μM, incubated at 30 °C for 1 hour and stopped by addition of EDTA. Instructions from the manufacturer are followed for subsequent steps. The Abl kinase assay is performed in a DELFIA solid phase europium-based detection assay format. Biotinylated peptide (2 μM) is bound to streptavidin-coated microtiter plates for 1.5 hours in 1 mg/mL ovalbumin in PBS. The plates are washed for 1 hour with PBS/0.1% Tween 80, followed by a PBS wash. The kinase reaction is incubated for 1 hour at 30°C. Abl kinase (10 units) is mixed with 50 mM Tris-HCl (pH 7.5), 10 mM MgCl₂, 80 μM EGTA, 100 μM ATP, 0.5 mM Na₃VO₄, 1% DMBO, 1 mM HEPES (pH 7.0), 200 μg/mL ovalbumin and various concentration of Bosutinib. The reaction is stopped with EDTA at a final concentration of 50 μM. The reaction is monitored with Eu-labeled phosphotyrosine antibody and DELFIA enhancement solution.

**Cell Assay**[2]

**Cell Lines**

Abi-MLV, Rat 2, KU812, K562, and MEG-01 cells

**Concentrations**

Dissolved in DMSO, final concentrations ~1 μM

**Incubation Time**

72 hours

**Methods**

Cells are exposed to various concentrations of Bosutinib for 72 hours. Anchorage-independent proliferation of Abi-MLV-transformed fibroblasts is measured in 96-well ultra-low binding plates treated with Sigmoidac to block residual cell attachment. Cell proliferation is measured with MTS or Cell-Glo. For the determination of cell cycle or cell death, cells are prepared for FACS analysis in the CycleTest Plus DNA reagent kit and analyzed on a fluorescence-activated cell sorter flow cytometer.

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Animal Study[2]

Animal Models | Nude female mice injected with K562 cells
Formulation | Suspended in 0.5% methocel/0.4% Tween 80
Doses | ~150 mg/kg/day
Administration | Oral gavage

References

Customer Reviews

Bosutinib (SKI-606) purchased from Selleck
SFK inhibitors abrogate tyrosine phosphorylation associated with sperm capacitation. Mouse sperm were incubated in the absence or in the presence of SKI806 for 60 min in capacitating (cap, with HCO3) or non-capacitating media (NC, without HCO3). Western blot analyses were performed with anti-pY antibodies.

Data from [J Virol, 2011, 85, 2296–2303]
Bosutinib (SKI-606) purchased from Selleck
A, IC50 of Bosutinib that block ANDV-induced EC permeability. Endothelial cells were ANDV-infected, and 3 days postinfection the permeability of cells in response to VEGF addition was determined in the presence or absence of increasing amounts of kinase inhibitor. The effect of inhibitors is presented as the percentage of ANDV-induced permeability of inhibitor-treated monolayers 3 days postinfection and 30 min post-VEGF and FITC-dextran addition. B, VEGFR2-Src inhibitors block ANDV-induced permeability. Endothelial cells were plated on vitronectin-coated Transwell inserts and infected at an MOI of 0.5 in triplicate with ANDV. Three days postinfection, the permeability of ANDV- and mock-infected endothelial cell monolayers was determined as described for Fig. 1 at indicated times in the presence or absence of Bosutinib.

PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.

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