BMS-911543

Cat. No.: HY-15270
CAS No.: 1271022-90-2
Molecular Formula: C₂₃H₂₈N₈O
Molecular Weight: 432.52
Target: JAK
Pathway: Epigenetics; JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Stem Cell/Wnt
Storage: Powder -20°C 3 years
4°C 2 years
In solvent -80°C 2 years
-20°C 1 year

SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (57.80 mM; Need ultrasonic)

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mM</td>
<td>2.3120 mL</td>
<td>11.5602 mL</td>
<td>23.1203 mL</td>
</tr>
<tr>
<td></td>
<td>5 mM</td>
<td>0.4624 mL</td>
<td>2.3120 mL</td>
<td>4.6241 mL</td>
</tr>
<tr>
<td></td>
<td>10 mM</td>
<td>0.2312 mL</td>
<td>1.1560 mL</td>
<td>2.3120 mL</td>
</tr>
</tbody>
</table>

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.78 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.78 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

BMS-911543 is a selective JAK2 inhibitor, with IC₅₀s of 1.1 nM, less selective at JAK1, JAK3 and TYK2 (IC₅₀, 75, 360, 66 nM, respectively).

IC₅₀ & Target

<table>
<thead>
<tr>
<th>IC₅₀</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 nM (IC₅₀)</td>
<td>JAK2</td>
</tr>
<tr>
<td>66 nM (IC₅₀)</td>
<td>Tyk2</td>
</tr>
<tr>
<td>75 nM (IC₅₀)</td>
<td>JAK1</td>
</tr>
<tr>
<td>360 nM (IC₅₀)</td>
<td>JAK3</td>
</tr>
</tbody>
</table>

BMS-911543 is a selective JAK2 inhibitor, with IC₅₀s of 1.1 nM, less selective at JAK1, JAK3 and TYK2 (IC₅₀, 75, 360, 66 nM, respectively). BMS-911543 displays IC₅₀ of >25 μM for all targets except PDE4 (IC₅₀, 5.6 μM). BMS-911543 exhibits potent antiproliferative effect on the SET-2 and BaF3-V617F engineered cell lines (both dependent upon JAK2 pathway), with IC₅₀s of 60 and 70 nM, respectively, and such an effect on SET-2 and BaF3-V617F cells is correlated with similar activity on...
constitutively active pSTAT5 (IC50, 80 and 65 nM, respectively)\textsuperscript{[1]}. BMS-911543 (>20 μM) is cytotoxic to murine or human pancreatic ductal adenocarcinoma (PDAC) cell lines. BMS-911543 (5 and 10 μM) also blocks T regulatory cell differentiation in vitro\textsuperscript{[2]}.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

| In Vivo | BMS-911543 is well tolerated up to 100 mg/kg in rats (mean AUC0-72 h, 11300 μM·h) and dogs (AUC0-24 h, 610 μM·h). A 15 mg/kg/day dose (Day 14 AUC0-24 h, 3200 μM·h) is well tolerated\textsuperscript{[1]} in two-week repeat dose studies in rats. BMS-911543 (30 mg/kg, p.o.) suppresses the growth of tumor and prolongs the median survival in KPC-Brcal mice. BMS-911543 also selectively reduces pSTAT5 expression in pancreatic tumors and decreases levels of intratumoral FoxP3\textsuperscript{+} T regulatory cells in mice administered BMS-911543\textsuperscript{[2]}.

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| PROTOCOL | **Cell Assay**\textsuperscript{[2]} | Human and murine pancreatic ductal adenocarcinoma (PDAC) tumor cells or PSC are cultured in 96 well plates and the following day treated with BMS-911543 or DMSO vehicle control for 48 hours. After 48 hours, MTT reagent (ATCC) is added for 2 hours at 37°C. Samples are analyzed on a plate reader testing for absorbance at 450 nM\textsuperscript{[2]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only. |
| **Animal Administration**\textsuperscript{[2]} | Mice\textsuperscript{[2]} | Pancreatic tumors are confirmed in KPC-Brcal mice by bioluminescent imaging (BLI) at 5-6 weeks of age. Briefly, mice are maintained on isofluorane anesthesia and imaged 10-15 minutes following intraperitoneal injection of Luciferin on a heated platform. Animals with a pancreatic mass of approximately 50-100 mm\textsuperscript{3} are randomized, and treatment is initiated the day following imaging. Mice are then treated for 2 weeks by daily oral gavage at a dose of 30 mg/kg BMS-911543. Following 2 weeks of treatment, animals are euthanized via CO\textsubscript{2} asphyxiation followed by cardiac puncture. Plasma, splenocytes and tumor tissue are collected for further analysis. Pathology is assessed by H&E to determine differentiation state of the tissue as PanIN, papillary carcinoma or PDAC. For long term in vivo experiments, 8 week old KPC-Brcal mice with advanced disease are continuously treated by oral gavage at 30 mg/kg of BMS-911543 until mice meet specified early removal criteria \textsuperscript{[2]}.

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