Imatinib Mesylate

Cat. No.: HY-50946
CAS No.: 220127-57-1
Molecular Formula: C₃₀H₃₅N₇O₄S
Molecular Weight: 589.71
Target: c-Kit; Bcr-Abl; PDGFR; Autophagy
Pathway: Protein Tyrosine Kinase/RTK; Autophagy
Storage: Powder
-20°C 3 years
4°C 2 years
In solvent
-80°C 6 months
-20°C 1 month

SOLVENT & SOLUBILITY

In Vitro
H₂O : ≥ 50 mg/mL (84.79 mM)
DMSO : ≥ 49 mg/mL (83.09 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>1.6957 mL</td>
<td>8.4787 mL</td>
<td>16.9575 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3391 mL</td>
<td>1.6957 mL</td>
<td>3.3915 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1696 mL</td>
<td>0.8479 mL</td>
<td>1.6957 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: ≥ 2.08 mg/mL (3.53 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.53 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.53 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
Imatinib Mesylate (STI571 Mesylate) is a tyrosine kinases inhibitor that inhibits c-Kit, Bcr-Abl, and PDGFR (IC₅₀=100 nM) tyrosine kinases.

IC₅₀ & Target
IC₅₀: ~100 nM (c-Kit, Bcr-Abl, and PDGFR)[¹]
### In Vitro

Imatinib (STI571) mesylate inhibits c-Kit autophosphorylation, activation of MAPK, and activation of Akt without altering total protein levels of c-kit, MAPK, or Akt. The concentration that produces 50% inhibition for these effects is approximately 100 nM. Imatinib (STI571) mesylate is very effective (in vitro IC\textsubscript{50} of 25 nM) against the chronic myeloid leukemia-causing kinase Bcr-Abl. Imatinib also efficiently inhibits Kit (in vitro IC\textsubscript{50} of 410 nM) and PDGFR (in vitro IC\textsubscript{50} of 380 nM). Imatinib (STI571) mesylate is a multi-target inhibitor of v-Abl, c-Kit and inhibits Bcr/Abl, v-Abl, Tel/AbI, the native PDGFB\(\beta\) receptor, and c-Kit, but it does not inhibit Src family kinases, c-Fms, Flt3, the EGFR or multiple other tyrosine kinases. Imatinib inhibits tyrosine phosphorylation and cell growth of Ba/F3 cells growing in IL-3 or on Ba/F3 cells transformed by Tel/JAK2. Imatinib mesylate selectively inhibits the activity of Bcr/Abl, c-Kit and PDGFR kinases. Imatinib mesylate reveals distinct and rapid antileukemic activity in chronic myelogenous leukemia (CML) and Philadelphia-positive (Ph\(^+\)) acute lymphoblastic leukemia (ALL).

### In Vivo

Animals treated with Imatinib mesylate show a decrease of mean body weight throughout the whole study. Body weight loss is noticeable in mice from groups that receive chemotherapy and the vitamin D analog combined treatment. The body weight decrease of mice treated with both combined Imatinib mesylate and PRI-2191 is the highest (15%) on Day 22 of the experiment, but after that day, mice start to recover. In a rat Ischemia/reperfusion injury (IRI) model, Imatinib mesylate attenuates lung injury by an antipermeability and antiinflammatory effect. The delivery and function of Imatinib mesylate in the lung is also confirmed in this model.

### PROTOCOL

#### Cell Assay

Tested A549 cells are placed in 96-well flat-bottom plates at a density of 5\(\times\)10\(^3\) cells per well 24 h before the addition of the test compounds. The cells are incubated for 96 h with two different concentrations (10 and 100 nM) of PRI-2191 and concurrently with various concentrations of Imatinib mesylate (10, 100, 1000 and 10,000 ng/mL) and other cytostatic drugs (Docetaxel (DTX) or Idarubicin (ID): 0.1, 1, 10, 100 ng/mL; Cisplatin (CIS): 1, 10, 100, 1000 ng/mL). The sulforhodamine B (SRB) assay is performed to evaluate the cytotoxic effect. As a result, IC\textsubscript{50} is calculated for each separate experiment in Cheburator 0.4, Dmitry Nevozhay software. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

#### Animal Administration

**Mice**

NOD/SCID female mice, 12-16 weeks old, body weight of 20-25 g, are used. Mice are subcutaneously (s.c.) inoculated in the right flank of the abdomen with A549 tumor cells suspension (5\(\times\)10\(^6\) cells in 0.2 mL of Hank's medium per mouse, Day 0) and then are randomized into groups receiving varied combinations of vitamin D analogs and chemotherapeutics. One out of two experimental protocols is applied in the respective experiments: 1. The treatment is started from Day 7 after inoculation of tumor cells (when tumors become palpable). Imatinib mesylate is administered intraperitoneally (i.p.) at a dose of 75 mg/kg/day, daily for 19 days (from Days 7-25). PRI-2191 is administered s.c. or by oral gavage at a dose of 2 \(\mu\)g/kg/day, 3 times a week (on Days 7, 12, 14, 16, 19, 21 and 23). 2. The treatment is started from Day 7 after inoculation of tumor cells (when tumors become palpable). Imatinib mesylate is administered intraperitoneally (i.p.) at a dose of 50 mg/kg/day, daily for 13 days (from Days 7-19). PRI-2191 and PRI-2205 are administered s.c. at doses of 1 or 10 \(\mu\)g/kg/day, respectively, 3 times a week (on Days 7, 10, 12, 14, 17, 19, 21, 24 and 26). At the end of the experiments, blood is collected under anesthesia; then, the mice are sacrificed.

**Rats**

Male Lewis rats weighing 270 to 320 g are used in the experiments. Imatinib mesylate (50 mg/kg) is injected intraperitoneally in the Imatinib group (n=7), and 0.5 mL of 20% DMSO without Imatinib is administered in the vehicle group (n=7). The dose of 25 mg/kg is preliminarily tested, and it produces a little improvement in lung function without statistical significance. The dose of 50 mg/kg and intraperitoneal administration are adopted based on this result and past reports. The animals undergo left thoracotomy, and the left hilum is occluded with a small metallic clamp. The occlusion is performed 20 minutes after Imatinib or vehicle administration. During clamping, the
tidal volume (TV) and respiratory rate (RR) are adjusted to 8 mL/kg and 80 breaths/min, respectively. After 90 minutes of ischemia, the clamp is removed and reperfusion is maintained for 120 minutes. During reperfusion, blood flow and ventilation are restored in the bilateral lung. In the sham group (n=6), the animals are heparinized, thoracotomized, and ventilated for 210 minutes.

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REFERENCES


