Midostaurin

Cat. No.: HY-10230
CAS No.: 120685-11-2
Molecular Formula: C₃₅H₃₀N₄O₄
Molecular Weight: 570.64
Target: PKC
Pathway: Epigenetics; TGF-beta/Smad
Storage: Powder
-20°C  3 years
4°C    2 years
In solvent
-80°C  6 months
-20°C  1 month

SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 50 mg/mL (87.62 mM)
H₂O : < 0.1 mg/mL (insoluble)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>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>1.7524 mL</td>
<td>8.7621 mL</td>
<td>17.5242 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3505 mL</td>
<td>1.7524 mL</td>
<td>3.5048 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1752 mL</td>
<td>0.8762 mL</td>
<td>1.7524 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 >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.65 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.08 mg/mL (3.65 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description
Midostaurin (PKC412; CGP 41251) is a multi-targeted protein kinase inhibitor which inhibits PKCα/β/γ, Syk, Flk-1, Akt, PKA, c-Kit, c-Fgr, c-Src, FLT3, PDGFβ and VEGFR1/2 with IC₅₀ ranging from 16-500 nM.

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>nPKC-η</th>
<th>cPKC-α</th>
<th>cPKC-γ</th>
<th>cPKC-β1</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 nM (IC₅₀)</td>
<td>22 nM (IC₅₀)</td>
<td>24 nM (IC₅₀)</td>
<td>30 nM (IC₅₀)</td>
<td></td>
</tr>
<tr>
<td>cPKC-β2</td>
<td>nPKC-δ</td>
<td>nPKC-ε</td>
<td>aPKC-ζ</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>IC_{50}</td>
<td>Protein</td>
<td>IC_{50}</td>
<td>Protein</td>
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<td>--------------------</td>
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<tr>
<td>PPK</td>
<td>38 nM</td>
<td>KDR</td>
<td>86 nM</td>
<td>c-Syk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Protein kinase A</td>
<td>570 nM</td>
<td>c-Fgr</td>
<td>790 nM</td>
<td>c-Src</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>EGF-R</td>
<td>1100 nM</td>
<td>Myosin-light chain kinase</td>
<td>1900 nM</td>
<td>Flk-1</td>
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<tr>
<td></td>
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<tr>
<td>P70S6 kinase</td>
<td>5000 nM</td>
<td>CSK</td>
<td>8000 nM</td>
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</table>

**In Vitro**

Midostaurin (PKC412) shows a broad antiproliferative activity against various tumor and normal cell lines in vitro, and is able to reverse the Pgp-mediated multidrug resistance of tumor cells in vitro. Exposure of cells to Midostaurin (PKC412) results in a dose-dependent increase in the G2/M phase of the cell cycle concomitant with increased polyploidy, apoptosis and enhanced sensitivity to ionizing radiation[1]. Midostaurin (PKC412) induces substantial inhibition of KIT-, Lyn-, and STAT5 activity, but does not suppress Btk in HMC-1 cells and primary neoplastic mast cells[2]. Midostaurin (PKC412) inhibits EN fusion tyrosine kinase in hematopoietic Ba/F3 cells. Midostaurin (PKC412) significantly inhibits EN phosphorylation in M0-91 and IMS-M2 cells in a dose-dependent manner[3].

**In Vivo**

Midostaurin (PKC412) strongly inhibits retinal neovascularization as well as laser-induced choroidal neovascularization in murine models[1]. Midostaurin (PKC412) (25 mg/kg, i.p.) protects mouse livers of the K18 Arg90Cys-overexpressing transgenic mice from Fas-induced apoptosis[4].

**PROTOCOL**

**Cell Assay [3]**

Proliferation is determined by trypan blue dye exclusion test. Cells in suspension are seeded in six-well plates at a density of 1×10^5 cells/mL in the presence of different concentrations of PKC412 for 3 days. In control wells, DMSO instead of Midostaurin (PKC412) is added. After the treatment, 10 μL of the cell suspension is mixed with 10 μL of 0.4% trypan blue, and alive cells are counted manually using a hemacytometer. Results are calculated as the percentage of the values measured when cells are grown in the absence of the reagent. All experiments are performed in triplicate[3].

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

**Animal Administration [4]**

K8-deficient, K18-deficient, and human K18 R90C-overexpressing mice with age of 6-8 weeks are used in the assay. Age and sex matched mice are treated with Midostaurin (25 mg/kg), daily for 4 d or with an equal volume of DMSO as vehicle (both administered intraperitoneally). On day 5 post-treatment, apoptosis is induced by intraperitoneal injection of Fas ligand (Fas-L) (0.15 μg/g body weight). Mice are fasted overnight before Fas Ab injection, and 18 mice are used per DMSO or Midostaurin (PKC412) group for the Fas-treated mice while 6 mice are used per DMSO or Midostaurin (PKC412) group for the control non-Fas-treated mice. Mice are sacrificed by CO₂ inhalation 6 h after Fas Ab injection. Blood is collected by intracardiac puncture, and livers are harvested for hematoxylin and eosin (HE) staining (after fixation in 10% formalin) or frozen in optimum cutting temperature compound for immunofluorescence staining[4].

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REFERENCES


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