G-5555

Cat. No.: HY-19635
CAS No.: 1648863-90-4
Molecular Formula: C₂₅H₂₅ClN₆O₃
Molecular Weight: 492.96
Target: PAK
Pathway: Cell Cycle/DNA Damage; Cytoskeleton
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: ≥ 27 mg/mL (54.77 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Mass</th>
<th>Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td></td>
<td></td>
<td>2.0286 mL</td>
<td>10.1428 mL</td>
<td>20.2856 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td></td>
<td></td>
<td>0.4057 mL</td>
<td>2.0286 mL</td>
<td>4.0571 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td></td>
<td></td>
<td>0.2029 mL</td>
<td>1.0143 mL</td>
<td>2.0286 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 (5.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.07 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
G-5555 is a potent p21-activated kinase 1 (PAK1) inhibitor with Ki of 3.7 nM and 11 nM for PAK1 and PAK2, respectively.

IC₅₀ & Target

<table>
<thead>
<tr>
<th>IC₅₀ &amp; Target</th>
<th>PAK1</th>
<th>PAK2</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7 nM (Ki)</td>
<td></td>
<td></td>
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<tr>
<td>11 nM (Ki)</td>
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</tr>
</tbody>
</table>

In Vitro
G-5555 is a potent PAK1 inhibitor with a Ki of 3.7 nM. G-5555 shows excellent kinase selectivity and inhibits only eight out of
the 235 kinases tested other than PAK1 with inhibition >70%: PAK2, PAK3, KHS1, Lck, MST3, MST4, SIK2, and YSK1. The IC_{50}s of G-5555 against SIK2, PAK2, KHS1, MST4, YSK1, MST3 and Lck are 9, 11, 10, 20, 34, 43, 52 nM, respectively. In general, G-5555 demonstrates high selectivity for the group I PAKs. There is negligible activity for G-5555 against the hERG channel with IC_{50} more than 10 μM in a patch clamp assay\[1\]. G-5555 potently inhibits PAK2, with a K_i of 11 nM. In an array of 23 breast cancer cell lines, G-5555 has significantly greater growth inhibitory activity in cell lines that are PAK-amplified compared to non-amplified lines\[2\].

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

**In Vivo**
G-5555 exhibits low blood clearance and an acceptable half-life. Good oral exposure (AUC = 30 μM•h) and high oral bioavailability (F = 80%) are achieved\[1\]. In an H292 non-small cell lung cancer (NSCLC) xenograft study in mice, G-5555 inhibits phosphorylation of the PAK1/2 downstream substrate mitogen-activated protein kinase 1 (MEK1) S298 and, when administered at an oral dose of 25 mg/kg b.i.d., imparts 60% tumor growth inhibition in this model\[13\] and a PAK1 amplified breast cancer xenograft model, MDAMB-175\[2\].

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**PROTOCOL**

**Kinase Assay**\[1\]
The 10 µL assay mixtures contain 50 mM HEPES (pH 7.5), 0.01% Brij-35, 10 mM MgCl\(_2\), 1 mM EGTA, 2 µM FRET peptide substrate, and PAK enzyme (20 pM PAK1; 50 pM PAK2; 90 pM PAK4). Incubations are carried out at 22°C in black polypropylene 384-well plates. Prior to the assay, enzyme, FRET peptide substrate and serially diluted test compounds (G-5555, etc.) are preincubated together in assay buffer (7.5 µL) for 10 minutes, and the assay is initiated by the addition of 2.5 µL assay buffer containing 4× ATP (160 μM PAK1; 480 μM PAK2; 16 μM PAK4). Following the 60-minute incubation, the assay mixtures are quenched by the addition of development reagent, and 1 hour later the emissions of Coumarin (445 nm) and Fluorescein (520 nm) are determined after excitation at 400 nm\[1\].

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**Animal Administration**\[1\]
Three mice in each of the two groups are administered 25 mg/kg oral suspension dose twice, with the second dose given 6 hours after the first dose. The dose volumes are 5 mL/kg for the IV group and 10 mL/kg for the PO groups. Following administration of G-5555, 15 µL of blood is collected at each time point are stored at -70 to -80°C until analysis\[1\].

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**REFERENCES**


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