Ravoxertinib

Cat. No.: HY-15947  
CAS No.: 1453848-26-4  
Molecular Formula: C₂₁H₁₈ClFN₆O₂  
Molecular Weight: 440.86  
Target: ERK  
Pathway: MAPK/ERK Pathway; Stem Cell/Wnt  
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: ≥ 35 mg/mL (79.39 mM)  
* "≥" means soluble, but saturation unknown.

<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>2.2683 mL</td>
<td>11.3415 mL</td>
<td>22.6829 mL</td>
</tr>
<tr>
<td></td>
<td>5 mM</td>
<td>0.4537 mL</td>
<td>2.2683 mL</td>
<td>4.5366 mL</td>
</tr>
<tr>
<td></td>
<td>10 mM</td>
<td>0.2268 mL</td>
<td>1.1341 mL</td>
<td>2.2683 mL</td>
</tr>
</tbody>
</table>

In Vivo  
1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline  
Solubility: ≥ 1.67 mg/mL (3.79 mM); Clear solution

2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)  
Solubility: ≥ 1.67 mg/mL (3.79 mM); Clear solution

3. Add each solvent one by one: 10% DMSO >> 90% corn oil  
Solubility: ≥ 1.67 mg/mL (3.79 mM); Clear solution

BIOLOGICAL ACTIVITY

Description  
Ravoxertinib (GDC-0994) is an orally bioavailable ERK kinase inhibitor with an IC₅₀ of 6.1 nM and 3.1 nM for ERK1 and ERK2, respectively.

IC₅₀ & Target  
<table>
<thead>
<tr>
<th>ERK2</th>
<th>ERK1</th>
<th>p-RSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 nM (IC₅₀)</td>
<td>6.1 nM (IC₅₀)</td>
<td>12 nM (IC₅₀)</td>
</tr>
</tbody>
</table>
In Vitro

Ravoxertinib (GDC-0994) also inhibits p90RSK with an IC$_{50}$ of 12 nM$^1$. Ravoxertinib (GDC-0994) is highly selective for ERK1 and ERK2, with biochemical potency of 1.1 nM and 0.3 nM, respectively$^2$.

In Vivo

In CD-1 mice, a 10 mg/kg oral dose of Ravoxertinib (GDC-0994) is sufficient to achieve the desired target coverage for at least 8 h$^1$. Daily, oral dosing of Ravoxertinib results in significant single-agent activity in multiple in vivo cancer models, including KRAS-mutant and BRAF-mutant human xenograft tumors in mice$^2$.

PROTOCOL

Animal Administration$^1$

Mice$^1$

PK/PD data for Ravoxertinib (GDC-0994) in the HCT116 mouse xenograft model. HCT116 tumors are established in nude mice to a tumor volume of 400-600 mm$^3$. Mice are treated with a single oral dose of 22 at 15, 30, or 100 mg/kg versus vehicle control alone (40% PEG400/60% (10% HPβCD)) follow by tumor and plasma collection at 2, 8, 16, and 24 h postdose. Tumor levels of phosphorylated p90RSK (pRSK) relative total p90RSK (tRSK) are measured by quantitative Western blot and are normalized to vehicle control at 2 h postdose (set to 100%). Plasma and tumor concentrations are measured by LC−MS.

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

CUSTOMER VALIDATION

- Cell. 2018 Sep 20;175(1):186-199.e19.
- ACS Comb Sci. 2019 Nov 5.

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REFERENCES

$^1$. Blake JF, et al. Discovery of (S)-1-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1H-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1H)-one (GDC-0994), an Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) Inhibitor in Early Clinical Development.
