GDC-0084

Cat. No.: HY-19962
CAS No.: 1382979-44-3
Molecular Formula: C₁₈H₂₂N₈O₂
Molecular Weight: 382.42
Target: PI3K; mTOR
Pathway: PI3K/Akt/mTOR
Storage:
- Powder: -20°C 3 years, 4°C 2 years, In solvent -80°C 6 months, -20°C 1 month

SOLVENT & SOLUBILITY

In Vitro

<table>
<thead>
<tr>
<th>Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.6149 mL</td>
<td>13.0746 mL</td>
<td>26.1493 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.5230 mL</td>
<td>2.6149 mL</td>
<td>5.2299 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2615 mL</td>
<td>1.3075 mL</td>
<td>2.6149 mL</td>
</tr>
</tbody>
</table>

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

BIOLOGICAL ACTIVITY

Description
GDC-0084 is a brain penetrant inhibitor of PI3K and mTOR, with $K_i$s of 2 nM, 46 nM, 3 nM, 10 nM and 70 nM for PI3K α, PI3Kβ, PI3Kδ, PI3Kγ and mTOR, respectively.

IC₅₀ & Target

<table>
<thead>
<tr>
<th>Target</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3Kα</td>
<td>2 nM</td>
</tr>
<tr>
<td>PI3Kδ</td>
<td>3 nM</td>
</tr>
<tr>
<td>PI3Kγ</td>
<td>10 nM</td>
</tr>
<tr>
<td>PI3Kβ</td>
<td>46 nM</td>
</tr>
<tr>
<td>mTOR</td>
<td>70 nM</td>
</tr>
</tbody>
</table>

In Vitro
GDC-0084 (Compound 16) maintains inhibition of each of the Class I PI3K isoforms but with more potent inhibition of mTOR. GDC-0084 is also tested in five different GBM cell lines and is found to have antiproliferative EC₅₀s ranging from 0.3 to 1.1 μM[^1].

In Vivo
After a 25 mg/kg dose of GDC-0084 (Compound 16) administered orally, pAKT in normal mouse brain tissue is
significantly inhibited at 1 and 6 h postdose. The potent inhibition of pAKT at both time points in this study demonstrates that GDC-0084 inhibits its target behind a fully intact BBB. In addition to the pharmacodynamic effect in normal brain tissue, GDC-0084 is studied in a subcutaneous U87 tumor xenograft model of glioblastoma in mice. In this study, GDC-0084 achieves significant and dose-dependent tumor growth inhibition. Tumor growth inhibition is first observed at a 2.2 mg/kg dose level. Higher doses led to greater tumor growth inhibition, including tumor regressions at the 17.9 mg/kg dose level. Each of these doses is well tolerated for the duration of the study[1].

**PROTOCOL**

**Kinase Assay**[1]

Enzymatic activity of PI3Kα is measured using a fluorescence polarization assay that monitors formation of the product 3,4,5-inositoltriphosphate molecule (PIP3) as it competes with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidyl inositide-3-phosphate product results in a decrease in fluorescence polarization signal as the labeled fluorophore is displaced from the GRP-1 protein binding site. PI3Kα is expressed and purified as heterodimeric recombinant protein. PI3Kα is assayed under initial rate conditions in the presence of 10 mM Tris (pH 7.5), 25 uM ATP, 9.75 uM PIP2, 5% glycerol, 4 mM MgCl2, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, 2% (v/v) DMSO at a 60 ng/mL concentration of PI3Kα. After assay for 30 min at 25°C, reactions are terminated with a final concentration of 9 mM EDTA, 4.5 nM TAMRA-PIP3, and 4.2 ug/mL GRP-1 detector protein before reading fluorescence polarization on an Envision plate reader. IC50s are calculated from the fit of the dose-response curves to a 4-parameter equation. Apparent K_i's, where measured, are determined at a fixed concentration of ATP near the measured Km for ATP for PI3Kα, and are calculated by fitting of the dose-response curves to an equation for tightbinding competitive inhibition[1].

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

**Animal Administration**[1]

PTEN-null U-87 MG/M human glioblastoma cancer cells are cultured in RPMI 1640 media plus 1% L-glutamine with 10% fetal bovine serum. Cells in log-phase growth are harvested and resuspended in HBSS:Matrigel (1:1, v:v) for injection into female NCr nude mice aged 20 weeks. Animals receive five million cells subcutaneously in the right lateral thorax in 0.1 mL. Mice bearing established tumors in the range of 200-500 mm³ are separated into groups of equally sized tumors (n=6-7/group) to receive escalating doses of GDC-0084 (Compound 16). GDC-0084 is formulated once weekly in 0.5% methylcellulose and 0.2% Tween-80 at concentrations needed for target doses in a volume of 0.2 mL. All formulations are stored in a refrigerator and brought to room temperature and mixed well by vortex before oral administration by gavage once daily for 23 days. Tumor volumes are calculated. Changes in body weights are reported as a percentage change from the starting weight.

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

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**REFERENCES**
