LXH254

Cat. No.: HY-112089
CAS No.: 1800398-38-2
Molecular Formula: C₂₅H₂₅F₃N₄O₄
Molecular Weight: 502.49
Target: Raf
Pathway: MAPK/ERK Pathway
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: 100 mg/mL (199.01 mM; Need ultrasonic)

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mM</td>
<td>1.9901 mL</td>
<td>9.9504 mL</td>
<td>19.9009 mL</td>
</tr>
<tr>
<td></td>
<td>5 mM</td>
<td>0.3980 mL</td>
<td>1.9901 mL</td>
<td>3.9802 mL</td>
</tr>
<tr>
<td></td>
<td>10 mM</td>
<td>0.1990 mL</td>
<td>0.9950 mL</td>
<td>1.9901 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 (4.98 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.98 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.98 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: 2.5 mg/mL (4.98 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description
LXH254 is a potent B/C RAF inhibitor extracted from patent WO2018051306A1, Compound A.

IC₅₀ & Target
<table>
<thead>
<tr>
<th>Braf</th>
<th>c-Raf</th>
</tr>
</thead>
</table>

In Vitro
LXH254 (Compound A) is an adenosine triphosphate (ATP)-competitive inhibitor of BRAF (also referred to herein as b-RAF or
b-Raf) and CRAF (also referred to herein as c-RAF or c-Raf) protein kinases. Throughout the present disclosure, LXH254 is also referred to as a c-RAF (or CRAF) inhibitor or a C-RAF/c-Raf kinase inhibitor. In cell-based assays, LXH254 has demonstrated anti-proliferative activity in cell lines that contain a variety of mutations that activate MAPK signaling. Moreover, LXH254 is a Type 2 ATP-competitive inhibitor of both B-Raf and C-Raf that keeps the kinase pocket in an inactive conformation, thereby reducing the paradoxical activation seen with many B-Raf inhibitors, and blocking mutant RAS-driven signaling and cell proliferation[1].

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

**In Vivo**

Treatment with LXH254 (Compound A) generates tumor regression in several KRAS-mutant models including the NSCLC-derived Calu-6 (KRAS Q61K) and NCI-H358 (KRAS G12C). LXH254 exhibits efficacy in numerous MAPK-driven human cancer cell lines and in xenograft tumors representing model tumors harboring human lesions in KRAS, NRAS and BRAF oncogenes [1].

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**PROTOCOL**

**Animal Administration**[1]

Mice[1]

SCID beige female tumor-bearing NCI-H358 mice, n=8 per group, are randomized into 3 groups 14 days post tumor cell inoculation with an average tumor volume range of 259.44–262.47 mm³. Animals are administered an oral dose of either vehicle, LXH254 at 30mg/kg or 200mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment.

Female nude tumor bearing Calu6 mice, n=6 per group are randomized into treatment groups on day 17 following tumor implantation, when the average tumor volume is 180 mm³. Treatments with LXH254 are initiated on Day 17 and continued for 16 days. Dosing volume is 10 mL/kg. Tumor volumes are collected at the time of randomization and twice weekly thereafter for the study duration.

Nude female mice tumor bearing NCI-H358, n=8 per group, are randomized into 2 groups with an average tumor volume range of 275.74 mm³. Animals are administered an oral dose of either vehicle or LXH254 at 100 mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment[1].

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

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**REFERENCES**
