MRX-2843

Cat. No.: HY-101549
CAS No.: 1429882-07-4
Molecular Formula: C_{29}H_{40}N_{6}O
Molecular Weight: 488.67
Target: FLT3
Pathway: Protein Tyrosine Kinase/RTK
Storage: Powder
-20°C 3 years
4°C 2 years
In solvent
-80°C 2 years
-20°C 1 year

SOLVENT & SOLUBILITY

In Vitro
DMSO: 20 mg/mL (40.93 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Mass</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.0464 mL</td>
<td>10.2319 mL</td>
<td>20.4637 mL</td>
<td></td>
</tr>
<tr>
<td>5 mM</td>
<td>0.4093 mL</td>
<td>2.0464 mL</td>
<td>4.0927 mL</td>
<td></td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2046 mL</td>
<td>1.0232 mL</td>
<td>2.0464 mL</td>
<td></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 (4.26 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2 mg/mL (4.09 mM); Clear solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2 mg/mL (4.09 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description
MRX-2843 (UNC2371) is an orally active, ATP-competitive dual MERTK and FLT3 tyrosine kinases inhibitor (TKI) with enzymatic IC_{50}s of 1.3 nM for MERTK and 0.64 nM for FLT3, respectively\(^1\).

IC_{50} & Target
MERTK, FLT3\(^1\)

In Vitro
In the Kasumi-1 cell line, treatment with MRX-2843 results in dose-dependent inhibition of MERTK phosphorylation. Decreased phosphorylation is evident at concentrations as low as 10 nM, with near-complete abrogation of MERTK
activation at 100 to 300 nM. Similarly, treatment of Kasumi-1 cells with MRX-2843 mediates inhibition of downstream signaling through pathways important for tumor cell survival and proliferation. MRX-2843 treatment results in a decrease in relative cell numbers, with an IC\(_{50}\) of 143.5±14.1 nM, indicating that MRX-2843 significantly inhibits tumor cell proliferation and/or survival. Similarly, there are 34.1%±5.6% and 67.1%±2.7% apoptotic and dead cells in NOMO-1 cultures treated with 150 nM or 300 nM MRX-2843, respectively, compare with 6.8%±0.7% in vehicle-treated cultures (P<0.001). Treatment with 50 nM and 100 nM MRX-2843 results in 62.3%±6.4% and 84.1%±7.8% inhibition of colony formation, respectively, in Kasumi-1 cultures (P<0.02). Similarly, in NOMO-1 cultures, colony formation is inhibited by 54.8%±18.1% in response to treatment with 100 nM MRX-2843 (P<0.001). In MOLM-14 cells, treatment with MRX-2843 inhibits phosphorylation of FLT3 and downstream signaling through STAT5, ERK1/2, and AKT. Activation of FLT3 and its signaling pathways is almost completely abrogated by treatment with 50 nM MRX-2843, indicating somewhat higher cellular potency against FLT3 relative to MERTK \[1\].

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

In Vivo

MRX-2843 is 78% orally bioavailable at a dose of 3 mg/kg with a C\(_{\text{max}}\) of 1.3 μM and a t\(_{1/2}\) of 4.4 hours. In MOLM-14 parental xenografts, both quizartinib and MRX-2843 increase median survival compare with that of vehicle-treated mice (172.5 days versus 40 days and 121 days versus 36 days, respectively, P<0.001). In this model, quizartinib is more effective than MRX-2843 (P<0.005), although higher doses of MRX-2843 are not evaluated. In MOLM-14:D835Y xenografts, quizartinib prolongs survival compare with that of vehicle-treated mice, but the effect is minimal (median survival 45 days vs. 36 days, P<0.001). In MOLM-14:F691L xenografts, treatment with MRX-2843 prolongs survival by almost 2-fold in NSG and NSGS mice (median survival 87 vs. 44.5 days and 87 vs. 48 days, respectively, P<0.005). Increased survival is observed in response to treatment with MRX-2843 versus quizartinib, but the difference is only significant in NSG mice\[1\].

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REFERENCES


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