TMC353121

Cat. No.: HY-11097
CAS No.: 857066-90-1
Molecular Formula: C₃₂H₄₂N₆O₃
Molecular Weight: 558.71
Target: RSV
Pathway: Anti-infection
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 : 50 mg/mL (89.49 mM; Need ultrasonic)
H₂O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>1.7898 mL</td>
<td>8.9492 mL</td>
<td>17.8984 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3580 mL</td>
<td>1.7898 mL</td>
<td>3.5797 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1790 mL</td>
<td>0.8949 mL</td>
<td>1.7898 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 (4.47 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.47 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.47 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
TMC353121 is a potent respiratory syncytial virus (RSV) fusion inhibitor with pEC₅₀ of 9.9.

IC₅₀ & Target
pEC₅₀: 9.9 (RSV)¹

In Vitro
TMC353121 shows activity against groups A and B RSV and against a panel of clinical isolates with equal potency¹.
TMC353121 is a potent RSV fusion inhibitor in vitro. TMC353121 is active against wild-type RSV (strain LO), with a 50%
Effective concentration (EC\textsubscript{50}) of 0.07 ng/mL in HeLaM cells\textsuperscript{[2]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

### In Vivo

After i.v. bolus administration of a single dose of 10 mg/kg to Sprague-Dawley rats, the plasma drug concentration-time profile of TMC353121 exhibits multicompartamental pharmacokinetics. Mean plasma drug concentrations decrease rapidly during the first hours after dosing and then more slowly, with a half-life of about 12 h, as determined for the last part of the curve between 8 and 24 h postdose. TMC353121 is rapidly eliminated from plasma (CL=8.6 liters/h/kg) and extensively distributed (V\textsubscript{ss}=55 liters/kg)\textsuperscript{[2]}. TMC353121 is administered once, i.v. at 2.5 mg/kg or at 0.25 mg/kg. Drug levels are determined in lung tissue, serum, and BAL fluid at different time points. TMC353121 followed multicompartiment pharmacokinetics, with a fast decay in serum within the first hour after i.v. injection, followed by a slower decay. The drug is eliminated quickly from the blood resulting in very low blood levels after 24 h. Lung concentrations are much higher than serum concentrations and in BAL fluid the drug is just above the limit of detection at 8 h after injection. Very low drug levels can still be detected in the lungs 5 days after treatment\textsuperscript{[3]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

### PROTOCOL

#### Animal Administration \textsuperscript{[2][3]}

**Rats**\textsuperscript{[2]}

Sprague-Dawley and cotton rats are given a single-bolus dose of 10 mg/kg TMC353121 intravenously (i.v.). Blood samples are taken from the orbital venous plexus of three Sprague-Dawley rats at 15 min and 1, 8, and 24 h postdose and from six Sprague-Dawley rats and six cotton rats at 3 h postdose. Blood samples are centrifuged at 1,500× g for 10 min, and plasma is separated and frozen until bioanalysis. After blood sampling, the rats are exsanguinated from the vena femoralis under isoflurane-oxygen anesthesia. Then they are euthanized by CO\textsubscript{2} asphyxiation, and the lungs are subjected to lavage once via a tracheal cannula with phosphate-buffered saline (PBS) containing 2% bovine serum albumin (BSA) at room temperature at a volume of 5 mL per Sprague-Dawley rat or 2.5 mL per cotton rat. After gentle injection of the lavage fluid into the lungs, the fluid is withdrawn for collection of the bronchoalveolar lavage fluid (BALF) and the lungs are dissected. BALF is collected in order to assess TMC353121 concentrations in the lung epithelial lining fluid (ELF) after correction for the dilution with lavage fluid. A single lavage with a short dwelling time is applied as previously recommended for better accuracy of the determination of ELF dilution. BSA is added to the lavage fluid in order to prevent the adsorption of TMC353121 to syringes or other containers. The BALF is centrifuged at 300× g for 10 min, and the supernatant is separated. BALF supernatant and lung tissue samples are then frozen until bioanalysis. BALF supernatant is referred as BALF throughout this paper.

**Mice**\textsuperscript{[3]}

Inbred 8- to 12-week-old female BALB/c mice are used. TMC353121 is administered intravenously in saline at doses of 0.25-10 mg/kg, and at various times in relation to the RSV infection. Mice are infected with 2×10\textsuperscript{6} plaque-forming unit (PFU) of plaque-purified human strain RSV A2 (100 μL intranasally). Individual body weight is used to monitor animal health and response to infection, and is recorded daily.

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### CUSTOMER VALIDATION


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### REFERENCES

[1]. Bonfanti JF, et al. Selection of a respiratory syncytial virus fusion inhibitor clinical candidate. 2. Discovery of a morpholinopropylaminobenzimidazole derivative


Caution: Product has not been fully validated for medical applications. For research use only.

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