Background: TP-271 is a novel, fully synthetic fluorocycline antibiotic in preclinical development for IV/IVN oral treatment of respiratory infections caused by susceptible and multidrug-resistant (MDR) public health and biothreat pathogens.

Method: In vitro susceptibility testing against recent isolates was done according to CLSI guidelines. Time-kill-specific resistance and ESBL genes were detected by PCR.

Results: TP-271 was potent against Streptococcus spp., Staphylococcus aureus, Haemophilus influenzae, and Moraxella catharralis isolates and Gram-positive pathogens vancomycin-resistant Enterococcus faecium and Enterococcus faecalis (see Table). The MIC₅₀ values of TP-271 against ESBL-Enterobacter cloacae (n=34) and Klebsiella pneumoniae (n=46) were 0.51/1 and 0.25/1 μg/mL, respectively. Against other Enterobacteriaceae, the MIC₅₀ and MIC₉₀ values of TP-271 were 0.25 - 4 and 1-8 μg/mL, respectively. The MIC₅₀ values against Acinetobacter baumannii (n=34), Acinetobacter lactosolestes (n=2), and Shewanella pyocyanus (n=1) were 0.5, 0.063, and 0.25 μg/mL, respectively. TP-271 was active against biothreat pathogens Yersinia pestis (n=30), Bacillus anthracis (n=30), Francisella tularensis (n=27), Burkholderia mallei (n=20) and Burkholderia pseudomallei (n=20) were ≤0.016/0.031, ≤0.008/0.063, ≤0.016/0.031, and ≤0.016/0.031 μg/mL, respectively.

Conclusions: TP-271 is active against community-acquired respiratory and biothreat pathogens, and problematic multidrug-resistant (MDR) pathogens.

Results

Table 1. Determination of MIC₅₀ and MIC₉₀ values for biothreat pathogens

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC₅₀</th>
<th>MIC₉₀</th>
<th>MIC₅₀</th>
<th>MIC₉₀</th>
<th>MIC₅₀</th>
<th>MIC₉₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkholderia mallei</td>
<td>0.25</td>
<td>0.063</td>
<td>0.25</td>
<td>0.063</td>
<td>0.25</td>
<td>0.063</td>
</tr>
<tr>
<td>Burkholderia pseudomallei</td>
<td>0.063</td>
<td>0.031</td>
<td>0.063</td>
<td>0.031</td>
<td>0.063</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Sensitivity testing. All minimal inhibitory concentration (MIC) assays were performed per CLSI guidelines [1]. Testing of public health pathogens was performed at Tetraphase Pharmaceuticals, Inc. and International Health Management Associates (IHMA) using recent clinical isolates obtained from Eurofins Medion and IHMA. Testing of biothreat agents was performed at United States Army Medical Research Institute for Infectious Diseases (USAMRID). Genotypic characterization of ESBL-producing isolates was done by standard PCR methodology and sequence confirmation.

Conclusions

TP-271, a novel fully synthetic tetrasaccharide, showed high potency against key MDR public health respiratory pathogens, including S. pneumoniae, MRSA, S. pyogenes, H. influenzae and M. catarrhalis. TP-271 also exhibited potent activity against five important biothreat agents: Y. pestis, B. anthracis, F. tularensis, B. mallei, and B. pseudomallei. TP-271 has shown potential for the treatment of biothreat infections such as Lassa fever, Nipah virus, and SARS-CoV-2. The broad spectrum potency of TP-271 is demonstrated by good activity against difficult-to-treat MDR Gram-negatives and Gram-positive pathogens including VRE.

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