Activity of BAY 73-7388, a novel aminomethylcycline, and other novel antibiotic classes against resistant bacteria in vitro


Boston, USA

Objectives: The emergence of antibiotic resistance among Gram-positive pathogens has impacted the clinical management of these infections. Paratek Pharmaceuticals initiated a programme to apply medicinal chemistry to the core structure of tetracycline (TET) with the goal of creating novel classes of proprietary antibiotics that would (a) be unaffected by the known TET resistance mechanisms and (b) retain the safety and tolerability profile of the TET family. Since there is no cross-resistance between the TETs and other antibiotics, such new agents would be expected to be active against isolates resistant to all other currently available classes. The aim of the programme was to synthesise new agents active against Gram-positive, common Gram-negative, atypical and anaerobic bacteria.

Methods: A series of 7-position and 7,9-position derivatives of sancycline were synthesised and tested for activity in vitro against MRSA, VRE, Enterococcus faecalis and Streptococcus pneumoniae by microdilution. The presence of TET-resistance determinants was assessed by PCR and confirmed by resistance to currently available TETs.

Results: A number of 7-dimethylamino-9-aminomethylcyclines (AMC) and 7-aryl or heteroaryl sancyclines with potent activity in vitro (MIC range less than or equal to 0.06–2.0 mg/L) were identified. Both novel series were more potent against one or more of the resistant strains than currently available antibiotics tested (MIC range 16–64 mg/L). The AMC derivatives were active against bacteria resistant to TET by both efflux and ribosome-protection mechanisms.

Conclusions: This study identified the AMCs as a novel class of antibiotics evolved from TET that exhibit potent activity in vitro against TET-resistant bacteria, including Gram-positive bacteria resistant to currently available antibiotics. One agent of this class, BAY 73-7388 (discovered by Paratek Pharmaceuticals, Inc., Boston, MA, and designated PTK 0796) has been chosen for development.
Activity of BAY 73-7388, a Novel Aminomethylcycline, and Other Novel Antibiotic Classes against Resistant Bacteria in Vitro

Paratek Pharmaceuticals, Inc., Boston, MA.

Abstract

Objectives: The emergence of antibiotic resistance among gram-positive pathogens has impacted the clinical management of these infections. Paratek Pharmaceuticals initiated a program to apply medicinal chemistry to the core structure of tetracycline (TET) with the goal of creating novel classes of proprietary antibiotics that would (a) be unaffected by the known TET resistance mechanisms and (b) retain the safety and tolerability profile of the TET family. Since there is no cross-resistance between the TET and other antibiotics, such new agents would be expected to be active against isolates resistant to all other currently available classes. The aim of the program was to synthesize new agents active against gram-positive, common gram-negative, atypical, and anaerobic pathogens.

Methods:
A series of 7-position and 7,9-position derivatives of sancycline were synthesized and tested for activity in vitro against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), Enterococcus faecalis, and Streptococcus pneumoniae by microdilution. The presence of TET resistance determinants was assessed by polymerase chain reaction (PCR) and confirmed by resistance to currently available tetracyclines.

Results:
A number of 7-dimethylamino-9-aminomethylcyclines (AMC, 1) and 7-aryl and heteroaryl sancyclines (2) were synthesized as outlined in Scheme 1. MIC values were obtained for each new analog against a broad range of tetracycline-resistant and susceptible strains including gram-positive and gram-negative isolates. The AMC derivatives were active against bacteria resistant to TET by both efflux and ribosome protection mechanisms.

Conclusions:
This study identified the AMCs as a novel class of antibiotics evolved from TET that exhibit potent activity against TET-resistant bacteria, including gram-positive bacteria resistant to currently available antibiotics. One agent of this class, BAY 73-7388 (discovered by Paratek Pharmaceuticals, Inc., Boston, MA, and designated PTK 0796) has been chosen for development.

Introduction

The emergence of antibiotic resistance among bacterial pathogens responsible for serious infections is impacting clinical management strategies, and there is an urgent need for novel classes of antibiotics not affected by resistance to current agents. A number of approaches have been developed in the search for new classes of antibiotics, including applying novel chemistry techniques to known core structures; the tetracycline class of natural products has been used for more than 50 years as standard broad-spectrum antibiotics. The mechanism of action of tetracyclines is distinct from that of other classes of antibiotics, meaning that they do not exhibit cross-resistance. In order to take advantage of the low toxicity and broad spectrum of activity typically displayed by the tetracyclines, Paratek Pharmaceuticals, Inc. has developed a medicinal chemistry approach to create new classes of antibiotics. The novel classes designed are active against the tetracycline resistance mechanisms of efflux and/or ribosome protection, and exhibit no cross-resistance to other classes of antibiotics.

Figure 1. Tetracycline structures.

Methods
- Novel 7-dimethylamino-9-aminomethylcyclines (AMC, 1) and 7-aryl and heteroaryl sancyclines (2) were synthesized as outlined in Scheme 1.

Results
- The novel AMC (BAY 73-7388, 1a-c) and 7-aryl and heteroaryl sancyclines (2a-d) were active in vitro against all resistant strains tested (MIC, 0.06-1 µg/mL) against one or more of the resistant strains than currently available antibiotics tested (MIC range, 16-64 µg/mL). The AMC derivatives were active against bacteria resistant to TET by both efflux and ribosome protection mechanisms.

Conclusions
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Scheme 1. Synthesis of novel classes of antibiotics (aminomethylcyclines and sancyclines)

Results
- The novel AMC (BAY 73-7388, 1a-c) and 7-aryl and heteroaryl sancyclines (2a-d) were active in vitro against all resistant strains tested (MIC, 0.06-1 µg/mL) against one or more of the resistant strains than currently available antibiotics tested (MIC range, 16-64 µg/mL). The AMC derivatives were active against bacteria resistant to TET by both efflux and ribosome protection mechanisms.

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References

Table 1. MIC values (µg/mL) for aminomethylcyclines (BAY 73-7388, 1a-c), 7-aryl and heteroaryl sancyclines (2a-d), and comparators against strains with known tetracycline resistance mechanisms (Tet K = efflux; Tet M = ribosome protection; Tet L = efflux). Values in RED indicate resistance.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC (µg/mL)</th>
<th>MIC (µg/mL)</th>
<th>MIC (µg/mL)</th>
<th>MIC (µg/mL)</th>
<th>MIC (µg/mL)</th>
</tr>
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<tr>
<td>AMC</td>
<td>0.06-1</td>
<td>0.06-1</td>
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<td>0.06-1</td>
<td>0.06-1</td>
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<tr>
<td>Comparator</td>
<td>16-64</td>
<td>16-64</td>
<td>16-64</td>
<td>16-64</td>
<td>16-64</td>
</tr>
</tbody>
</table>

Note: MIC values were obtained for each new analog against a broad range of tetracycline-resistant and susceptible strains including gram-positive and gram-negative isolates. The AMC derivatives were active against bacteria resistant to TET by both efflux and ribosome protection mechanisms.