Discovery of zosurabalpin

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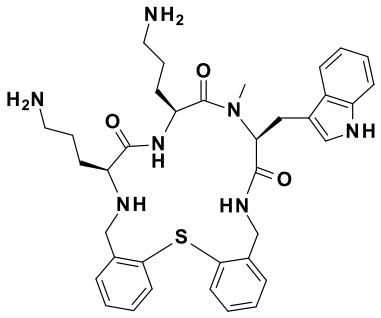
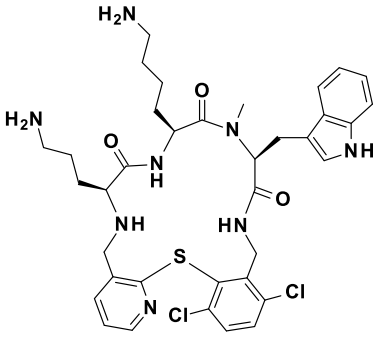
Drug resistance to all existing classes of antibiotics has been on the rise in various gram-negative bacteria for several decades, but we have seen very few new antibiotics in development with the potential to overcome this threat. Any new antibiotic class that has the ability to treat infections caused by difficult to treat bacteria such as carbapenem-resistant *Acinetobacter baumannii* (CRAB) would be a significant breakthrough. Zosurabalpin is the first representative of a structurally distinct compound class of antibiotics, which has many features that position it to be a medical breakthrough.

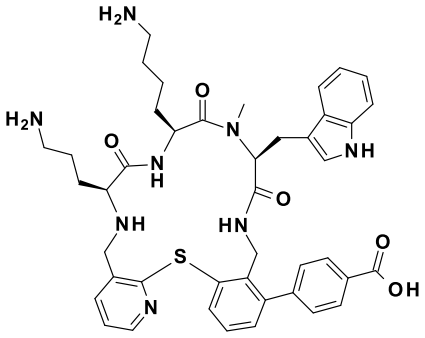
Phenotypic high-throughput screening of a library of tethered macrocyclic peptides (MCPs) identified RO7036668, which was selectively targeting *Acinetobacter baumannii*. Medicinal chemistry efforts rapidly resulted in RO7075573, which was able to cure bacterial infections in mice, where established antibiotics failed. However, RO7075573 suffered from poor intravenous tolerability and multi-organ toxicity in rats. The lead optimisation was guided by consideration of the antibiotic drug-like space and supported by a customised plasma compatibility assay, producing highly efficacious compounds with improved intravenous tolerability and no organ toxicity. The development compound zosurabalpin is currently in phase 1 clinical trials, and if approved it would become the first antibiotic of a new class in more than 50 years to be used against infections caused by gram-negative bacteria [1].



RO7036668



RO7075573



zosurabalpin

In the final chapter of the talk, the mechanism of action will be presented, which has been elucidated in a collaboration with Harvard University. By interacting with a protein target that is unique to gram-negative bacteria, zosurabalpin blocks the trafficking of lipopolysaccharide (LPS). Surprisingly, this new class of antibiotics binds both to the transport complex in the inner membrane, as well as the LPS itself, preventing its transport to the outer membrane [2].

[1] C. Zampaloni, P. Mattei, K. Bleicher et al., *Nature* **2024**, *625*, 566-571.
[2] K. S. Pahil, M. S. A. Gilman, V. Baidin et al., *Nature* **2024**, *625*, 572-577.

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