Discovery and process development of the new antibiotic zosurabalpin

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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. The first part of the talk will present its optimization from a phenotypic HTS hit. Zosurabalpin is a tethered macrocyclic peptide, currently in phase 1 clinical trials. It kills specifically Acinetobacter baumannii by blocking the trafficking of lipopolysaccharide, a protein target that is unique to gram-negative bacteria. [1,2]
In the second part, the current state of development of the manufacturing process of the drug substance will be discussed. A significant improvement of the output and robustness of the process was obtained, by simplifying operations and changing reaction conditions in two key steps of the process (the macrolactamization and the Suzuki coupling steps). Furthermore, replacing diethylamine with dimethylbarbituric acid in the cleavage of the protecting groups (step 4) allowed a 5-fold reduction in catalyst loading in that step, while also improving the purity profile of the intermediate, despite significantly lower loading of the reagent.

[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.