Identification, Optimization and Validation of a New Triaromatic Pleuromutilin Antibiotic Subclass

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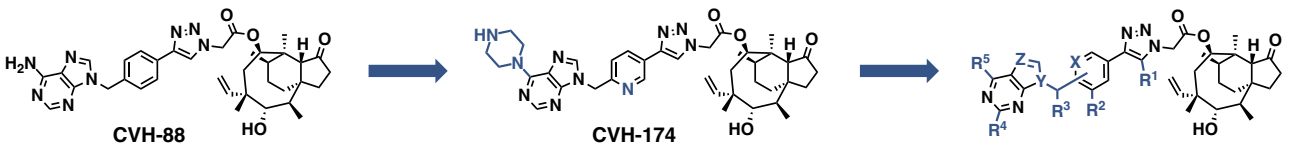
Semi-synthetic conjugation onto the natural product pleuromutilin is a very attractive foundation from which to build new antibiotics as it is a class with both high inherent levels of efficacy and importantly also slow resistance development.

In late 2020, we reported the discovery of a new pleuromutilin subclass, illustrated by **CVH-88**.[1] Since then, we sought to identify a lead based on this triaromatic scaffold – a successful quest which we recently reported.[2] In this presentation, the identification of our current lead **CVH-174**[2] will be outlined, along with the extensive evaluation and validation of its drug-like properties and ADMET performance as well as benchmark against lefamulin (Nabriva Therapeutics),[3] the only systemically approved pleuromutilin. This evaluation included solubility, P-gp affinity, Caco-2 cell permeability, plasma protein binding, hERG inhibition, cytotoxicity, metabolism in microsomes and CYP3A4, resistance-induction and time-kill kinetics. *In vivo* efficacy of **CVH-174** furthermore showed rapid reduction of blood bacteriaemia in systemically infected mice (*Staphylococcus aureus*). The intravenous pharmacokinetic profile of **CVH-174** proved satisfactory in both mice and pigs, however oral bioavailability was limited, likely due to insufficient intestinal solubility of the formulation.

In our continuous quest to discover potential fast-followers with further enhanced drug-like properties, we have identified several new linkers that meet our well-established pharmacophore. We are furthermore also taking advantage of an advanced formulation technology to improve the absorption of our most promising candidates.

Through our comprehensive studies, our triaromatic pleuromutilin class has emerged as a highly promising scaffold from which to build safe antibiotic candidates for the treatment of multiresistant Gram-positive bacterial infections.



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Bibliography

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