Fragment class with carbapenemase inhibition and antibacterial activity

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Background

The rapid emergence of carbapenemases is a threat to the current operation of modern healthcare with widespread consequences, since infection prevention plays a crucial role for other healthcare practices e.g. surgery, immuno-affective treatments for cancer etc. These enzymes confer resistance against all types of ß-lactam antibiotics – including last-line carbapenems. As carbapenemase-positive pathogens also commonly express resistance to other classes of antibiotics, treatment options are even further limited. Novel treatment options are needed: new chemistries with new modes of action to (sustainably) overcome resistance mechanisms, in particular for Gram-negative carbapenem-resistant pathogens, assigned by WHO priority pathogens list as critical status.

We are working to develop a new class of carbapenemase inhibitors for clinical use in combination with current antibiotics, alongside its own standalone antibiotic activity in all WHO priority I pathogens.

Methods

We have utilised a chemistry-driven developmental process for optimising each activity of our novel fragment class: through checkerboard assays to improve metallo- and serine-based carbapenemase inhibition and through MIC screening to improve antibiotic activity in attenuated lab strains and in wild-type bacteria.

Results

The identified fragment class (MW <300g.mol^{-1}) shows inhibitory activity of carbapenemases and binding to the active site of metallo- and serine-carbapenemases (X-ray and NMR). We have made significant gains in biological activity to potentiate the activity of meropenem 64-fold at 16 mg/L. The fragment has clear, strong protection effects for carbapenems from a wide range of carbapenemases including metallo-based, Ambler class B, and the serine-based of class A and D. Furthermore, we have developed multiple series of compounds with antibacterial activity with MIC of 32 mg/L.

Conclusions

We have significantly improved the activity of a novel fragment class with a dual mode of action as pan-carbapenemase inhibitor and independent antibiotic. This is an invaluable starting point for an innovative antibiotic drug development. We aim to continue growing the fragment class to improve each activity. With a non-beta-lactam pharmacophore, the impact of such a molecule will be substantial for treatment of resistant infections.