

A novel class of metalloid-based antibiotic compounds

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With the traditional sources for antibiotics failing to refill the drained antibiotic pipeline, there is an urgent need for novel approaches to fight multidrug-resistant bacterial infections. Metal-based compounds have recently gained prominence as potential metalloantibiotics, displaying high hit-rates against ESKAPE pathogens.¹ Metalloids, elements which lie between the metals and nonmetals in their properties, have also found applications in medicine. Boron (e.g. bortezomib), arsenic (arsenic trioxide) and antimony (stibogluconate) are all clinically used drugs containing metalloids. In contrast, germanium-based compounds have remained underexplored.

Here we describe the discovery and properties of a series of Germanium-based antibacterial agents identifying **Ge5** as a promising lead compound. **Ge5** shows high activity against Gram-positive bacteria with low levels of cytotoxicity and haemolysis. Co-treatment with polymyxin nonapeptide leads to improved activity against Gram-negative strains, suggesting the potential for further chemical optimisation of this compound class. Initial mode of action studies show that **Ge5** acts on the bacterial membrane, leading to depolarisation but not pore-formation. Lastly, **Ge5** significantly increases survival in a *Galleria mellonella* infection model (*S. aureus*), while not showing signs of toxicity at the highest tested dose. Overall, these data suggest germanium compounds could be an entirely novel class of metalloid-based antibiotics.

[1] **A. Frei*** et al. "Metal-complexes as a Promising Source for New Antibiotics". Chem. Sci., 2020, DOI: [10.1039/C9SC06460E](https://doi.org/10.1039/C9SC06460E)