Design, synthesis and evaluation of novel hamamelitannin analogues that increase the susceptibility of *Staphylococcus aureus* to vancomycin.

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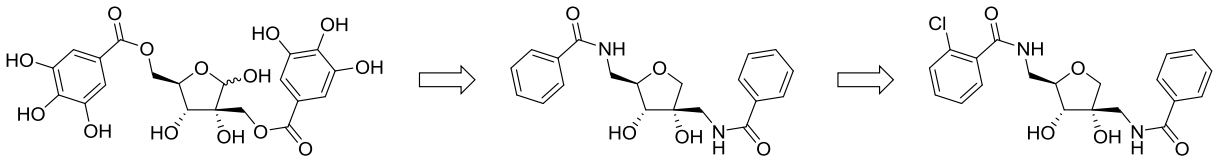
Antimicrobial resistance is a global public health challenge and the development of new antibiotics is scarce. The inherent property of conventional antibiotics to impose selective pressure on bacteria, together with their misuse and overuse, contributed to the development of multi-resistant pathogens. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of these 'superbugs'. In both healthcare and community settings, MRSA is a major cause of infections worldwide.[1] In addition to this, staphylococcal pathogens are a frequent cause of biofilm-associated infections.[2] Bacterial cells within a biofilm are protected from attack by the immune system and antibiotics often fail to pierce the biofilm matrix.

Hamamelitannin (HAM), a natural product isolated from the witch hazel (*Hamamelis virginiana*) has recently been identified as an antimicrobial potentiator and may be used in the fight against biofilm-related staphylococcal infections.[3] HAM increases the susceptibility of *S. aureus* biofilms towards vancomycin (VAN) *in vitro* as well as *in vivo*.[3,4]

A first round of hit to lead optimization of HAM led to bisbenzamide **1**, with enhanced druglikeness. Starting from this HAM-derived pharmacophore, we focused on optimizing potency further. Our work resulted in the identification of compound **2** with potent *in vitro* activity and exceptional antibiofilm activity in a *Caenorhabditis elegans* infection model and a murine mastitis model, while lacking cytotoxicity against MRC-5 lung fibroblast cells.



HAM
cLogP: -0.47
EC_{50}: 145.5 µM

1
cLogP: 2.17
EC_{50}: 96.97 µM

2
cLogP: 2.26
EC_{50}: 0.3890 µM

1 Chambers, H. F.; Deleo, F. R. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. *Nature reviews. Microbiology* **2009,** 7, 629-641.

2 Otto, M. Staphylococcal Biofilms. *Current topics in microbiology and immunology* **2008,** 322, 207-228.

3 Kiran, M. D.; Adikesavan, N. V.; Cirioni, O.; Giacometti, A.; Silvestri, C.; Scalise, G.; Ghiselli, R.; Saba, V.; Orlando, F.; Shoham, M.; Balaban, N. Discovery of a quorum-sensing inhibitor of drug-resistant staphylococcal infections by structure-based virtual screening. *Molecular pharmacology* **2008,** 73, 1578-1586.

4 Brackman, G.; Cos, P.; Maes, L.; Nelis, H. J.; Coenye, T. Quorum sensing inhibitors increase the susceptibility of bacterial biofilms to antibiotics *in vitro* and *in vivo*. *Antimicrobial Agents and Chemotherapy* **2011,** 55, 2655-2661.