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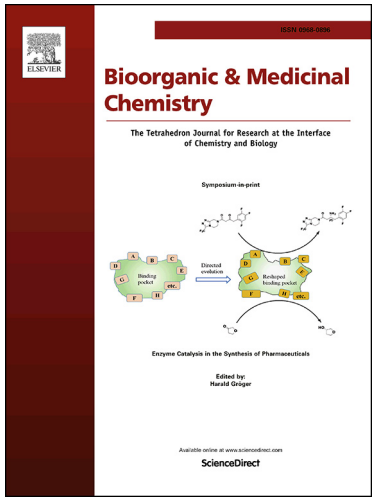

Amphipathic sulfonamidobenzamides mimicking small antimicrobial marine natural products; investigation of antibacterial and anti-biofilm activity against antibiotic resistant clinical isolates

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Manuscript for submission

Amphipathic sulfonamidobenzamides mimicking small antimicrobial marine natural products; investigation of antibacterial and anti-biofilm activity against antibiotic resistant clinical isolates

Elizaveta M. Igumnova [a,†], Ekaterina Mishchenko [b,†], Tor Haug [b], Hans-Matti Blencke [b], Johanna U. Ericson Sollid [c], Elizabeth G. Aarag Fredheim [a], Silje Lauksund [a], Klara Stensvåg [b], Morten B. Strøm [a,*]

[a] *Department of Pharmacy, Faculty of Health Sciences, UiT – The Arctic University of Norway, NO-9037 Tromsø, Norway*
[b] *The Norwegian College of Fishery Science, Faculty of Biosciences, Fisheries and Economics, UiT – The Arctic University of Norway, NO-9037 Tromsø, Norway*
[c] *Department of Medical Biology, Faculty of Health Sciences, UiT – The Arctic University of Norway, NO-9037 Tromsø, Norway*
[†] *These authors contributed equally to this work.*

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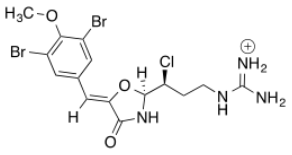
ABSTRACT

There is an urgent need for novel antimicrobial agents to address the threat of bacterial resistance to modern society. We have used a structural motif found in antimicrobial marine *hit compounds* as a basis for synthesizing a library of antimicrobial sulfonamidobenzamide *lead compound*s. Potent *in vitro* antimicrobial activity against clinically relevant bacterial strains was demonstrated for two compounds, **G6** and **J18**, with minimal inhibitory concentrations (MIC) of 4–16 μg/ml against clinical methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE). The two compounds **G6** and **J18**, together with several other compounds of this library, also caused ≥90% eradication of pre-established biofilm of methicillin-resistant *S. epidermidis* (MRSE) at 40 μg/ml. Using a luciferase assay, the mechanism of action of **G6** was shown to resemble the biocide chlorhexidine by targeting the bacterial cell membrane.

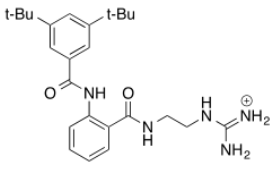
1.Introduction

Development of novel antimicrobial drugs is a high-risk business due to the general massive costs of any drug R&D program, potential limited sales volume, and restricted use of any innovative antimicrobial to avoid development of resistance.[1] Most antimicrobial drugs on the market interfere with highly specific targets in bacteria, and few novel unique targets have been identified. Design of antimicrobial agents killing bacteria through interactions with non-specific targets can be a valuable strategy to encounter the challenges of antimicrobial resistance. Cationic antimicrobial peptides (AMPs) have gained much attention in recent decades since they attack the cell membrane of bacteria.[2] The pharmacokinetics of AMPs may however disfavor them as drugs because of poor bioavailability and low proteolytic stability.

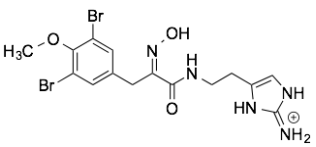
We have previously prepared a library of small cationic amphipathic aminobenzamides based on a common structural motif found in several isolated marine antimicrobials and that may also be considered as peptidomimetics of small AMPs (Figure 1).[3] The pharmacophore or active motif of this class of antimicrobial *marine natural product mimics* (MNPMs) was explored by investigating a central benzamide group linked to a lipophilic 3,5-di-*tert*-butyl-benzyl group and various cationic groups through amide bonds. Improved antimicrobial activity was achieved compared to the marine natural products that formed the motivating *hit molecules* for the design, such as ianthelline[4] and the synoxazolidinones.[5] This strategy has also been successfully explored in synthesis of amphipathic 1,2,3-triazole MNPM antimicrobials.[6,7]



Synoxazolidinone A



E23



Ianthelline

Figure 1. Isolated cationic amphipathic marine natural products *synoxazolidinone A*[5] and *ianthelline*,[4] and the synthetic aminobenzamide *marine natural product mimic* **E23**.[3]