



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: Implications of Self-Assembly and Metal Binding on the Bactericidal Potential of Synthetic Amphiphiles

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SHORT ABSTRACT

The unabated menace of antibiotic-resistant pathogenic bacteria has fueled the need to develop potent antibacterials that can contravene the resistance barrier. To address this contemporary healthcare issue, the present work highlights the prospect of synthetic amphiphiles, whose unique design enabled integration of multiple attributes in a single molecule so as to provide a distinct edge in annihilation of the target pathogen. A salicaldehyde based amphiphile (C1), exhibiting broad-spectrum bactericidal activity could self-assemble in solution and form a micelle (C1_M), which could serve as a repository of therapeutic antibiotics rifampicin (R) and vancomycin (V). On interaction with cells of methicillin-resistant *Staphylococcus aureus* (MRSA) and subsequent disassembly of the antibiotic-loaded micelles (C1_M-R and C1_M-V), the amphiphilic warhead triggered membrane damage and paved the way for enhanced cellular uptake of the released antibiotics, resulting in significantly higher level of killing of clinical MRSA, in contrast to free antibiotics used alone. The antibiotic-loaded micellar constructs were non-toxic to HEK 293 cells even at concentrations exceeding their MICs against the MRSA strain and could also prevent formation MRSA biofilm on surgical sutures. Alteration of the salicaldehyde head group of the amphiphile C1 with a naphthaldehyde group in amphiphile C2 resulted in a change in the hydrophilic-lipophilic balance and a new structure-function relationship emerged, wherein the overall bactericidal potential of C2 was reduced as compared to C1. The amphiphile C2 could potentiate the efficacy of antibiotics such as polymyxin B and erythromycin against target bacteria and a favorable interaction was observed between C2 and the antibiotics. C2 was non-toxic to HEK 293 cells at a concentration equivalent to the MIC against *S. aureus* MTCC 96 strain. The head groups of C1 and C2 were specially grafted with functional groups that enabled metal coordination, induce metal starvation and thereby suppress the growth of MRSA, while the more potent amphiphile C1 had a distinct effect on the expression of genes involved in synthesis and transport of a zincophore implicated in metal starvation in MRSA. C1 and C2 also displayed supramolecular interactions with staphylococcal lipoteichoic acid (LTA), which enhanced their anchorage onto MRSA cell surface. Interestingly, C1 could inhibit MRSA biofilm growth on collagen, simulated wound fluid-infused collagen as well as on an orthopedic stainless-steel wire. Oral administration of 300 mg/kg and 1000 mg/kg of C1 was essentially non-toxic to BALB/c mice. Interestingly, topical application of C1 (50 mg/kg and 100 mg/kg) on a skin excision wound model in female BALB/c mice rendered effective wound closure, highlighting the prospect of C1 as a topical skin wound healing agent. The pluri-active synthetic amphiphiles described in the present investigation provide a framework for development of synthetic antibacterials that hold therapeutic potential against antibiotic-resistant pathogenic bacteria.