CHAPTER 3.
PURPOSE OF THE WORK

3.1. Motivation

Looking into the WHO report-2013, there is no ambiguity that development of antibiotic resistance needs urgent attention from researchers to discover novel anti-infective agents which can combat the infections caused by multi-drug resistant strains.

From the review of literature, it is clear that most of the lipopeptides and synthetically designed small cationic antimicrobial peptidomimetics exert their antimicrobial action through membrane binding and disruption, followed by aggregation, poration, and insertion into the membrane. Therefore, it could be extremely difficult for microbes to develop resistance against them by counteract all killing mechanisms at once. Generally, pathogens are unable to develop resistance against membrane active agents, which recommend their therapeutic application in other critical diseased conditions where the growing resistance to chemotherapeutic agents is a major concern. Moreover, peptide based antibiotics in particular lipopeptides display broad-spectrum antimicrobial activity against multi-drug resistant bacteria as well as fungi, which makes them suitable candidates for the development of new generation antibiotics.

Lipo-antibiotics available in the market are from natural origin which includes polymyxin B, daptomycin, and caspofungin not all but just for mention. However, literature reports highlight toxicity toward mammalian cells as their major drawback. Structurally, these native lipo-antibiotics have a somewhat complex structural framework which might be responsible for their non-cell selectivity. Proteolytic degradation is another drawback associated with peptide based therapeutics which renders them considerably inactive in intended bioenvironment. Although there are many reports published which underscores the better therapeutic potential of short lipopeptides and small cationic peptidomimetics but to our knowledge improvement of their druggability has so far escaped from serious attention of researchers.
3.2. Objectives
The research program described here, aimed at rationally structure based design, synthesis and biological evaluation of novel short lipopeptides and small cationic peptidomimetics. The specific objectives are illustrated below:

- To design and synthesize structurally small peptide based molecules.
- To evaluate the antimicrobial activity and therapeutic index of synthesized molecules.
- To examine proteolytic stability and pathogens ability to develop resistance against lead molecules.
- To study the mechanism involved in antimicrobial activity of lead molecules.
Structurally diverse short peptide-based molecules to be designed based on Structure-Activity Relationship (SAR) of native AMPs reported in literature with confirmation of novelty

Synthesis of designed molecules by using solid phase synthesis protocol

Purification and analytical characterization of synthesized molecules

Initial screening of all synthesized molecules against reference standard bacterial and fungal strains

Assessment of In Vitro Cytotoxicity using Hemolytic assay (HC_{50})

Molecules with selectivity index (HC_{50}/MIC) > 10 will be screened for their MIC against MDR bacterial as well as fungal strains

Establishment of Structure Activity Relationships (SAR) and Structure Property Relationships (SPR) of synthesized molecules

Further Designing of chemical library based on the SAR of first phase molecules.

Synthesis of designed molecules by using solid phase synthesis protocol

Purification and analytical characterization of synthesized molecules

Initial screening of all synthesized molecules against reference standard bacterial and fungal strains

Assessment of In Vitro Cytotoxicity using hemolytic assay (HC_{50})

Molecules with selectivity index (HC_{50}/MIC) > 10 will be screened for their MIC against MDR bacterial as well as fungal strains

Examination of the proteolytic stability
Evaluating the ability to develop resistance
Mechanistic study of most potent molecules