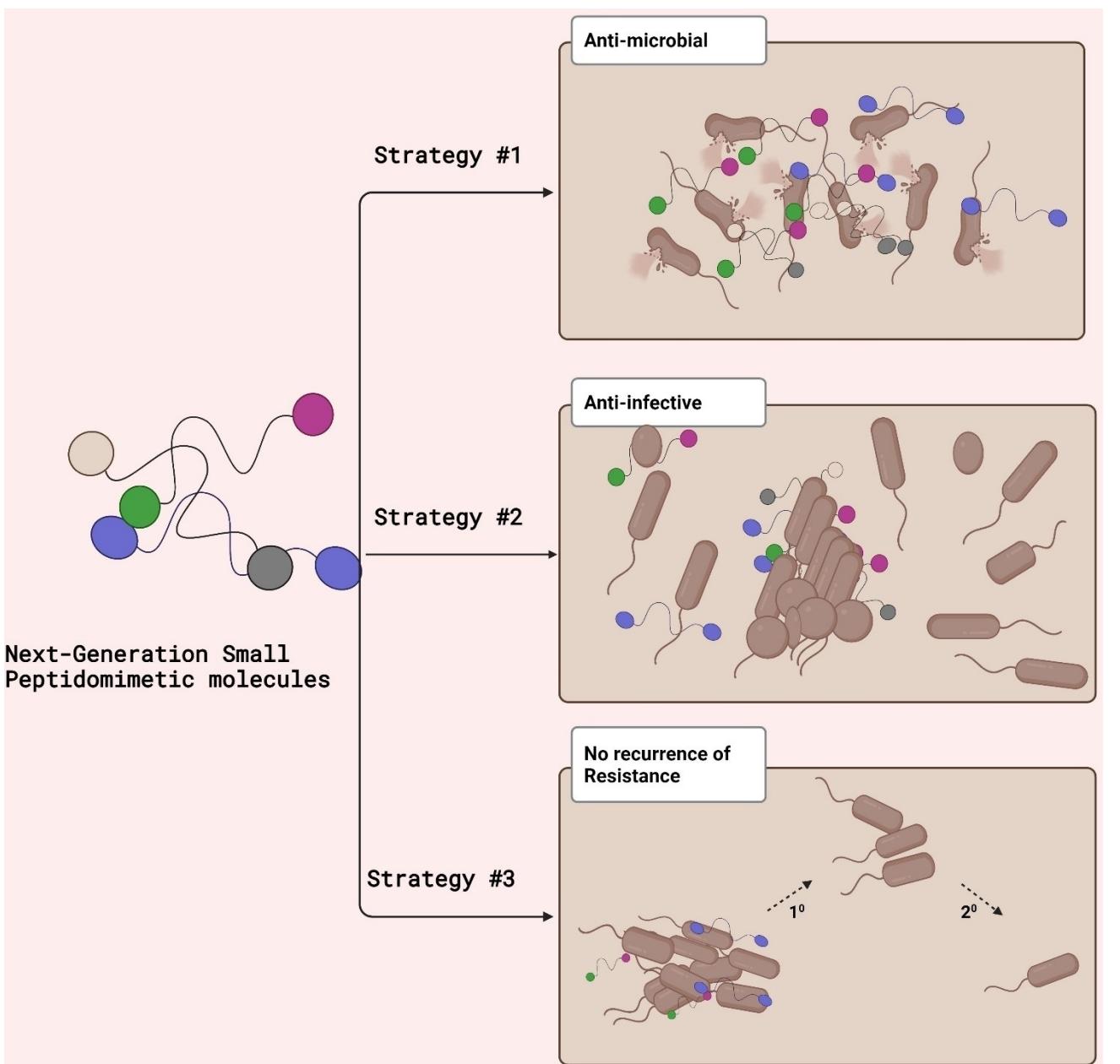


**■ Biological Chemistry & Chemical Biology**

# A Prospective Diversity of Antibacterial Small Peptidomimetic and Quorum Sensing Mediated Drug: A Review

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The global threat of antimicrobial resistance demands alternative tackling approaches with a unique mechanism of action. Antimicrobial peptides are currently explored widely as the potential next generation antimicrobials and anti-infectives. They provide multiple advantages in terms of wide spectrum activity ranging from antimicrobial, anti-infective to immunomodulatory agents. The most striking feature is the delayed resistance development. Owing to their reduced stability and easy degradation, the current research is focused on the

development of small peptidomimetic molecules (SPMs) provides longer half-life and improved stability. In addition, they are widely explored as quorum sensing inhibitors. These are proven to be effective quorum quenchers against both Gram - positive and Gram - negative bacteria. Specifically these molecules are shown to have potent anti-biofilm activity. In this regard, this review provides the structural aspects in the development of SPMs as both antibacterial and anti-quorum drugs for the last five years.

## 1. Bacterial World: The Positives and Negatives

The inevitable role of microorganisms which includes bacteria, archaea, fungi, algae etc. in different aspects of human needs is exemplified by the advent of "Human Microbiome".<sup>[1]</sup> With over 100 trillion microbes present in the human body, these "microbiota" defines the human in a health and diseased condition. Hence it is of paramount importance to understand such diversity for the development of the novel therapeutics. The commensals of the human microbiota have shown to contribute to the important physiological process. The importance of this "super organism" is evident from its association with systemic health and disorders. For instance, researchers have found an elaborate network of gut microbiome with host innate immune system,<sup>[2]</sup> oral microbiome and has been known to impact the proper functioning of gastrointestinal tract and brain.<sup>[3]</sup> Even though, microbial world is composed of various kingdoms such as bacteria, archaea, fungi, algae etc., bacteria are well exploited followed by fungal kingdom. Based on the Gram stain, they are divided into Gram- negative and Gram - positive bacteria differentiated by the presence of the peptidoglycan layer. While Gram - negative bacteria have a thin peptidoglycan layer, Gram - positive bacteria have thick peptidoglycan layer. The clinically relevant bacteria are present in both Gram - positive and Gram - negative classification, where they can also co-exist to bring dysbiosis leading to severe infections. *Staphylococcus sp.*, and *Streptococcus sp.*, are

the most common Gram - positive bacteria which are associated with common skin infections, dental plaque to life threatening sepsis and endocarditis. *Staphylococcus sp.* is often associated with the hospital - acquired or nosocomial infection. In the same rhythm, Gram - negative bacteria which includes *Vibrio cholera*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* etc., are responsible for disorders ranging from common urinary tract infections to lung infections to endemic cholera. The repertoire of the virulence factors, ease of transmission from animals to humans and more importantly their ability to develop resistance to the currently available antibiotics have worsened the management of the infections caused by these pathogens.

## 2. Bacterial Strategies to resist the Antibiotics

Bacteria have developed resistance mechanisms specific to each class of antibiotic to overcome the survival pressure. Figure 1 elaborates the extrinsic and intrinsic resistance drivers, evolved mechanisms to make the antibiotic ineffective against the bacterial pathogens. The extrinsic mode of bacteria acquiring antibiotic resistance genes (ARG) is mediated either through the transformation of genetic materials between the donor and the recipient cell, involving F-plasmid via., sex pili (conjugation), competent factors (transformation) or by bacteriophages (transduction). Also, the intrinsic mode of gaining resistance by the bacterial pathogens involves such as over-expression of efflux pump to expel antibiotics.<sup>[4]</sup> these transport factors (multi-drug efflux pumps) being a part of both Gram positive and Gram-negative bacteria are known to be specific to extrude an accumulated or a range of toxic substrates (various classes of antibiotics) to out of the cell. These transporters are classified into five major families MF (major facilitator), MATE (multidrug and toxic efflux), RND (resistance-nodulation-division), SMR (small multidrug resistance) and ABC (ATP binding cassette). Interestingly, these multi-drug resistant pumps affinity to that specific class of antibiotics.<sup>[5]</sup> Modification of Lipopolysaccharides affect the antibiotic activity: The lipopolysaccharide (LPS) is a key component of the outer membrane in Gram-negative bacteria and act as first line of defense barrier to prevent the permeability of antibiotics and antimicrobial peptides<sup>[10]</sup> to acquire resistance. The elaborate defence of LPS includes a "rough" and a "smooth" region where the rough includes a lipid A and core embedded in the outer membrane and the smooth region of LPS is capped with O antigen. Research evidence that the structural modification of

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*Sahana graduated summa cum laude from SASTRA Deemed to be University, Tamil Nadu, India with a B.Tech. in Industrial Biotechnology and a M. Tech in Biosciences and Engineering from the Defence Institute of Advanced Technology, Pune, India. She has gained significant research experience from the National Chemical Laboratory, Pune, Indian Institute of Technology, Madras and the National Institute of Oceanography, Goa. She is a recipient of the highly competitive and prestigious "INSPIRE fellow" awarded by Department of Science and Technology, Government of India. She is now a doctoral (PhD) student at SASTRA Deemed to be University, Tamil Nadu, India. Her doctoral thesis focuses on the diagnosis and treatment of urinary tract infections using functional metal oxide nanointerfaces, using a variety of state-of-the-art nanotechnology, microbiological and biomedical approaches.*



*Hema is currently pursuing Ph. D degree at SASTRA University, Thanjavur, Tamil Nadu. She has a postgraduate degree in Biotechnology from Shri Venkateshwara Arts and Science College, Chennai. Her research work is focused on the targeted drug release to subdue *V. cholerae* virulence. Hema's research interests include microbial virulence and infection biology.*



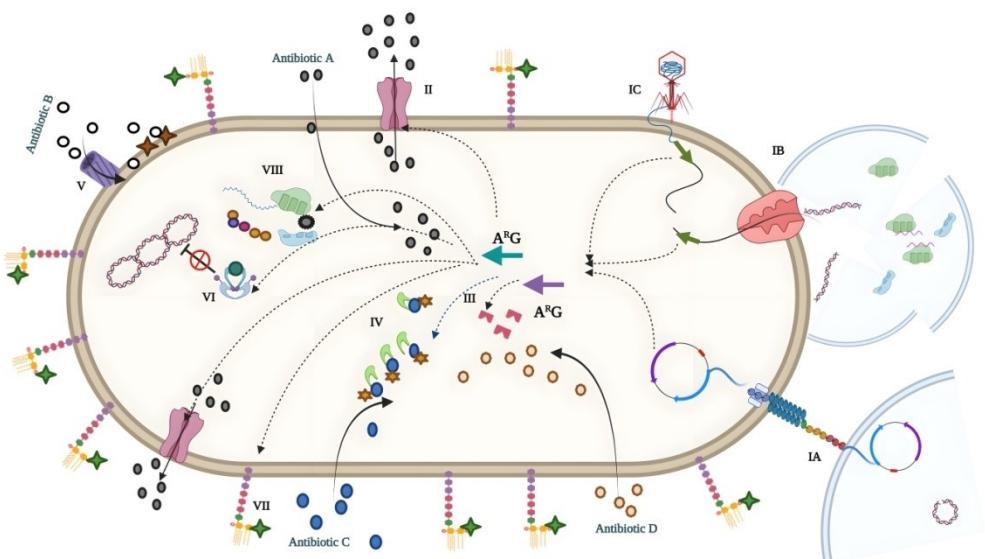
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**Figure 1.** Major Drivers of antibiotic resistance of Gram-ve and Gram +ve bacteria: Acquired resistance via., gene transfer methods (IA- Conjugal transfer of antibiotic resistance genes (ARG) from one bacterial cell to another cell via., pilus; IB – transformation of extracellular DNA encoding antibiotic resistance genes (ARG) to a bacterial cell; IC-Bacteriophage mediated transduction of antibiotic resistance genes (ARG)). Intrinsic Resistance (II) Overexpression of efflux pump to expel -lactams, fluroquinolones, aminoglycosides, tetracyclines, antibiotics ( macrolides) (III) Target modification to neutralise the antibiotic action (IV) Resistance enzymes modify antibiotics by adding bulky adducts to antibiotic as to prevent them from binding to its target (V) Enzyme mediated inactivation of -lactams) (VI) Mutation in the essential gene encoding antibiotics (Topoisomerase IV/DNA gyrase not to affect the DNA integrity (supercoiling) (VII) Modification of Lipopolysaccharides affect the antibiotic activity (Colistin)(VIII) Decreased affinity for ribosomal subunits (30S, 50S), elongation factor (EF-Tu), Peptide bond formation between A and P sites, translocation factor (EF-G) and termination factors (Streptomycin, Tetracyclines, Glycylcyclines, blasticidin S, Chloramphenicol, Lincosamides, Oxazolidinones, Pleuromutilins, Puromycin, Streptogramin A, Sparsomycin, tuberactinomycins capreomycin, viomycin, hygromycin, neomycin and paromomycin, fusidic acid, spectinomycin).

the acylation patterns/addition of positively charged substituents to the lipid A phosphate groups is one of the sole reasons to affect the permeability of antimicrobial peptides and in turn affect the inflammatory responses of the host.<sup>[11]</sup> Meanwhile, the structural modification in the O antigen in *P. aeruginosa* enhance its adherence to host epithelial cells either through the mimicry of host system or activation of host complement system.<sup>[12]</sup> Decreased affinity for ribosomal subunits (30S, 50S), elongation factor (EF-Tu), Peptide bond formation between A and P sites, translocation factor (EF-G) and termination factors: Several classes of antibiotics such as macrolide, lincosamide and streptogramin interact with the larger ribosomal 50S subunit, and block protein synthesis.<sup>[13]</sup> In addition, mutation in the 16sRNA that retains in the smaller ribosomal subunit confer resistance to the aminoglycosides in the nosocomial pathogens.<sup>[15]</sup> In addition to antibiotic specific resistance mechanisms, bacteria can form a three dimensional complex structure called biofilm. The important components of biofilm include extra polysaccharide matrix, proteins, eDNA and other polysaccharides. This robust aggregated form is known to be the leading cause of antibiotic resistance. These biofilms are clinically relevant and are responsible for 65–80% chronic infections.<sup>[14]</sup> Various aspects of biofilm confer resistance to antibiotics. The biofilm matrix is one of the important factors that reduce the effective penetration of antibiotics and also contain antibiotic modifying enzymes. Another important

aspect is the physiology of the biofilm with varying oxygen and nutrient availability.<sup>[15–17]</sup>

It can be clearly seen that with every new class of antibiotic, there is a development of an elaborate resistance mechanism to overcome the survival pressure by the microorganisms. Hence, it is a need of the hour to look for smart alternatives as next generation anti-bacterial/anti-quorum drugs to disarm the bacterial pathogenesis without imposing any survival pressure on them.<sup>[17]</sup>

### 3. Next Generation Peptidomimetic Antibacterial

Naturally occurring host defense peptides (HDPs) which are an integral part of the innate immune response are well exploited as anti-bacterial agents. They are naturally produced by the multicellular organisms against the disease-causing pathogens.<sup>[18]</sup> HDPs are either cationic or hydrophobic in nature which cannot interact with the zwitter ionic mammalian cells. This feature provides a selective advantage in the specific activity against pathogens. HDPs are proven to have wide range antimicrobial activity against bacteria, fungi, viruses, and parasites.<sup>[19]</sup> Their role in immunomodulation as well as anti-cancer agents are well established. Hence, these versatile HDPs are the most sorted choice to circumvent antimicrobial resistance.<sup>[20]</sup> Even though there are a few reports on the development of resistance against HDPs, it is a quite slow

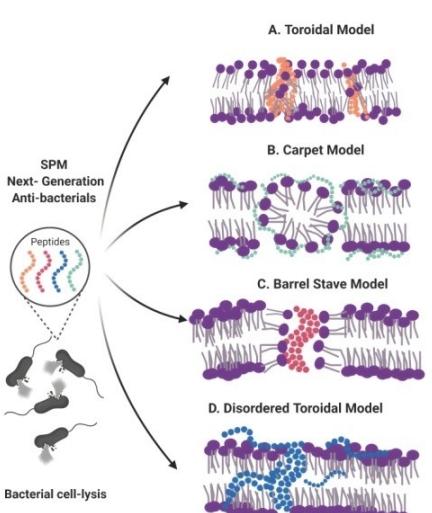
process. The bacterial disintegration by HDPs is non-specific and unique that it becomes energetically unfavorable for the resistance development.<sup>[21]</sup> However, HDPs suffer from disadvantages to be developed as drugs. The high molecular weight, lesser yield with increased production cost and their biological instability have limited the commercial usefulness of HDPs.<sup>[22]</sup> These challenges are overcome by the advent of synthetic small peptidomimetics (SPMs) which possess the essential pharmacophore of natural HDPs having the intact biological activity with more stability and less degradation.<sup>[23]</sup> The recent research is focused on improving the biological efficacy better than the naturally occurring HDPs. SPMs offer greater advantage in terms of longer half-life, improved bioavailability and overcome protease degradation.<sup>[24]</sup> Thus, with multiple advantages, SPMs are exploited as promising antibacterial agents to overcome the alarming rise of antimicrobial resistance.<sup>[25]</sup>

Initially, it was shown that HDPs and SPMs mainly target the bacterial cell membrane through ionic interactions.<sup>[26]</sup> The cationic antimicrobial peptides interact with the anionic bacterial cell surface, causing disintegration of the bacterial cell membranes and ultimately leading to the cell lysis. There are different models (Figure 2) proposed by the researcher to explain the mode of bacterial cell membrane disruption by SPMs<sup>[27]</sup> barrel stave model where SPM form a bundle with central lumen leading to a transmembrane pore.<sup>[28,29]</sup> Peardaxin, Protegrins are the few examples that follow the barrel stave drilling model.<sup>[30,31]</sup> Toroidal model in which SPM insert into the membrane and induce the bending of the layer until forming a

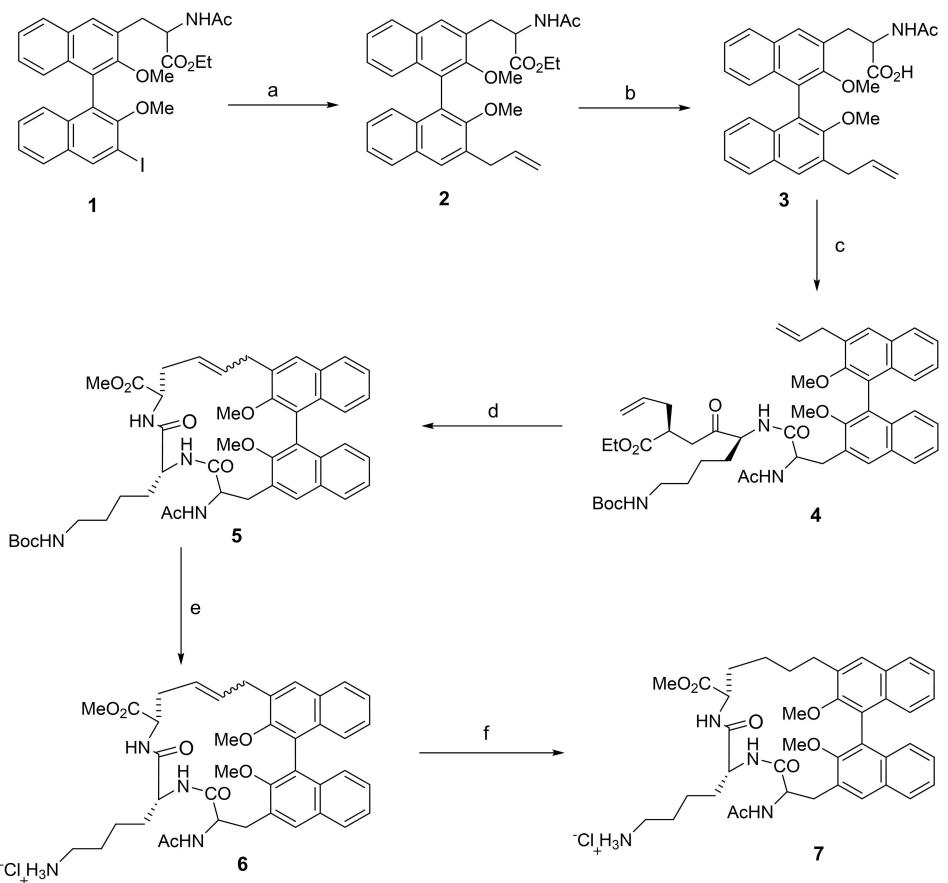
pore,<sup>[32,33]</sup> Carpet Model At high concentration, SPM accumulate and cover the bilayer surface and behave like a surfactant to destabilize the membrane and form toroidal pores.<sup>[34]</sup> Few drugs as cecropin, aurein follow carpet pathway<sup>[35,36]</sup> and disordered toroidal model SPM form unstructured clusters to destabilize the bacterial membrane and cause leakage of intracellular content. It should be noted that these models were formulated based on the experimental model membranes. In addition to their membrane interaction, the SPMs were also shown to target microbes intracellularly through several mechanisms<sup>[37]</sup> and play a role in immune modulation.<sup>[38]</sup> Further, omics-based studies revealed that these peptides bring changes in the processes such as transcription and protein.<sup>[39,40]</sup> The exact mechanism of action of HDPs and SPMs are still under investigation and needs to be further explored. There are major classes of peptidomimetics – Peptoids, AApeptides, staple peptides and peptides having non-natural amino acids.<sup>[41]</sup> Each of these classes have more stability and longer half-life compared to the natural HDPs. Additionally, these SPMs have been shown to act in synergy with the existing antibiotics.<sup>[42–45]</sup> Following is the systematic account of the SPMs in the structural aspect which was proven to have excellent antibacterial activity.

Molchanova et.al had shown that,  $\alpha$ -peptides,  $\beta\beta$ -peptoids, peptide/peptoid hybrids are less toxic and more efficient cationic peptidomimetic antibiotic compared to conventional natural antimicrobial peptide.<sup>[46]</sup> Similarly, Wei et al. synthesized a series of lipo- $\alpha$  / sulfono- $\gamma$ -AA hybrid peptides, among these hybrid peptides **45** (Figure 5) exhibit potential antibacterial activity, MIC<sub>50</sub> against *S. aureus*, *E. coli* and *P. aeruginosa* are 5, 2 and 5  $\mu$ g/mL respectively also they have showed that, **45** (Figure 5) was able to eradicate bacterial biofilm with moderate hemolytic toxicity. Their consecutive work suggests that incorporation of hydrophobic tail into peptides/peptidomimetics compounds improves drugs-membrane interaction.<sup>[46]</sup> Again it was supported by another work, synthesized of many symmetrically substituted xanthone derivative that was able to combat bacterial resistance due to their small rigid hydrophobic counterpart. Compound **48** (Figure 5) is the most selective compound that leads to prominent antibacterial activity MIC<sub>50</sub> (0.78–6.25  $\mu$ g/mL) against MRSA in various strains. SPM drug **48** (Figure 5) showed balance between antibacterial and hemolytic activities due to its unique structural properties, water-solubility, amphiphilicity and suitable pKa of cationic side chain. This concept suggests that systematic drug design to ascertain this entire characteristic is especially important for validation studies.<sup>[47]</sup> As can be seen, these SPM's are effective against MRSA. They are widely spread and are associated with the hospital acquired infections. They are considered "superbugs" and are extremely difficult to treat.<sup>[48,49]</sup> Thus, SPM's which can eradicate MRSA are deemed to be very effective.

Again, the outer membrane-targeted approach was developed by Pyne and Keller et.al. They had shown that binaphthyl peptide based SPM drug **7** (Scheme 1) a modified version of vancomycin that could disrupt bacterial cell wall by crosslinks with peptidoglycan containing both L-Lys-D-Ala-D-Ala and L-Lys-D-Ala-D-Lac where these two termini pose in vancomycin



**Figure 2.** Representative image to depict the various models of the aggregation of the folded (helices, sheets, turns) of the next generation small peptidomimetic molecule (SPM) in destabilizing the bacterial membrane and cause cell death (A) Toroidal Model: SPM insert into the membrane and induce the bending of the layer until forming a pore (B) Carpet Model: At high concentration, SPM accumulate and cover the bilayer surface and behave like a surfactant to destabilize the membrane and form toroidal pores (C) Barrel Stave Model: SPM form a bundle with a central lumen (D) Disordered Toroidal Model: SPM form unstructured clusters to destabilize the bacterial membrane and cause leakage of intracellular content.

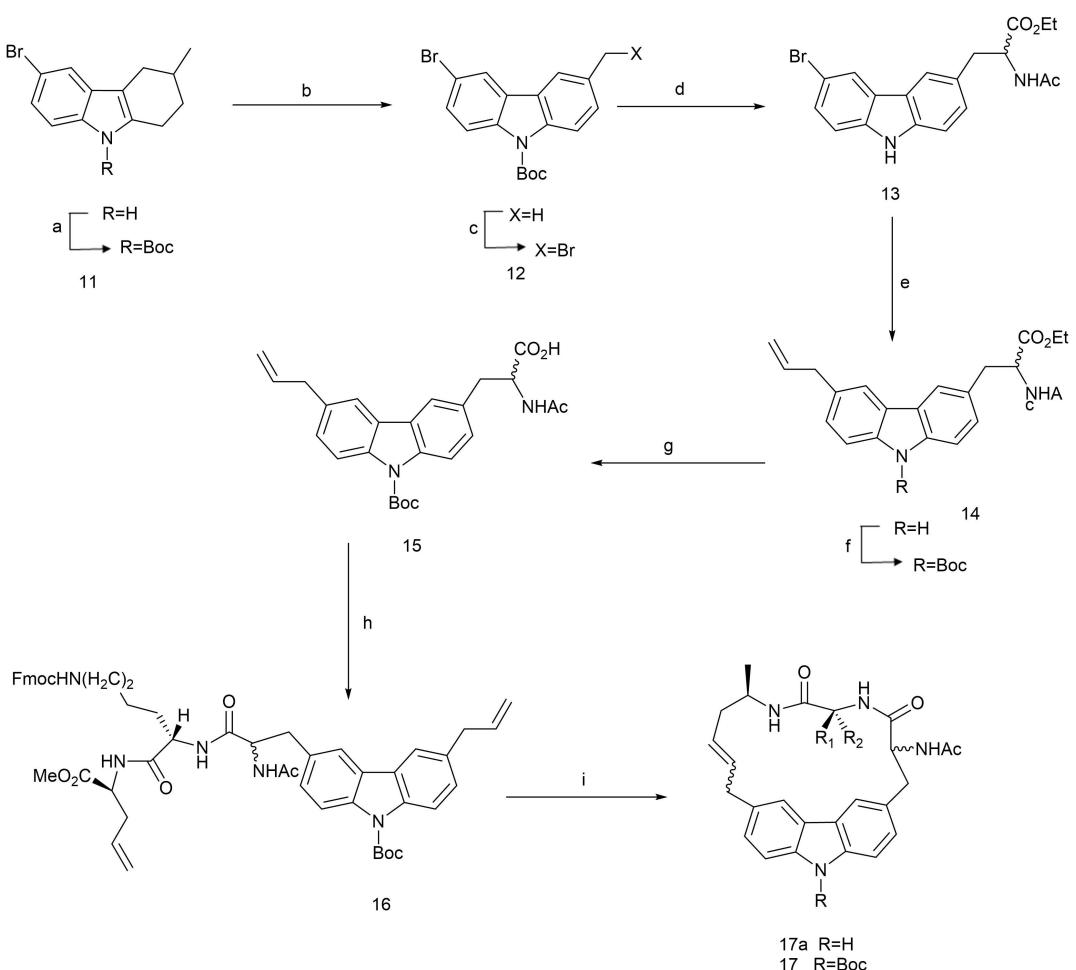


**Scheme 1.** (a)  $\text{PdCl}_2$  (10 mol %),  $\text{PPh}_3$  (40 mol %), allyltributylstannane, dioxane; (b) 5 h,  $\text{LiOH}$ ,  $\text{H}_2\text{O}/\text{THF}$  (1:2),  $0^\circ\text{C}$ ; (c)  $\text{N-Boc-D-Lysine-L-allylglycine-methyl ester}$ ,  $\text{DCC}$ ,  $\text{DMAP}$ ,  $\text{DCM}$ ,  $0^\circ\text{C}$ ; (d) benzylidene[bis(tricyclohexylphosphine)] dichlororuthenium (Grubbs' catalyst, 5 mol%); (e) Trifluoro-acetic acid, 4 M-HCl in ether,  $0^\circ\text{C}$ , (f)  $\text{H}_2/\text{Pd-C}$

resistance bacteria. Unlike vancomycin, a basic amino acid residue of 7 will interact with a terminal carboxylic acid of D-Ala and D-Lac in termini of peptidoglycan precursors and another peptoid form hydrogen bond with two amino acid residues, where hydrophobic binaphthyl functionality lockout water molecule from aqueous environment. The S-isomer of this peptide is more active against vancomycin. 7 exhibit moderate antibacterial activity against *S.aureus* by inhibiting bacterial growth,  $\text{IC}_{50}$  (17  $\mu\text{g/mL}$ ).<sup>[50]</sup>

Pyne and keller also studied tripeptide moiety linked carbazole scaffold, 17 that showed moderate MIC against *S.aureus* when they had applied basic residues such as lysine and arginine (Scheme 2). They replaced N–H proton in carbazole lysine mediated cyclic peptide by ‘Boc’ that would give 16-fold decrease of MIC and it suggested that hydrophobicity is important for drug’s antibacterial activity. Another compound that was a D-arginine derivative had shown promising antibacterial activity against *S.aureus*. This small primary biological result gives a new direction in modern antibacterial drugs.<sup>[50]</sup> Pyne and co-workers had displayed the antibacterial activity of binaphthyl based cyclic peptoids, but Naresh Kumar et al. tried to explore the structure-activity relationship of binaphthyl and glyoxamide based peptide derivatives. Compound 23

(Scheme 3) is one of their expected compounds. They switched to the glyoxamide derivative instead of binaphthyl or carbazole based cyclic peptide, where it acted as parent scaffold. When bromine moiety was introduced in glyoxamide parent scaffold and embedded guanidine on its side chain instead of cationic amine, antibacterial activity dramatically improved,  $\text{MIC}_{50}$  (6  $\mu\text{g/mL}$ ) against *S.aureus*.<sup>[51]</sup> Wu et al. developed a number of biaryl oxazolidinone derivatives that are analogs of linezolid and radizolid. These two potential antibiotics have been widely used several bacterial infections in the last few decades. Moreover, these two drugs are known to inhibit bacterial protein synthesis through binding with the 50S subunit of ribosome. In recent times, the working efficacy of linezolid and radizolid have reduced due to mutation of ribosomal subunit. Compounds 8a-d and 9a-d (see Figure 3) have shown potential antibacterial activity against resistance acquired gram-positive bacteria. Compound 9a ( $X=\text{NCH}_3$ ) showed the least  $\text{MIC}_{50}$  value of 0.0675  $\mu\text{g/mL}$  among all other compounds and was 15 to 30-fold higher active than linezolid and radizolid. Unfortunately, this 9a compound was found to be moderately toxic towards hepatic cells and showed very less metabolism in the human liver microsome. Pharmacokinetics studies of 9a demonstrated that it is less stable and water solubility in an

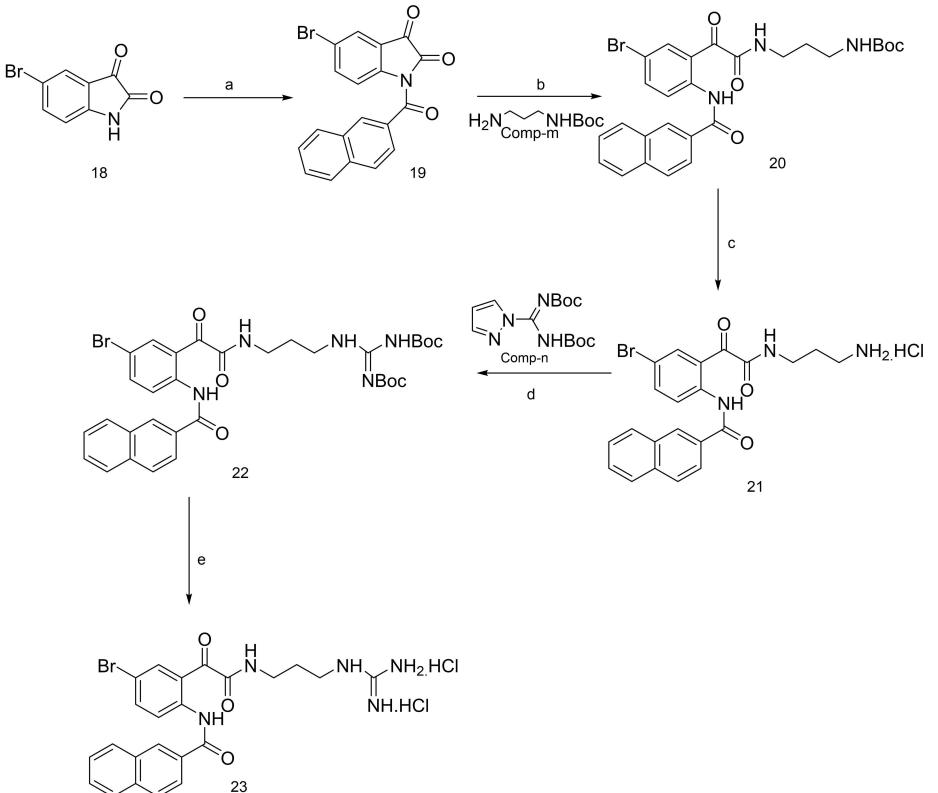


**Scheme 2.** (a) Sodium hydride in THF, (tert-Bu)<sub>2</sub>CO, rt, 21 h, (86 % yield); (b) DDQ (2eq), 3 A mol. Sieves, benzene, reflux, 20 h, (83 % yield); (c) NBS (1.1eq) CCl<sub>4</sub>, reflux with irradiation (150 W Hg lamp), 2.5 h, (69 % yield); (d) (i) NaH, Diethyl acetamido-malonate, DMSO, rt, 0.5 h. ii) Water (2eq), LiCl (1eq), reflux 1.75 h, (70 % yield); (e) PdCl<sub>2</sub> (5 mol%), PPh<sub>3</sub> (20 mol%), allyltributyl stannane (1.2eq), sealed tube, 100° C, 22 h, (91 % yield); (f) Cs<sub>2</sub>CO<sub>3</sub> (2eq), (tert-Bu)<sub>2</sub>CO (1.5eq), DMF, rt, 20 h, (78 % yield); (g) Lithium hydroxide (0.15 M), THF/H<sub>2</sub>O (2.5:1), 0°C, 3 h, (92 % yield). h) Diprotected dipeptide methyl ester (1eq), EDCl (1eq), DMAP (1 crystal), DCM/DMF/MeCN (5:2:15), r.t, 16 h, (60 % yield); (i) (Cy)<sub>2</sub>(Cl)<sub>2</sub>Ru=CHPh, (10 mol%), DCM, reflux, 25 h, (97 %).

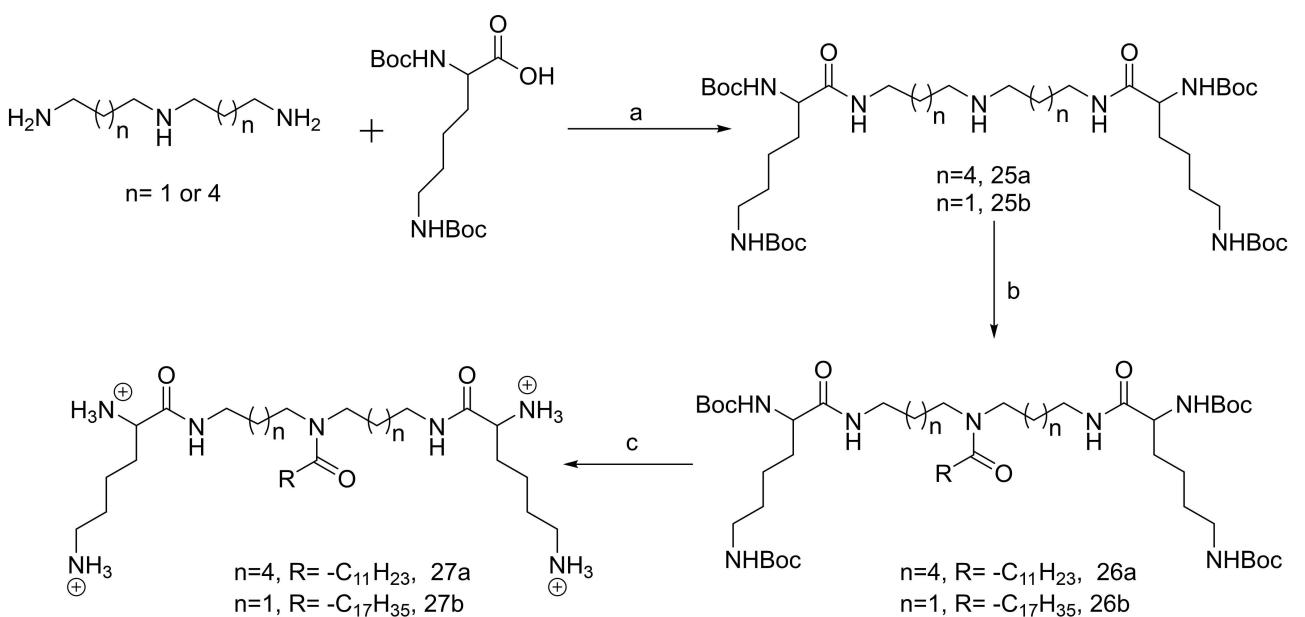
ambient condition also very less. Hence, further refinement of physicochemical properties is required to take it for clinical application.<sup>[52]</sup> Wu. et al. further studied structural optimization of **9a** that exhibited great stability as well as solubility with unaltered antibacterial activity. Moreover, improvement of **9a** occurs by incorporating an 'N'-atom at C-ring and introduces  $-SO_2$  at hydrazone termini. Finally, compound **10** among other homolog derivatives achieved excellent water solubility (11.9  $\mu$ g/mL) and moderate stability in simulated gastric acid solution with unaltered antibacterial activity MIC<sub>50</sub> (0.125  $\mu$ g/mL) against three gram-positive bacteria *S. aureus*, MRSA, VRE (Vancomycin-resistant-*E. faecalis*). Likely, this result occurs may be for hindered hydrophilic substitution and charge distribution.<sup>[53]</sup>

In most of the cases, drugs are toxic, expensive, or less selective against specific bacteria. Towards this, Konai and co-workers developed a new class of membrane sensitive antibacterial agents. They portrayed a tetra-ammonium peptide mimetic to reveal drug toxicity and attenuation of bacterial cell

membranes. Molecular dynamics simulation delivers that the compound **27a** and **27b** (Scheme 4) are desirable for disruption on bacterial cell membranes. Compound **27a** is highly potent on bacterial cell membranes superior to mammalian cell viability ( $94 \pm 7.8\%$ ). Compound **27a** has great antibacterial activity, MIC<sub>50</sub> (1.6–3.1  $\mu$ g/mL) slightly over compound **27b** MIC<sub>50</sub> (3.1–6.3  $\mu$ g/mL) probably for four cationic amines and optimize hydrophobicity.<sup>[54]</sup> Also, they prepared cylam-based small peptidomimetic molecules to eradicate bacterial biofilm-ex-vivo that refer to combat human corneal infection. At 8  $\mu$ g/mL, the derivative reduced the bacterial burden to 1.9log against the colistin resistant strain of *P. aeruginosa* in the ex-vivo studies. Hence it was proven to be effective against both sensitive and resistant strains.<sup>[55]</sup> Similarly, it has been observed that tuning of hydrophobicity leads to excellent antibiotic activity against *A. baumannii*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*. When  $-C_{13}H_{23}$  was used as a pendant modulator leading to enhancement of drug's activity, also it can disrupt biofilm in infected retinal plasma. Therefore, hydrophobicity has a good



**Scheme 3.** (a) 2-naphthoyl chloride, NaH/DMF, rt, 16 h. (b) Comp-m, TEA/DCM, rt, 1 h. (c) 4 M-HCl in dioxin. (d) Comp-n, TEA/DCM, rt, 16 h. (e) 4 M-HCl in dioxin.



**Scheme 4.** (a) Boc-Lys-(Boc)-OH (2 eq.), Dry DCM/ DMF (4:1), DIPEA (6eq), HBTU (2eq), 0 °C, 48 h. (b) Dodecanoic or Octanoic acid (1.5eq), DIPEA (4eq), HBTU (1.5eq), DCM/DMF (4:1), 0 °C – rt, 24 h. (c) TFA/DCM (1:1), 0 °C – rt, 24 h.

propensity to enhance the antibacterial activity for desirable antibiotics.<sup>[55]</sup> Hence, the diversification of current antibacterial drugs is required that will procure to discovering a cost-effective and durable antibiotic upon bacterial resistance.

M. Lee and his group have studied a small anti-cancer drug that was synthesized efficiently and economically, called degrasyn (DGS) that has potential antibacterial activity against *S. aureus*. Likely they had interest to elucidate structure-activity

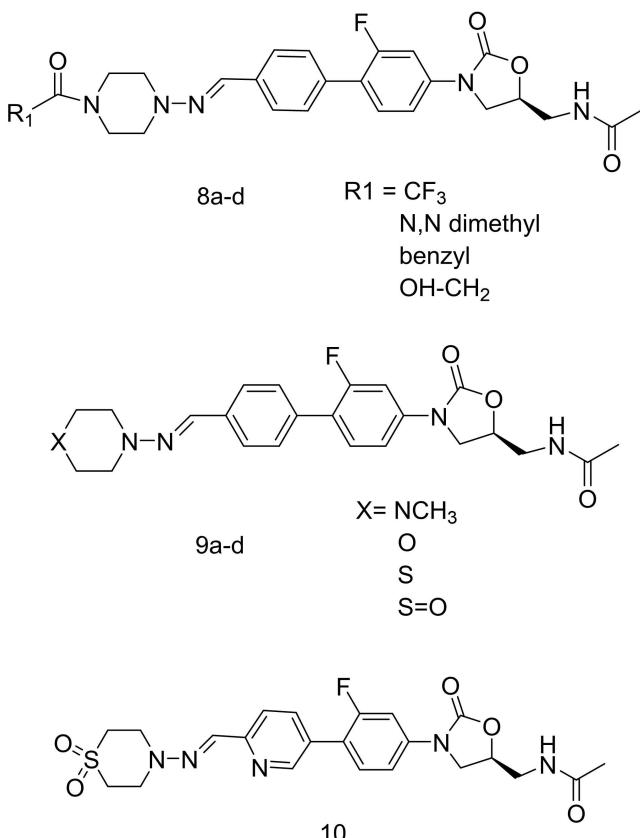
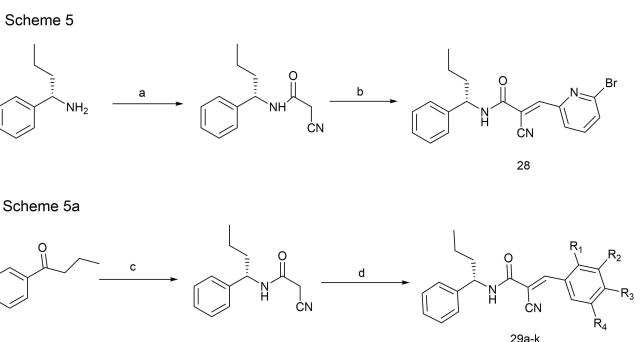


Figure 3. Molecular structures of Linezolid analogs.

relationship (SAR) of DGS homologs and *S. aureus* for discovering a novel antibiotic barring drug resistance. Initially, this group synthesized a series of compounds, **28** and **29a–k** (Table 1). Primarily, they had shown the activity of building blocks of synthesizing compounds prior to the functional group. DGS- **28** and its enantiomer were preparing in Scheme 5, surprisingly none of this enantiomer had no significant antibacterial activity, rather, racemic mixture having MIC<sub>50</sub> 6.25 μM. In this manner, it has been concluded that chirality is less pivotal for a suitable antibiotic. Another



**Scheme 5.** (a) 1-Cyanoacetyl-3,5-dimethyl-1H-pyrazole, toluene, reflux, 2 h, (yield 75%); (b) 6-bromo-2-pyridinecarboxaldehyde, piperidine, EtOH, reflux, 3 h, (yield 65%). a: (c)(i) NH<sub>2</sub>OH, HCl, NaOH, EtOH/H<sub>2</sub>O, 3 h. (ii) H<sub>2</sub>, Pd/C, MeOH, 24 h (iii) 1-cyanoacetyl-3,5-dimethyl-1H-pyrazole, toluene, reflux, 2 h, (yield 69%); (d) aryl aldehyde, piperidine, EtOH, reflux, 3 h, (yield 33–75 %).

homolog has been prepared in Scheme 5a, bromine, and chlorine substitutions were showing a significantly antibacterial activity in compounds **29a–c**. If substituents are iodine, fluoro, hydroxyl, methoxy, posed in compound **29d–i** was negligible antibacterial activity revealed that Br and Cl substituent have required for antibiotic improvement. Eventually, the un-substituted pyridine compound **32a** and **32b** loses its business entirely. Compound **32a–d** (Table 2) homolog of DGS was prepared, using aryl instead of pyridine. Substitution occurs by bromine in **32c** and **32d** would be able to show moderate activity, MIC<sub>50</sub> 25 μM, 6.25 μM, respectively. Along with covalent interaction perspective, compound **31** (See Figure 4) irreversibly inhibits cysteine residue, and compound **30a** reduces form of **31**. Both compounds have activity against *S. aureus*, but alfa-cyanoacrylamide shows potential antibacterial activity (MIC<sub>50</sub> 6.25 μM). In this way, cyanoacrylamide functionality has necessary preamble for a newly developed antibiotic.<sup>[56]</sup>

Table 2. IC <sub>50</sub> of compound <b>32a</b> to <b>32d</b> .					
Comp name	R <sub>1</sub>	R <sub>2</sub>	X	Y	MIC50(μM)
<b>32a</b>	H	H	C	N	> 100.0
<b>32b</b>	H	H	N	C	> 100.0
<b>32c</b>	H	Br	C	N	25.0
<b>32d</b>	Br	H	N	C	6.25

Table 1. IC <sub>50</sub> of compound <b>29a</b> to <b>29k</b> .					
Comp-name	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	MIC(μM)
<b>29a</b>	H	H	Br	H	12.5
<b>29b</b>	Br	H	H	H	12.5
<b>29c</b>	H	H	Cl	H	12.5
<b>29d</b>	H	F	H	H	50.0
<b>29e</b>	H	I	H	H	> 100.0
<b>29f</b>	H	H	I	H	> 100.0
<b>29g</b>	H	OH	OH	H	> 100.0
<b>29h</b>	H	Br	OH	H	50.0
<b>29i</b>	H	Br	OH	OMe	50.0
<b>29j</b>	H	-O <sub>X</sub> F	NA	H	6.25
<b>29k</b>	H	H	≡H	H	12.5

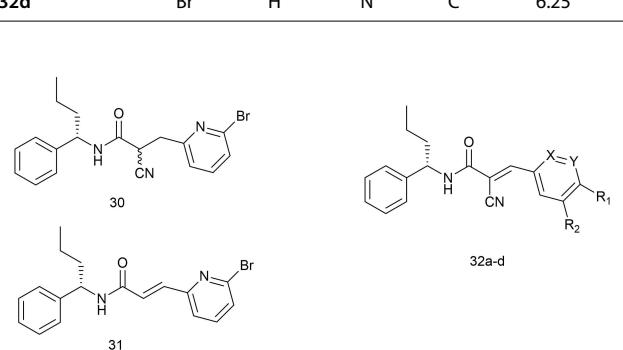


Figure 4. Molecular structures of Degrasyn (DGS) analogs.

Zhou et al. reported hydantoin and reduced amide-based small molecules. Hydantoin based small molecules possess the required qualities to be developed as antibacterial agents. Compound **37** is the most potent hydantoin that could combat motility in both gram positive and gram-negative bacteria. As comparison of FDA approved Vancomycin and nitrofurantoin, compound **37** (figure 5) exhibits excellent antibacterial activity against *S.aureus* ( $\text{MIC}_{50}$ , 0.5  $\mu\text{g/mL}$ ), *E. coli* ( $\text{MIC}_{50}$ , 1  $\mu\text{g/mL}$ ), *P.aeruginosa* ( $\text{MIC}_{50}$ , 1  $\mu\text{g/mL}$ ) *in vivo* lungs infected rat model. Another compound **38** (Figure 5), which is reducing amide-based small molecules further studied for lung infection which

has modulated with a particular hydrophobic motif in **38** that shows a potent antibacterial activity. They also studied *in vivo* efficacy of **38** against MRSA induced Pneumonia rat model with respect to the level of cytokine TNF- $\alpha$ . When **38** were treated, the standard in the rat model can reduce TNF- $\alpha$  cytokine level half of the control within three days. This result suggests that **38** could eradicate chronic lungs infection.<sup>[57]</sup> **38** is currently successfully completed phase II clinical trial and marketed under brand name lytixar. Peng et al. synthesized the cationic antimicrobial polyurethane that is a most active antibacterial agent which acts as a narrow-spectrum antibiotic towards

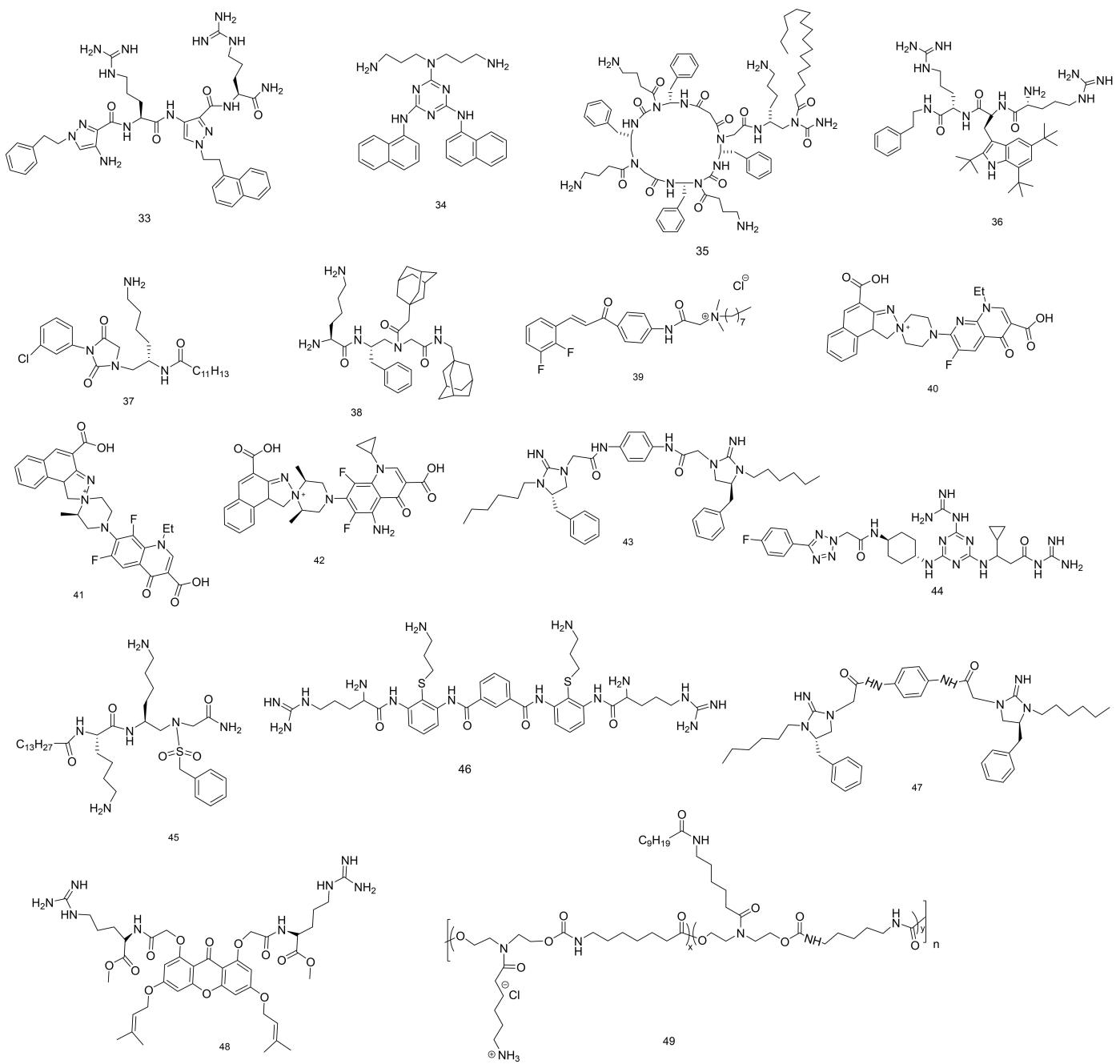
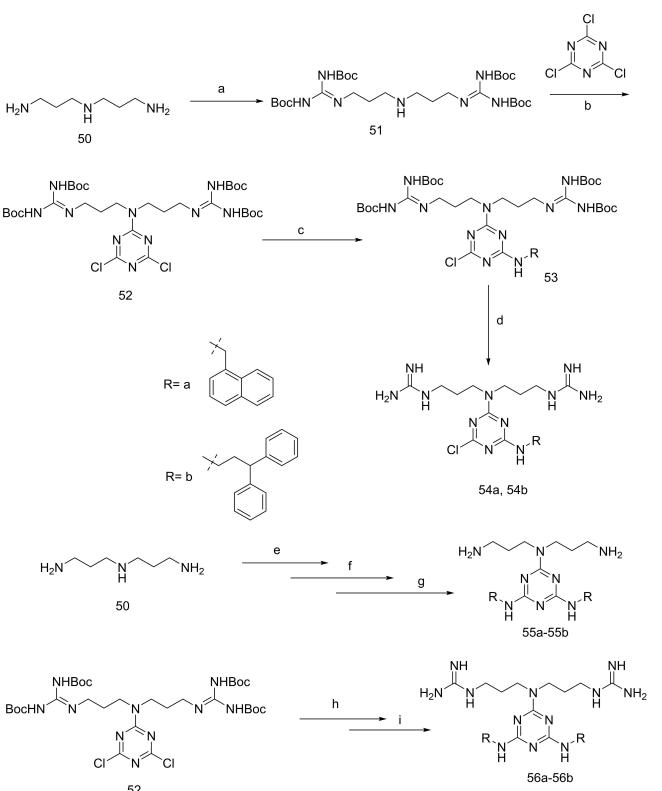


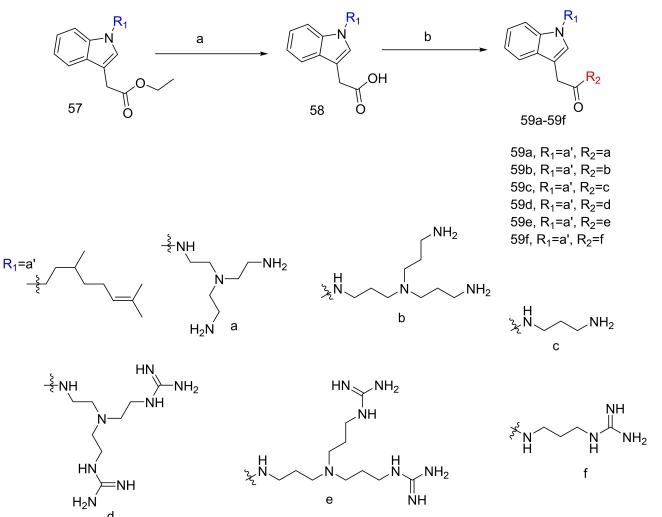
Figure 5. Summary of peptide-mimetics and fluoro quinolone drugs.

gram-negative bacteria viz. *E.coli*, *A. baumanii*. They explored switching narrow-spectrum to broad-spectrum antibiotics where they modified polyurethane drug activity by using various concentrations of fatty acid. Ultimately it has been found that compound **49** (Figure 5) with 4% decanoic acid exhibits remarkable antibacterial activity against gram-positive bacteria such as *S. aureus* and all MRSA. Though hemolytic study in mammalian RBCs (Red blood cells) express increasing toxicity *in vivo* due to excess hydrophobicity for long-chain fatty acid.<sup>[55,58]</sup> Chu et al. synthesized a series of chalcone derivatives using hydrothermal reaction by mimetic of the cationic small peptidomimetic antibacterial drug. Finally, all derivatives are being tested with the various strains of *S. aureus*, *E. coli* and *P. aeruginosa*. Compound **39** (Figure 5) had expressed the highest morbidity against *S.aureus* and *E.coli* due to its optimal chain length where n=7. Fedorowicz et al. synthesized a series of novel fluoroquinolone based on quaternary ammonium salt (Figure 5) via tandem mannich amination from profluorophoric isoxazolones. They tested all compounds against various strains of bacteria, among these compounds **40**, **41**, **42** having shown the most prominent antibacterial activity. Again, they verified molecular docking probe-protein interaction and it found that ser84 being hydrogen bond strongly with core quinolone part and quaternary ammonium triazolinium ring sharply interact with glutamic residue of GyrB/ParE<sup>[59]</sup>.

Another important class of triazine based SPMs are considerable medicinal properties in recent year, due to their diverse structural aspects. Yet, triazine based heterocyclic derivatives have many biological overview in cancer, malaria and treated as antiviral, Gunasekaran et. al. have shown a series of triazine based SPMs having strong antibacterial activity. Initially, norspermidine was used abundantly to the main precursor of desired derivatives. Compound **54a**, **54b**, **55a–b** and **56a–b** are the selective derivatives those are synthesized through multistep (Scheme 6) prior to antibacterial and hemolytic screening. These entire compounds have screened against multi drug resistance *P. aeruginosa* and Vancomycin resistance *E. faecium*. Among these compound **56a** and **56b** shown most active against above two strain but hemolytic activity is not satisfied,  $HC_{50}$  140  $\mu\text{M}$  and 88  $\mu\text{M}$  respectively. Instead **55a** and **55b** have moderate activity with high  $HC_{50} > 320 \mu\text{M}$  for **55b**.<sup>[60]</sup> Indole derivatives have enormous medicinal properties could be used as anti-cancer, antibacterial, anti-fungal, anti-inflammatory and anti-malarial candidate. Chen et. al synthesis indole based SPMs derivatives which delivered effective amphiphilic nature since it was bearing hydrophilic and hydrophobic moiety to its suitable moieties. However all derivatives were tested against *S. aureus* ATCC29213, MRSA NCT10442, *E. coli* ATCC25922 and it was found that the all derivatives exhibited moderate to high antibacterial activity (Scheme 7), selectively compound **59d**, **59e** and **59f** have promising anti-bacterial activity against *S. aureus* ATCC29213, MRSA NCT10442, *E. coli* ATCC25922 strain. However,  $HC_{50}$  is not tolerable while **59e** and **59f** is considered as suitable antibacterial candidate though it shows higher antibacterial activity than **59d**, where **59d** shows well balanced between



**Scheme 6.** (a) *N,N*'-di-Boc-*N'*-triflyguanidine, TEA, DCM, rt, 6 h, 68%; (b) cyanuric chloride, DIEA, DCM, 0 °C, 4 h, 97%; (c) R-NH<sub>2</sub>, DIEA, DCM, rt, 4 h; (d) TFA/ DCM (3:1), 0 °C - rt, 3 h.(e) (Boc)<sub>2</sub>O, DIEA, THF, 0 °C - rt, 21 h, 80%; (f) cyanuric chloride, DIEA, DCM, 0 °C, 3 h, 87%; (g) (i) R-NH<sub>2</sub>, DIEA, 1,4-dioxane, reflux, 14 h; (ii) TFA/DCM (3:1), 0 °C - rt, 3 h; (h) (i) R-NH<sub>2</sub>, DCM, rt, 4 h; (ii) TFA/ DCM (3:1), 0 °C - rt, 3 h.



**Scheme 7.** Synthesis of idole derivatives **59a–59f**

antibacterial activity ( $IC_{50}$  1.56  $\mu$ g/mL) and hemolytic activity ( $HC_{50} > 200$   $\mu$ g/mL) due to their excellent structural aspects.<sup>[61,62]</sup>

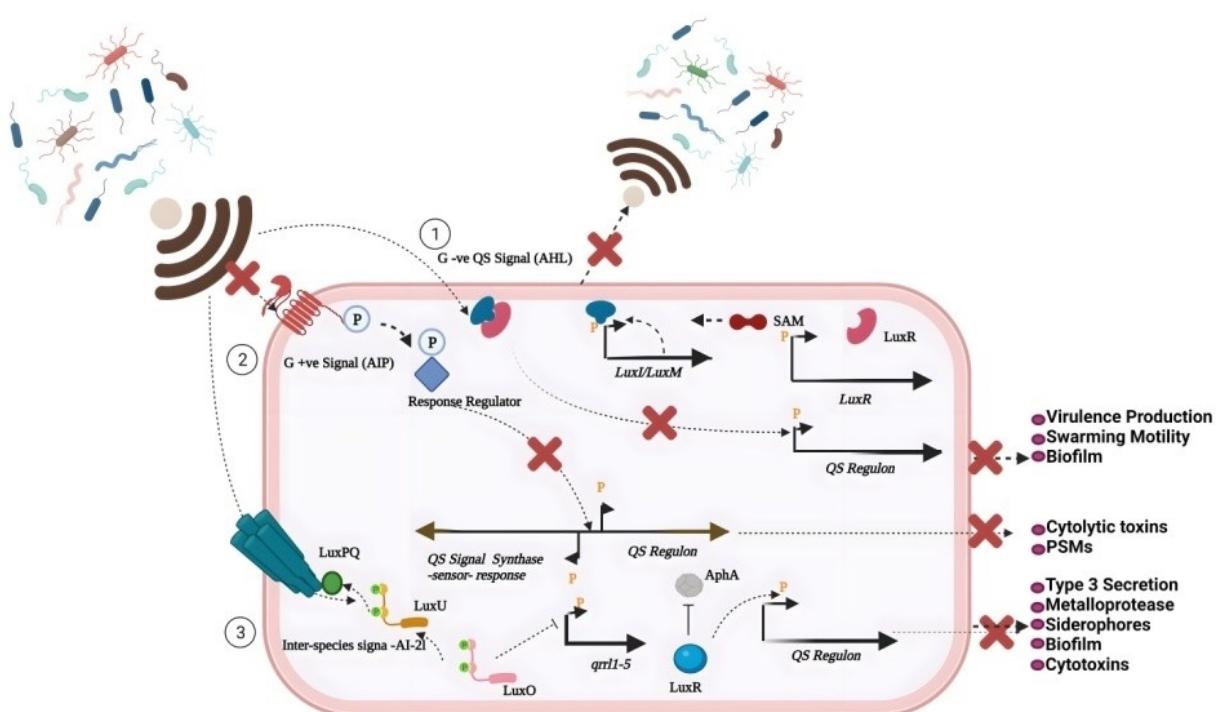
#### 4. Next Generation Anti-infective

With the increased understanding of genetic mechanisms of antimicrobial resistance, recent research is directed towards identifying novel targets and alternative therapies. Several techniques including vaccines targeting microbial virulence determinants,<sup>[63]</sup> bacteriophages,<sup>[64,65]</sup> probiotics,<sup>[66]</sup> and small-molecule inhibitors of the quorum-sensing system.<sup>[67,68]</sup>

Among the above techniques, targeting quorum-sensing signaling pathways is fast gaining attention. It is understood that clinically relevant bacteria namely ESKAPE pathogens are shown to express their virulence and pathogenesis through quorum sensing mechanisms. Quorum sensing is the cell density-dependent bacterial communication system through which they express group behavior, mostly, virulence characteristics. They communicate among each other (intraspecies) and with others (interspecies) by releasing specific quorum-sensing signaling molecules. The intraspecies signaling molecules are varied in Gram-negative and Gram-positive bacteria. In the case of Gram-negative bacteria, the signal molecule is Acyl homoserine Lactones (AHL) and for Gram-Positive bacteria, the signals are auto-inducing peptides. These signal molecules are species-specific and are regulated by a well-defined quorum sensing signaling network. It is interesting to note that the

quorum sensing mechanism is not an essential trait for survival but is required for the expression of virulence. The byproducts of these quorum-sensing-regulated phenotypes are often associated to affect the human host by invading the host system. Among them, biofilm formation is one of the most studied group behaviors regulated by quorum sensing. Bacteria rely on QS signal molecules to regulate the synthesis of polysaccharides and accessory molecules required for the formation and maturation of the biofilms.<sup>[69]</sup> Research shows that the AHLs are produced by bacteria thriving as alone or in mixed inter and intra species biofilms. These AHLs support the structure, dynamics and stress resistance of the biofilms.<sup>[49,70]</sup>

The regulation of gene expression in Gram-positive bacteria is achieved through autoinducing peptides (AIPs) that are recognized by two componentsystems (TCS) on the bacterial cell surface (Figure 6). AIPs are synthesized as propeptides and undergo hydrolysis by extracellular protease resulting in mature AIPs, which upon reaching the desired threshold are sensed by kinases. The sensory kinases upon interaction with AIPs get phosphorylated and upregulate the "group" behavior via a phosphorylated regulatory receptor.<sup>[71]</sup> The clinically relevant bacteria – *S. aureus*, *S. pneumoniae*, *E. faecalis*, and *S. mutans* regulate their virulence through this mechanism.



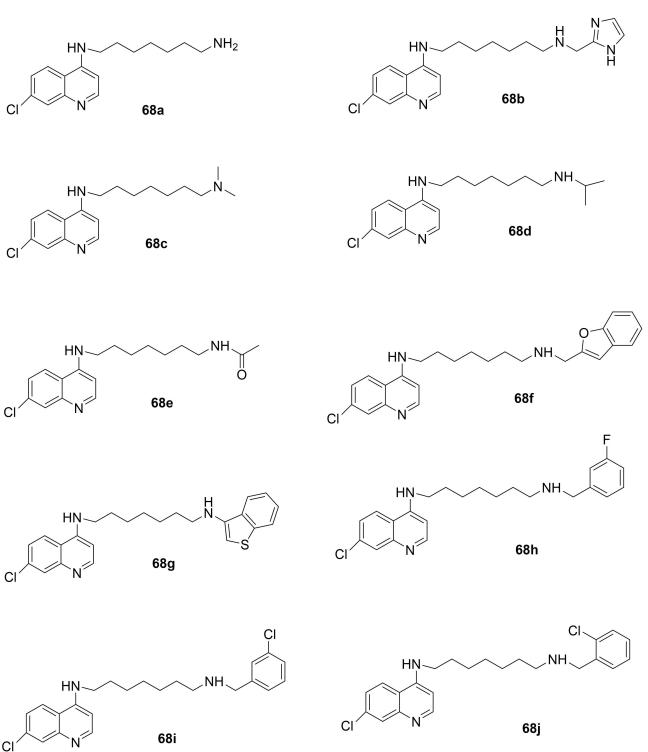
**Figure 6.** A generalized Scheme to depict the role of intra (gram +ve and gram-ve)/inter-species bacterial communication system in establishing pathogenesis. The diagram also shows the blockage of communication via, Next Generation Small Peptidomimetic Molecules (SPM) as anti-infective therapies. (1) The signal, Acyl homoserine lactone (AHL) is sensed by the cytoplasmic receptor (LuxR), the active form of LuxR-AHL complex regulate the expression of QS-responsive genes to effect gram-ve bacteria pathogenesis (2) The signal, Autoinducing Peptide (AIP) is received by the sensor and activate its kinase domain to further transfer the phosphate flow to the response regulator to switch on the QS-responsive genes and effect gram +ve pathogenesis (3) The inter-species signal, autoinducer -2 (AI-2) is responded by the LuxPQ receptor and the activation of phosphatase will reverse the flow of phosphate and once when the global regulator, LuxO is dephosphorylated it represses the activation of small molecule regulatory RNAs (qrr1-5) expression and in turn the LuxR switch on the QS-responsive gene to effect the pathogenesis of either the gram-ve/gram + ve pathogens.

In Gram-negative bacteria LuxI/LuxR type quorum sensing is a common and well-known process where LuxI is required for the synthesis of the quorum-sensing molecules – n-Acyl homoserine lactone and LuxR is the quorum-sensing regulator whereupon interaction with AHL molecules, changes its conformation to upregulate the group behavior. The most striking and most studied example of this category is the regulation of virulence using QS by *P. aeruginosa*. The conventional method of applying antibiotics to treat microbial infections has resulted in the generation of adverse effects like the development of antimicrobial resistance and the destruction of the beneficial commensal bacterium. The development of anti-virulence/anti-pathogenic drugs has gained momentum to subdue microbial infections. A comprehensive understanding of the QS systems coupled with development in the field of drug discovery has led to the identification of QS inhibitors of various bacterial species.

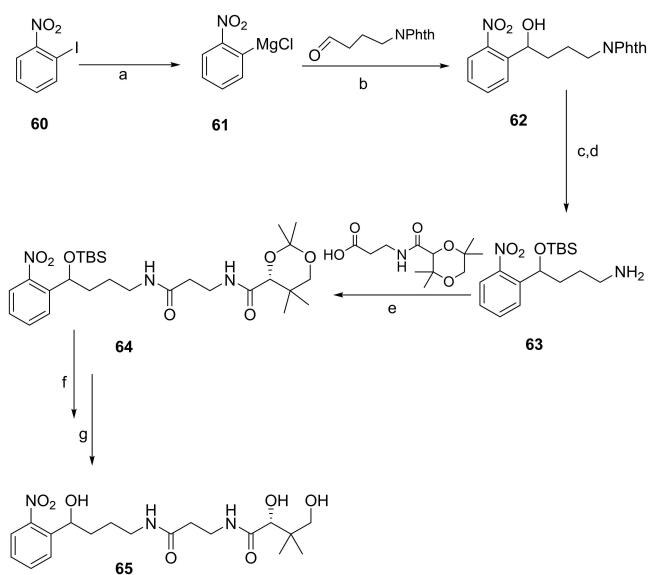
Quorum sensing inhibition is mediated by either enzymatic or non-enzymatic processes. In the enzymatic process, the released molecules are degraded by lactonase, acylase and oxidoreductase at specific sites of the released signaling molecules. On the other hand, non-enzymatic deals with the blocking the releasing of the signaling molecules through competitive inhibition. The non-enzymatic degradation is considered to be more effective than the enzymatic degradation process.<sup>[72]</sup>

Studies with *P. aeruginosa* have revealed that strategic modification of autoinducer (acyl-homoserine lactone) via altering the homoserine lactone moiety has been successful in inhibiting the production of pyocyanin (Scheme 8). Among several small anti-quorum sensing molecules of long-chain quinoline derivatives, N-octaneamino-4-aminoquinolines exhibit-

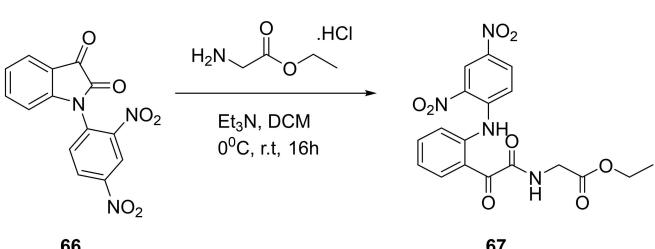
ited activity against *P. aeruginosa* via effective depletion of pyocyanin and defense PQS-signalling channel. While pyocyanin production could not be reduced significantly by compound **68a-d** (Figure 7), compound **68e** could diminish the pyocyanin production, owing to the agonistic effect exerted by the conversion of amine to amide. Compound **68a-d** could only inhibit the PqsR activity moderately, and compound **68f-j** exhibits a significant effect against PqsR activity.<sup>[73]</sup> Nizalapur et al. synthesized a N-arylisatin based glyoxamide derivative, compound **67** (Scheme 9) which also inhibited pyocyanin production in *P. aeruginosa* MH602. These non-AHL glyoxamide derivatives have potent QSI activity for the treatment of bacterial disease. GFP fluorescence reduction and QS inhibitory assay with *P. aeruginosa* MH602 and *E. coli* incubated with a



**Figure 7.** Compound **68a-k** reduce pyocyanine production ( $112 \pm 5$ ,  $93 \pm 5$ ,  $(117 \pm 15)$ ,  $(94 \pm 6)$ ,  $(157 \pm 6)$ ,  $(12 \pm 4)$ ,  $(8 \pm 2)$ ,  $(8 \pm 4)$ ,  $(7 \pm 2)$ ,  $(3 \pm 2)$ ,  $(11 \pm 4)$  respectively and inhibition (%) of PqsR activity ( $68 \pm 2$ ,  $(46 \pm 6)$ ,  $(97 \pm 4)$ ,  $(54 \pm 4)$ ,  $(113 \pm 10)$ ,  $(7 \pm 0.5)$ ,  $(25 \pm 2)$ ,  $(31 \pm 3)$ ,  $(27 \pm 2)$ ,  $(3 \pm 2)$ ,  $(11 \pm 4)$  respectively against *P. aeruginosa*.

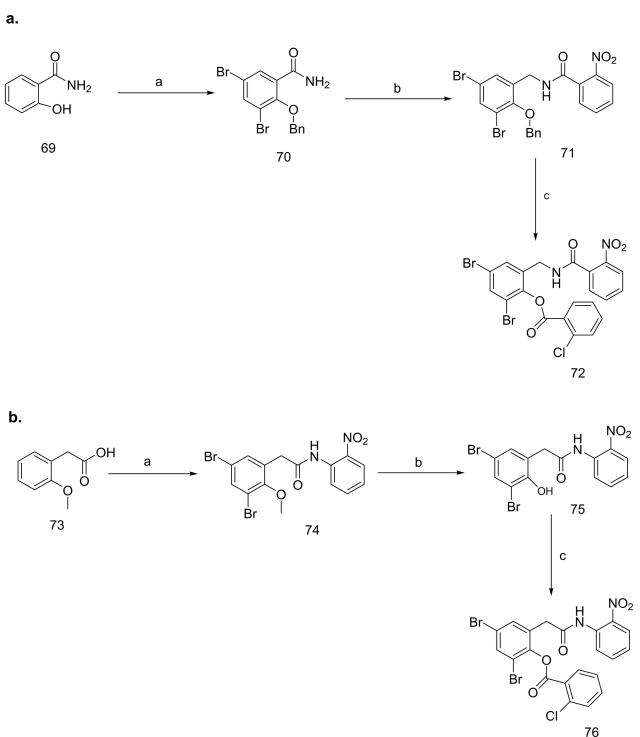


**Scheme 8.** (a) PhMgCl, THF,  $-40^{\circ}\text{C}$ , 30 min; (b) THF,  $-40^{\circ}\text{C}$ , 30 min, (yield 85%) (two steps); (c) TBSCl, imidazole, DMF, rt, 18 h, (yield 62%); (d)  $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ , EtOH, reflux, 2.5 h, (yield 98%); (e) DCC, 4-hydroxy-1H-benzotriazole, DMF, rt, 19 h, (yield 67%); (f)  $\text{H}_2$  (1 atm), Pd/C (10 wt %), ethyl acetate, rt, 20 h, (yield 87%); (g) 1 N-HCl in ethyl acetate, rt, 3 h

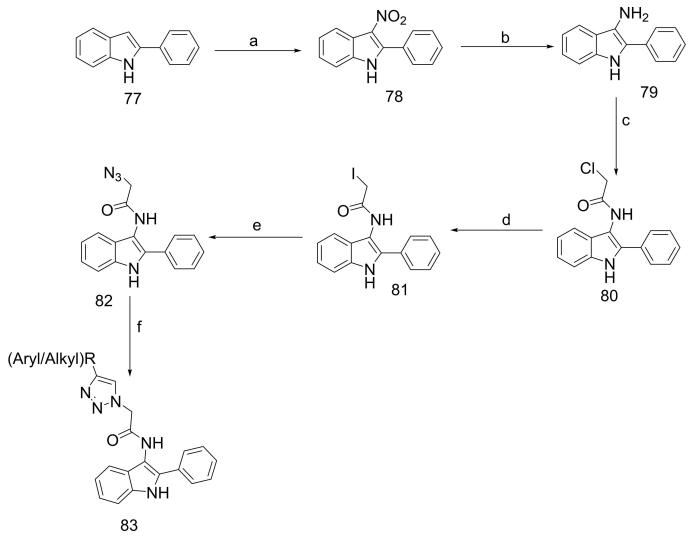


**Scheme 9.** (a) compound **66** (1 equiv.), Glycine-OEt (2.5 equiv.),  $\text{Et}_3\text{N}$  (2.5 eq.), DCM, rt, 16 h.

different kind of non-AHL glyoxamide derivatives showed that glycine-Oetglyoxamide **67**, at 250  $\mu$ M concentration exhibited



**Scheme 10.** **a:** (a) Br<sub>2</sub> / AcOH, BnBr/K<sub>2</sub>CO<sub>3</sub>, Acetone, (92% yield). (b) 2-nitrobenzoic acid, LiAlH<sub>4</sub>/THF, SOCl<sub>2</sub>/CAN, (58% yield). (c) BBr<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>, -78°C, EtN(iPr)<sub>2</sub>, 2-Chloro-benzoyl chloride, DCM. **b:** (a). i. 2-nitroaniline, PCl<sub>3</sub>/ACN, 80 °C, (92% yield), ii. BBr<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 60 min, NBS/ACN, (88% yield). (b) Lithium hydroxide/THF, rt, 3 h. (c). Et<sub>3</sub>N, (i-Pr)<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>, 2-chloro-benzoyl chloride, (91% yield).

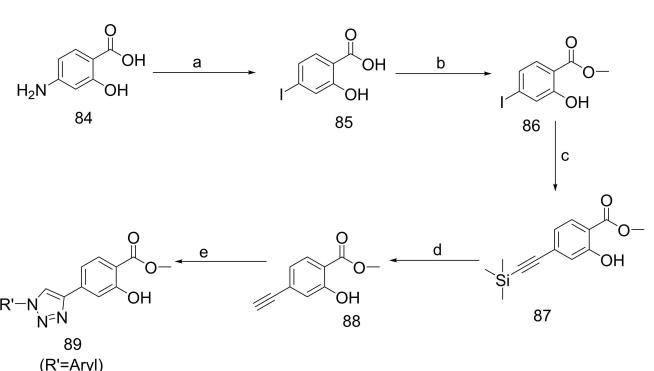


**Scheme 11.** (a) NaNO<sub>2</sub> (1.0 eq), Acetic acid, rt, 30 min; (b) 10% Pd/C (10% wt/vol), N<sub>2</sub>H<sub>4</sub>·2H<sub>2</sub>O (10.0 eq.), EtOH, reflux, 2 h; (c) Chloroacetyl chloride (1.0 eq.), Pyridine (3.0 eq.), DCM, 0 °C – rt, 1 h; (d) KI (1.5 eq.), acetone, 50 °C, 24 h; (e) NaI<sub>3</sub> (1.6 eq.), DMF/H<sub>2</sub>O (8:2), 0 °C; (f) Substituted terminal alkynes (1.5 eq.), CuSO<sub>4</sub>·5H<sub>2</sub>O, (10 mol%), Sodium ascorbate (10 mol%), DMF/H<sub>2</sub>O (8:2), rt-55 °C, 6–16 h.

about 48.7 ± 0.2% and 73.6 ± 0.6% inhibition against *P. aeruginosa* and *E. coli*, respectively.<sup>[74]</sup>

The expression of virulence factors in *P. aeruginosa* is regulated by transcriptional proteins LasR and RhlR<sup>[75]</sup>. Capilato et al. synthesized a series of triaryl substituted small molecules **72**, **76** (Scheme 10&10a) library to attenuate the LasR receptor and analyzed the binding effect of the LasR receptor with the series of synthesized molecules. It was reported that all amino acids in the HSL-binding pocket have significant interaction on substituted tri-aryl derivatives. Moreover, ortho-substituent potentially binds within the proximal hydrophobic region in the LasR receptor, while para or meta substituents exhibit weak binding ability with the various interacting sites. The ortho-substituted analogs (MMGBSA binding energy -87.12 ± 20.87 Kcal/mol) have a more binding affinity on HSL-binding pocket than para-substituted analogs (MMGBSA binding energy -18.86 ± 27.79 Kcal/mol).<sup>[76]</sup>

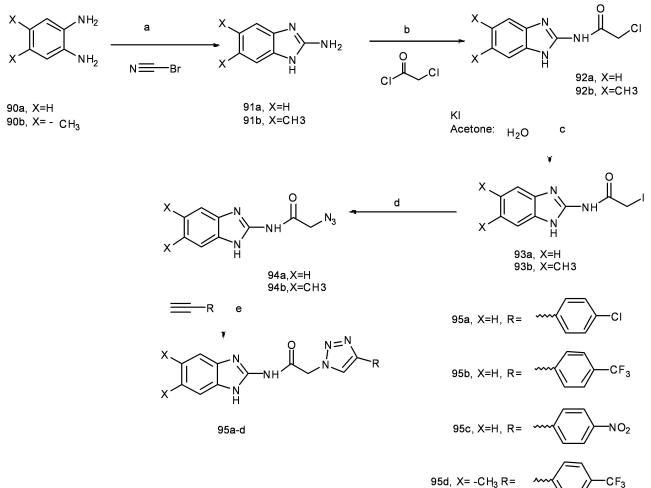
Likewise, a series of 2-phenyl indole-amide-triazole derivatives were evaluated for bacterial anti-QS activity against *P. aeruginosa* MH602. AHL functionalized 1, 2, 3 triazole has potent antibacterial activity boosts to elevate drug efficacy by the alternation of other functionality in triazole ring.<sup>[77]</sup> comparatively, compound **83** (Scheme 11) was found to be more efficient than other derivatives, which could effectively reduce AHL-QS molecule's concentration by inhibiting las-informer in *P. aeruginosa* MH602. Substitution with -C<sub>3</sub>H<sub>7</sub>, **83**, exhibited a significant reduction in GFP fluorescence (46.29 ± 3.58%), at 250  $\mu$ M concentration and with -C<sub>4</sub>H<sub>9</sub>, **89** (Scheme 12), at the same 250  $\mu$ M concentration resulted in greater inhibition of GFP expression by 58.89 ± 4.83%. In-vitro analysis with HEK-293 cell lines revealed the compounds **83** and **89** (Scheme 11 & 12) showed significant toxicity at very low concentrations (10–20  $\mu$ M). Compound **95d** inhibited the LasR cognate protein which was evident by the reduction of GFP fluorescence emission by *P. aeruginosa*. Benzimidazole **95c** with nitro functionality at p-substituent also demonstrated a significant potential to inhibit LasR (68.38%) while substitution of p-substituent with chloro functionality reduced the inhib-



**Scheme 12.** (a) NaNO<sub>2</sub> (2.2 eq.), KI (2.5 eq.), Con. HCl in H<sub>2</sub>O, 0 °-5 °C, 2 h; (b) SOCl<sub>2</sub> (4.1 eq.), MeOH, Reflux, 14 h; (c) TMS-acetylene (1.2eq), Pd(OAc)<sub>2</sub> (5 mol %), PPh<sub>3</sub> (5 mol %), rt 1 h then 90 °C; (d) LiOH (4.0 eq.), THF/H<sub>2</sub>O (10:3), rt, 12 h; (e) Substituted azide (1.5 eq.), CuSO<sub>4</sub> · 5H<sub>2</sub>O (10 mol %), Sodium ascorbate (10 mol %), DMF/H<sub>2</sub>O (8:2), rt, 12 h.

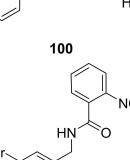
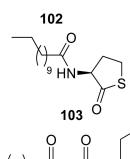
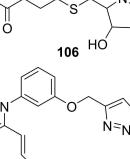
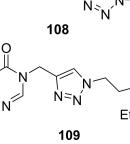
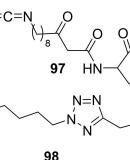
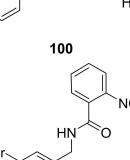
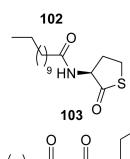
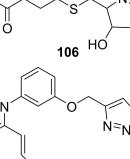
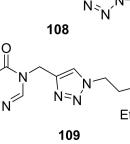
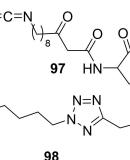
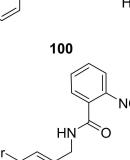
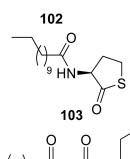
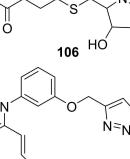
ition potential up to 3.24 %. This suggested that the electron-withdrawing functionality at p-position would significantly impact QS- activity in LasR protein. Furthermore, compound **95a-d** (Scheme 13) at 100  $\mu$ M concentration did not affect the viability of HEK (Human embryonic Kidney cells) cell line, demonstrating the non-toxic nature of these compounds.<sup>[78]</sup>

Müh et al. synthesized a library of compounds approximately 20,000, and all compounds were screened in various concentrations against *P. aeruginosa*. Compound **98** (Table 3) a tetrazolium motif with C-12 long chain had shown abundant inhibitory activity ( $\text{IC}_{50}$  30 nM). Compound **98** disrupted the activity of two QS-circuits in *P. aeruginosa* leading to attenuation of virulence factors including pyocyanin, elastase, etc. Based on these observations, it was suggested that compound **98** could function as a potent modulating agent of quorum sensing.<sup>[79]</sup> A series of  $\gamma$ -lactams and azahemiacetal analogous were extensively studied for their potential in inhibiting bacterial virulence. It had been found that  $\gamma$ -thiolactone analogous **103** inhibit LuxR activity and compound **104**, **105** (Table 3) can dramatically reduce *las* activity in all tested concentration.<sup>[80]</sup> Similarly, they had prepared 1,4 dideoxy-[4-aza] S-ribosylhomocysteine from D-glulonic acid  $\gamma$ -lactone via 1-amino- 1,4-anhydro-1-deoxy D-ribitol. Compound **106** (Table 3) could inhibit LuxS activity [ LuxS (S-Ribosylhomocysteinase), a key enzyme that produces autoinducer-2 initiating an interference within interspecies bacterial communication.<sup>[81]</sup> A library of 1,2,3 triazole linked 4(3H)- quinazolinones derivatives were tested against ESKAPE ["ESKAPE" enclosed six pathogenic bacteria- *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* species] pathogens. Further analysis revealed that these compounds exhibited minimum inhibitory concentration at very low concentrations (64–0.03  $\mu\text{g/mL}$ ) when compared to conventional antibiotic levofloxacin. While most of the compounds in this library



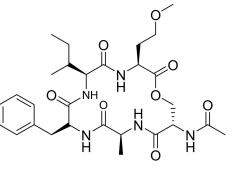
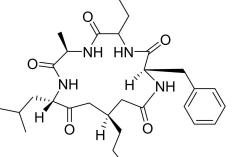
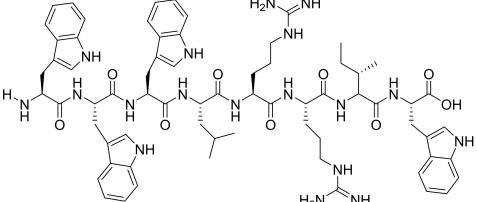
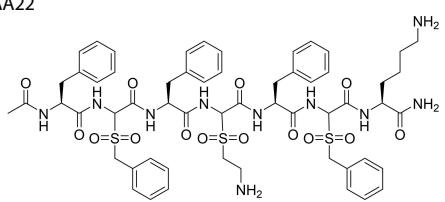
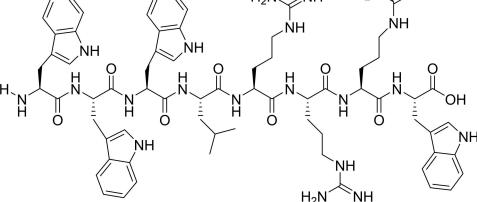
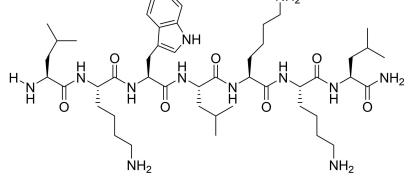
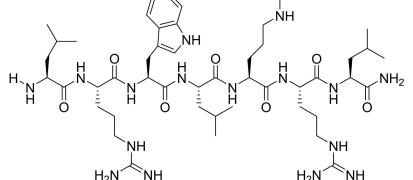
**Scheme 13.** (a) CNBr (1.1 eq.), MeOH, reflux, 5 min; (b) chloroacetyl chloride (1.0 eq.), pyridine (2.5 eq.), DCM, 0 °C-rt, 12 h; (c) potassium iodide (1.2 eq.), acetone, 55 °C, 12 h; (d) NaN<sub>3</sub> (1.5 eq.), DMF/H<sub>2</sub>O (8:2), 0 °C; (e) substituted terminal alkynes (1.4 eq.), Copper Sulphate penta hydrate, (5 mol%), sodium ascorbate (10 mol%), DMF / H<sub>2</sub>O (8:2), rt, 6–16 h.

**Table 3.** Summary of quorum sensing mediated small molecule.

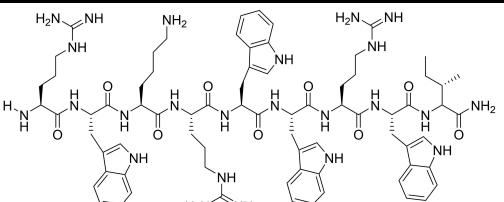
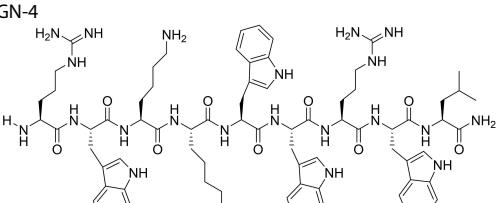
Compound structure and name	Inhibitory concentration(μM)	Ref.
	$IC_{50}$ 3μM LasR inhibitor in <i>P.aeruginosa</i>	[86]
	$IC_{50}$ 30μM LasR inhibitor in <i>P.aeruginosa</i>	[87]
	LasR Inhibitor in <i>P. aeruginosa</i> $IC_{50}$ <i>P.aeruginosa</i> (30 nM)	[79]
	$IC_{50}$ 0.6μM LasR inhibitor in <i>P.aeruginosa</i>	[88]
	$IC_{50}$ 0.4μM CviR inhibitor in <i>P.aeruginosa</i>	[89]
	$IC_{50}$ 3.6μM LasR inhibitor in <i>P.aeruginosa</i>	[90]
	$MIC_{50}$ <i>S.aureus</i> (25-50μg/mL) <i>E.coli</i> - Not tested <i>P.aeruginosa</i> - Not Tested	[91]
	$IC_{50}$ 0.04μM LasR inhibitor in <i>P.aeruginosa</i>	[80]
	$IC_{50}$ 10-15μM LasR Inhibitor in <i>P.aeruginosa</i>	[80]
	$IC_{50}$ 1.1μM LasR inhibitor in <i>P.aeruginosa</i>	[80]
	$IC_{50}$ 40μM LuxS inhibitor in <i>B.subtilis</i>	[81]
	$MIC_{50}$ <i>S.aureus</i> (0.5μg/mL)	[82]
	$MIC_{50}$ <i>S.aureus</i> ( 64μg/mL ) <i>P.aeruginosa</i> ( 16μg/mL )	[92]
	$MIC_{50}$ <i>S.aureus</i> ( 0.625μg/mL ) <i>P.aeruginosa</i> ( 0.625μg/mL )	[93]

demonstrated antibacterial activity against the ESKAPE pathogens, compound **107** (Table 3) inhibited *S. aureus* at very low concentration ( $\text{MIC}_{50}$ , 0.5–4  $\mu\text{g}/\text{mL}$ ) revealing its potential as

**Table 4.** Summary of gram-positive QS mimetics small molecules.

Chemical Structure	Inhibitory Concentration	Ref.
AIP-I (2)	<i>S. aureus</i> -5 nM	[94]
		
Solonamide-A	<i>S. aureus</i> 8.5-17 μM	[95]
		
TetraF2 W-RR	<i>S. aureus</i> 1.6-3.1 μM	[96]
		
γ-AA22	<i>E. faecalis</i> 2 μg/mL	[97]
		
Horine	<i>S. aureus</i> - 4 μM	[98]
		
P4	<i>S. aureus</i> , <i>C. albicans</i> 50 μM	[99]
		
P5	<i>S. aureus</i> , <i>C. albicans</i> 50 μM	[99]
		
GN-2	<i>S. aureus</i> 3.1 μg/mL	[100]

**Table 4.** continued

Chemical Structure	Inhibitory Concentration	Ref.
	<i>S. aureus</i> -3.1 µg/mL	[100]
	<i>S. aureus</i> - 3.1 µg/mL	[100]

narrow-spectrum antibiotic.<sup>[82]</sup> Similar to Gram-negative system, there are multiple inhibitors developed against Gram positive bacteria which targets the quorum sensing system. Table 4 gives a detailed account of the Gram positive inhibitors developed in the last five years. It should be noted that Gram positive signal molecules are peptides (Autoinducing peptides) and there are previous reports on the design of the peptides which mimics the natural AIPs and inhibition is promoted through competitive inhibition. Pathogenic Gram – positive organisms like *S. aureus* and *E. faecalis* are focussed more for the development of inhibitors.

## 5. Peptidomimetics – Answer to the growing problem of AMR?

The current report highlights the two clinically relevant microbial activities of small peptidomimetic molecules – Antibacterial and Anti-infective. In the era of antimicrobial resistance, such a dual role in addition to the immune modulatory role, SPMs are one of the promising tackling strategies. Peptidomimetic provides a greater molecular diversity, biological stability and bioavailable. Peptidomimetics are advantageous as they do not support the generation of resistance. They also could increase the antimicrobial activity of conventional drugs by acting synergistically. This technology also increases the receptor affinity towards the target, increases the specificity and also increases the transportation of the peptides. Current research is focused on the expanding the functionality of the SPMs, making it smart. These engineered SPMs include pH responsive peptides, peptide drug conjugates

and nanotechnology based SPMs having nanoscale size with self assembling properties. With the advent of precision medicine there are bacterial specific peptides designed. Such engineered SPMs are multifunctional and can penetrate cells with much ease, in addition to the other advantages of SPMs. Current report highlights the small molecules that have been mimicked with the antimicrobial peptides and QS peptides successfully. Further exploration and development on the aspects of the drug's scaffold, cationic charge, and lipophilicity are required. While much research is focused on small molecules, high molecular weight peptidomimetics should also be widened. Even with such advantages, studies have shown that these SPMs are not as effective as HDPs. Further improvement is required in terms of improving its clinical properties. This will help in maximizing the number of SPMs' performance in the clinical trials and bringing it to the market. Another striking challenge is the design of SPMs which should account for the dynamic conformations of the protein upon binding of these SPMs. The field of peptidomimetics is steadily improving and expanding with cutting edge technologies like nanotechnology accounting for smart drug as well as delivery system. With the wide spectrum activity as both antibacterial and anti-infective, SPMs provide the promise to be exploited as an individual drug or as an augmentative therapy along with the conventional antibiotics. Such versatility is the need of the hour for the ever-increasing antimicrobial resistance.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Antibacterial drug · Pathogenic bacteria · Quorum Sensing · Small peptidomimetic molecules

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