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Promising antibacterial agents against multidrug resistant *Staphylococcus aureus*

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ABSTRACT

Rapid emergence of multidrug resistant *Staphylococcus aureus* infections has created a critical health menace universally. Resistance to all the available chemotherapeutics has been on rise which led to WHO to stratify *Staphylococcus aureus* as high tier priorty II pathogen. Hence, discovery and development of new antibacterial agents with new mode of action is crucial to address the multidrug resistant *Staphylococcus aureus* infections. The egressing understanding of new antibacterials on their biological target provides opportunities for new therapeutic agents. This review underlines on various aspects of drug design, structure activity relationships (SARs) and mechanism of action of various new antibacterial agents and also covers the recent reports on new antibacterial agents with potent activity against multidrug resistant *Staphylococcus aureus*. This review provides attention on *in vitro* and *in vivo* pharmacological activities of new antibacterial agents in the point of view of drug discovery and development.

1. Introduction

Staphylococcus aureus, one of the widespread infectious pathogen has become an alarming health threat worldwide [1–6]. In view of this pressing issue, *Staphylococcus aureus* was recently stratified as high tier priorty II pathogen by World Health Organization (WHO) [7,8]. Alarmingly, rise in nosocomial and community infections caused by the multi drug resistant *Staphylococcus aureus* is driving the critical need for discovery and development of new antibacterial agents [9–12]. Multidrug resistant *Staphylococcus aureus* (MDR-SA) has emerged as the most formidable bacterial strains for the available antibiotics which includes methicillin, vancomycin (glycopeptide), daptomycin (lipopeptide), linezolid (oxazolidinone), tedizolid (anoxazolidinone), dalbavancin (lipoglycopeptide), oritavancin (glycopeptide), ceftaroline (β-lactam antibiotic), ceftobiprole and carbapenems [13–26]. Hence, discovery and development of new antibacterial agents to subdue the various resistance mechanisms is a vital step to address the multidrug resistant *Staphylococcus aureus* infections. Design, synthesis and quest for antibacterial agents of new heterocycles with new mode of action has recently gained significant attention. The egressing understanding of new antibacterials on multidrug resistant *Staphylococcus aureus* provides opportunities for new therapeutic agents.

Scrupulous utilization of various heterocycles for the design and synthesis of new antibacterial agents has recently gained enormous enthusiasm to combat drug resistance. In the search for new antibacterial agents against multidrug resistant *Staphylococcus aureus*, several research groups have discovered and reported different heterocyclic systems with promising antibacterial properties. This review underscores on the various aspects of *in vitro* and *in vivo* activity, design, structure activity relationships (SARs) and mechanism of actions of different new antibacterial agents.

Abbreviations: AMP, antimicrobial peptides; CPX, ciprofloxacin; CrtN, Diapophytoene Desaturases; *EPI*, Efflux Pump Inhibitors; GCHMs, glabridin-chalcone hybrid molecules; hERG, thehumanEther-à-go-go-RelatedGene; ITQs, isothiazoloquinolones; KPC-2, Klebsiella pneumoniae Carbapenemase-2; LREF, linezolid-resistant *Enterococcus faecium*; MDR-SA, multidrug resistant *Staphylococcus aureus*; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin sensitive *Staphylococcus aureus*; MRSE, methicillin-resistant *S. epidermidis*; MVRSA, methicillin and Vancomycin-resistant *Staphylococcus aureus*; MBC, Minimum Bactericidal Concentration; MK, menaquinone; NDM-1, New Delhi metallo-beta-lactamase-1; PK, pharmacokinetic; PRSP, penicillin-resistant *Streptococcus pneumonia*; PLAs, propargyl-linked antifolates; PBP2a, penicillin binding protein 2a; PYR-NEO B, Pyrene-Neomycin B; QR-SA, quinolone-resistant *Staphylococcus aureus*; RMA, Resistance-Modifying Agent; SAR, Structure Activity Relationship; TMP, trimethoprim; TMK, thymidylate kinase; VRSA, vancomycin resistant *Staphylococcus aureus*; VRE, Vancomycin-Resistant Enterococci; WHO, World Health Organisation

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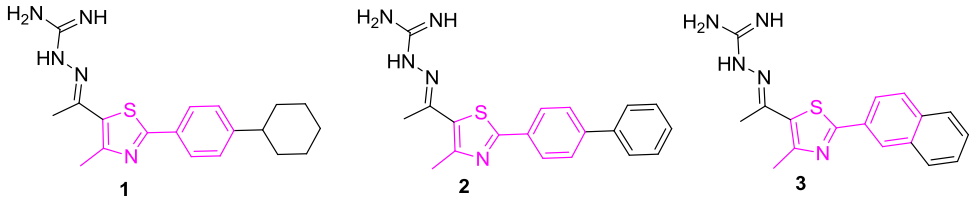


Fig. 1. Some phenyl thiazole derivatives with antibacterial activity.

2. Antibacterial agents

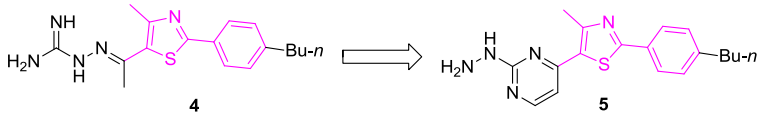
2.1. Phenyl thiazole derivatives

Phenyl thiazoles have been alluring several researchers due to virtue of its antibacterial properties. Mohammad et al. [27] reported the lead antibacterial compounds viz., thiazole and thiadiazole, which inhibited the growth of 18 strains of MRSA and VRSA. The lead consist of a central thiazole ring connected to two structural moieties paramount for antibacterial activity, viz., lipophilic moiety at the position C-2 and a cationic moiety at the position C-5. Thiazole and thiadiazole derivatives comprising variations to the lipophilic part was build to enhance the antibacterial activity against multidrug resistant *S. aureus* (MRSA and VRSA). The lead and its derivatives exhibited antibacterial activity against isolates of MRSA and VRSA at MICs 0.5–3.0 μg/mL. The antibacterial spectrum of some derivatives **1**, **2**, **3** (Fig. 1) surpassed that of several available antibacterial agents like linezolid, aminoglycosides, vancomycin, lincosamides, fluoroquinolones, and macrolides. Several thiazole derivatives were found to have good solubility and permeability properties. However, the activity data clearly suggested that the thiazole derivatives did not target the cell wall integrity or cytoplasmic membrane.

Seleem et al. [28] developed second-generation phenylthiazoles with hydrolyzable C=N bond joined to a more stable pyrimidine nucleus **5** (Fig. 2) with good pharmacokinetic profiles than first developed phenylthiazoles **4.** The SAR at the cationic region was thoroughly explored using various nitrogenous groups at position 2 of the pyrimidine nucleus. By tuning the lipophilic moiety, the research group found that the cyclohexenyl moiety to be the most active conformationally restricted derivative for the *n*-butyl moiety. Besides, with better safety margin and longer $t_{1/2,}$ these phenylthiazoles displayed a selective advantage of bactericidal action over drug Vancomycin. In 2017, Hagras et al. [29] reported a new series of biphenylthiazoles with a pyrimidine linker at position 5 of thiazole with various nitrogenous side chains at the position 2 of pyrimidine ring. Analysis of the SAR derivatives revealed that the piperazine side chain was preferable to piperidine derivative for better antibacterial activity. The aminopiperazine-containing compound **7** was reported to be more potent than the derivative **6** without the amine (Fig. 2). The augment in antibacterial activity of piperazinylcarboximidate derivative **8** was well validated in a *C. elegans* MRSA infection model. Among all the tested biphenylthiazoles, piperazinyl derivatives **6**, **7**, and **8** were found to be the most potent derivatives with MIC values ≤ 0.39 μg/mL.

Elsebaei et al. [30] reported the antibacterial activity of phenylthiazoles against multidrug-resistant strains. They have investigated a series of new phenylthiazoles with alkynyl side-chains **9**, **10** (Fig. 3). The most active lead compounds inhibited the growth of clinically relavant MRSA strains with MIC = < 0.5 μg/mL, by interfering with cell wall synthesis via inhibiting undecaprenyl diphosphate phosphatase and undecaprenyl diphosphate synthase enzymes. Among all the tested compounds, *in vivo* PK studies of compound **11** (Fig. 3) showed good stability to hepatic metabolism with a $t_{1/2}$ ~4.5 h. The studies also revealed that, compound **11** has similar potency to Vancomycin, in neutropenic mouse thigh-infection model at a lower dose and reduced the bacterial load of MRSA in a systemic, deep-tissue infection.

Mohammad et al. [31] conducted rigorous studies of the structure activity relationship of the synthesized compounds and revealed that the nonpolar, hydrophobic functional group was favoured at position 2 of thiazole and an ethylidenehydrazine-1-carboximidamide moiety is essential at position 5 for anti-MRSA activity. Furthermore, the MTS assay confirmed the derivatives **12**, **13**, and **14** (Fig. 4) to possess favourable toxicity profile. Studies with hepatic microsomes revealed that compound **12** was metabolically stable compared to the lead, (*Z*)-2-(1-(2-(4-butylphenyl)-4-methylthiazol-5-yl)ethylidene)hydrazinecarboximidamide (Fig. 4). Islam Eid et al. [32] reported the promising antibacterial potency of arylthiazole antibacterials. Tuning of the size and



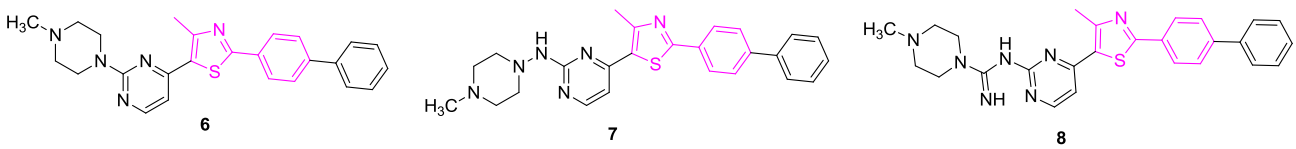


Fig. 2. Some second generation phenyl thiazole derivatives with antibacterial activity.

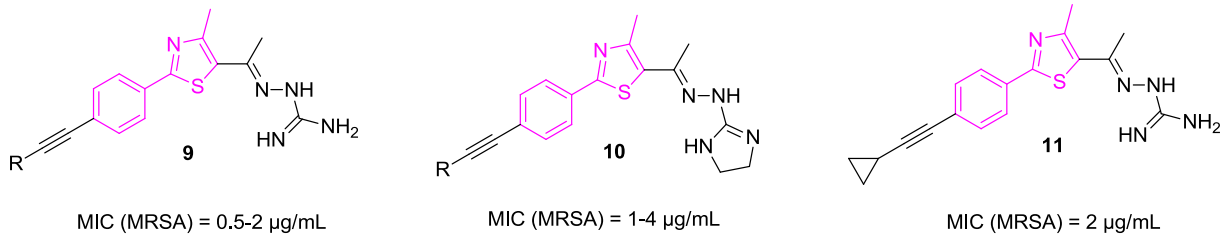


Fig. 3. Some second generation phenyl thiazole derivatives with anti-MRSA activity.

polar-surface-area of the linked heteroaromatic ring provided a new series of 5-thiazolylarylthiazoles with balanced properties that allowed them to penetrate macrophages infected with MRSA. The most potent compound **15** (Fig. 4) exhibited rapid bactericidal activity and good metabolic stability.

2.2. Oxazolidinone derivatives

Several researchers reported oxazolidinone derivatives as potent antibacterial agents. Poel et al. [33] reported the syntheses and *in vitro* and *in vivo* activity of new series of C-5 carboxamide oxazolidinone derivatives. This subclass of oxazolidinone derivatives **16** (Fig. 5) exhibited antibacterial activities similar to those of drug linezolid but with a diminished monoamine oxidase inhibitory activity. *In vitro* time kill studies revealed that, like linezolid, compound **17** (PF-00422602) (Fig. 5) was found to be bacteriostatic for staphylococci and enterococci but bactericidal for streptococci. Komine et al. [34] published the design, synthesis, and SAR studies of new biaryl oxazolidinones having a bicyclo[3.1.0]hex-6-yl ring. Most of the biaryl bicyclo[3.1.0]hex6-yl oxazolidinone derivatives exhibited potent antibacterial activity against clinically relevant gram-positive drug-resistant bacteria MRSA, PRSP and VRE. Among all the compounds screened, the biaryl bicyclo[3.1.0] hex-6-yl oxazolidinone derivative, **18** (Fig. 5) demonstrated its excellent antibacterial potency against MRSA and VRE.

Gordeev et al. [35] published compound **19** (Fig. 6) as a new oxazolidinone derivative with a broad antibacterial spectrum on gram positive pathogens over a standard linezolid [36]. A series of new oxazolidinone derivatives exhibited a potential to minimize the adverse effects met in linezolid therapy. The preliminary data indicated that the compound **19** paved way for further evaluation as a safe new next-generation oxazolidinone that may substitute present linezolid therapy. Wu et al. [37] reported a series of new linezolid analogues containing a hydrazone moiety with antibacterial activity. Most analogues displayed more potent inhibitory activity against clinical isolates of *S. aureus,* MSSA, MRSA, LREF and VRE as compared with the standard drugs radezolid and linezolid. Among all the compounds tested, the most potent compound **20** (Fig. 6) exhibited 15- to 30-fold more potent activity than linezolid against MRSA, MSSA, LREF and VRE strains with MIC = 0.0675 μg/mL.

2.3. Benzimidazole derivatives

Antibacterial properties of the benzimidazole derivatives enthused medicinal chemist to develop into potential leads. Göker and coworkers [38] reported the synthesis and *in vitro* antibacterial activities of series of new 1,2-disubstituted-1*H*-benzimidazole-*N*-alkylated-5-carboxamidine derivatives **21** (Fig. 7) against methicillin resistant *S. aureus* (MRSA) by the tube dilution method. The SAR results revealed that compounds having 3,4-dichloro substituted phenyl at the position 2 of *N*-bulky alkyl substituted benzimidazolecarboxamidines exhibited activity with MIC values of 1.56–0.39 μg/mL. The novel series of benzimidazole derivatives were synthesized and the antimicrobial properties of these compounds against methicillin-resistant *S. aureus* (MRSA, standard and clinical isolates) were evaluated by Tunçbilek et al. [39] SAR studies revealed that compounds which have no substitution at position *N*-1 displayed better antibacterial activities than those of standards drugs (sultamicillin, ciprofloxacin and ampicillin) against multidrug-resistant bacteria. The 2,5,6-trihalogenobenzimidazole derivatives (**22**,**23**), 5,6-dichloro-2-aminoderivative (**24**) and 5-chloro-2-(4-benzyloxyphenyl)benzimidazoles (**25**) (Fig. 7) exhibited potent antibacterial activity with MIC = 3.12 μg/mL against *S. aureus.*

In 2017, Picconi, et al. [40] designed, synthesized and evaluated a new class of nontoxic triaryl benzimidazole compounds, derived from DNA minor groove binders for their antimicrobial activity against multidrug resistant (MDR) gram-positive isolates. Molecular modeling experiments indicated that the newly synthesized class could not be fixed within the minor groove of DNA due to an alteration in the shape of the molecules. Compounds **26**, **27**, and **28** (Fig. 7) were found to be the most active in the series, with MICs in the range of 0.5–4 μg/mL against the MDR gram-positive isolates. Active compounds showed a bactericidal activity and suggested the inhibition of bacterial gyrase enzyme as the mechanism of action (MOA) of this series. Zhang et al. [41] reported a series of new benzimidazole quinolones as potential antimicrobial agents. Most of the prepared derivatives displayed good antimicrobial activities in comparison with reference standards. The most potent compound **29** (Fig. 7) inhibited the formation of biofilms

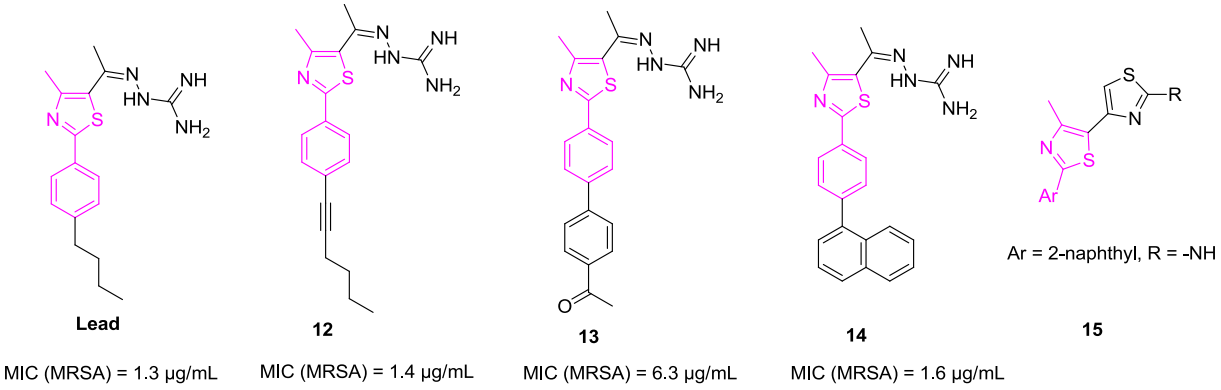


Fig. 4. Some phenyl thiazole derivatives with anti-MRSA activity.

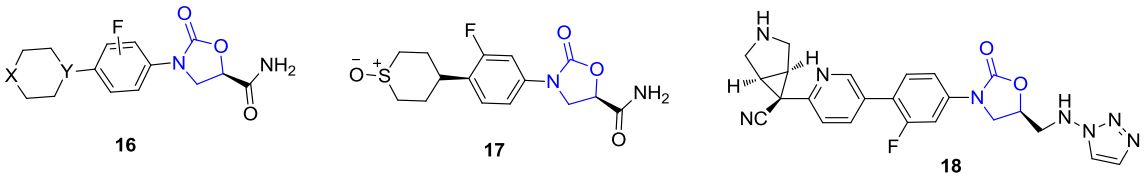


Fig. 5. Some oxazolidinone derivatives with anti-MRSA activity.

and did not spur the development of resistance. It could inhibit the relaxation activity of *E. coli* topoisomerase IV enzyme at 10 μM concentration. Additionally, this compounds also found benign to mammalian cells. Modeling studies and experimental investigation of compound **29** with DNA revealed that this compound could form a steady **29**-DNA complex and blocks DNA replication.

2.4. Chalcone derivatives

Kapkoti and co-workers [42] synthesized a new series of glabridin-chalcone hybrid molecules (GCHMs) and examined for their antibacterial and resistance reversal activity against methicillin resistant isolates of *Staphylococcus aureus* (MRSA) and together with drug norfloxacin. Glabridin hybrids exhibited remarkable antibacterial activity against various MRSA clinical isolates with MIC values 12.5 μg/mL. Among all the compounds tested, **30** (Fig. 8) exhibited synergy up to 16 fold diminish in MICs with drug norfloxacin. In systemically infected Swiss albino mice model, compound **30** significantly lowered the systemic bacterial burden in blood, kidney, liver, lung and spleen tissues. Chu et al. [43] reported the synthesis of a new chalcone derivatives **31** (Fig. 8) that mimic the cationic antimicrobial peptides. Antibacterial activities against clinically relevant multiple drug resistant isolates of methicillin-resistant *S. aureus* (MRSA), NDM-1-producing and KPC-2-producing Carbapenem-resistant Enterobacteriaceae were screened. Potent compounds **32** (0.5 μg/mL against MRSA) and **33** (0.25 μg/mL against MRSA) (Fig. 8) exhibited good bactericidal activity against drug-resistant isolates of MRSA. Furthermore, these molecules exhibited less cytotoxicity toward mammalian cells at a suitable concentration. Chalcone derivatives were designed and synthesized via a base catalyzed Claisen Schmidt condensation and screened for their anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity and compared with standard drug norfloxacin by Gaur et al. [44] Among these compounds, trans-3-(1*H*-indol-3-yl)-1-(4′-benzyloxyphenyl)-2-propen-1-one **34,** 1-(4″-hydroxy-3″-methylphenyl)3-(4′-hydroxyphenyl)-2-propen-1-one **35**, (Fig. 8) exhibited remarkable antibacterial activity with MIC values 12.5–50 μg/mL respectively. Flow cytometry analysis results clearly suggested that derivatives **34** and **35** significantly promote the inhibition of the Et-Br efflux. In infected Swiss albino mice model, both the compounds **34** and **35** remarkably lowered the systemic bacterial loads in blood, lung, kidney, liver and spleen tissues. Nielsen et al. [45] incorporated the "cationic" aliphatic amino groups in the chalcone moiety which resulted in potent anti-MRSA compounds. The SAR revealed that the most favourable position for the aliphatic amino group was the position 2 of the B-ring, importantly in combination with a lipophilic substituent in the position 5 of the B-ring. Introduction of an additional aliphatic amino group in the A-ring resulted in specific and potent antibacterial activity against both gram positive and gram negative microorganisms. Among all, the most potent compound **36** (Fig. 8) has an MIC = 2 μM against methicillin resistant *Staphylococus aureus.*

Stringer and team [46] have applied the linker system in the synthesis of a 174-member chalcone library. The use of the Rink linker allowed to construct the chalcone macroarray using milder reaction conditions. Antibacterial assays of the synthesized chalcones unveiled the potent MIC values of **37** (Fig. 9) against MRSA. These studies enabled to expand the use of the small molecule macroarray approach for the discovery and syntheses of biologically active compounds. From the SAR studies conducted by Feng et al.[47] in the chalcone chemical series, revealed that free OH group at position 4′ and one OH group at 2′/6′ position is essential for antibacterial activity as well as the 2-alkyloxy phenyl, 2-*n*-hexyloxyphenyl and bicyclic myrtenyl motif substitution on the alkene at R_2 favoured anti Gram-positive bacterial activities. 7-OH-4-chromanones (Fig. 9) did not exhibit anti Gram-positive activity (MIC = > 200 μg/mL). Excitingly, its corresponding ring-opened chalcone derivative **38** (Fig. 9) presented very good anti Gram-positive activity (MIC = 1.56–3.13 μg/mL).

2.5. N-methylpropenamine Hydrochloride derivatives

Several researchers reported *N*-methylpropenamine hydrochloride derivatives as potential anti-MRSA agents. Li et al. [48] synthesized a series of new analogues which target the enzyme CrtN. Analogues **39** and **40** (Fig. 10) displayed an antibacterial activity against pigmented *S. aureus* and MRSA strains (IC_{50} = 0.02–10.5 nM) and lowered hERG inhibition. Furthermore, analogues **39** and **40** were demonstrated to reduce the staphylococcal burden in the blood, kidney and heart in a mouse model and compared with reference standards vancomycin and linezolid. Remarkably, **39** could strongly block the pigment biosynthesis of multidrug-resistant isolates *in vivo.* Wang et al. [49] identified a new type of potent benzofuran-derived CrtN inhibitor **41** (Fig. 10) which inhibited the pigment production of *S. aureus* Newman and MRSA strains (IC_{50} = 0.38 to 5.45 nM). Compound **41** could significantly sensitize to immune clearance and could effectively attenuate the virulence *in vivo*. Better safety profiles and good oral bioavailability of **41** indicated that it could be a good drug template for the treatment of MRSA infections.

Wang et al. [50] also developed a series of new benzocycloalkane-derived CrtN inhibitors with submicromolar IC_{50}. *In vivo* studies revealed that compound **42** (Fig. 11) was proven to be efficacious in an *S. aureus* Newman sepsis model (> 60% survival after 8 days) and abscess

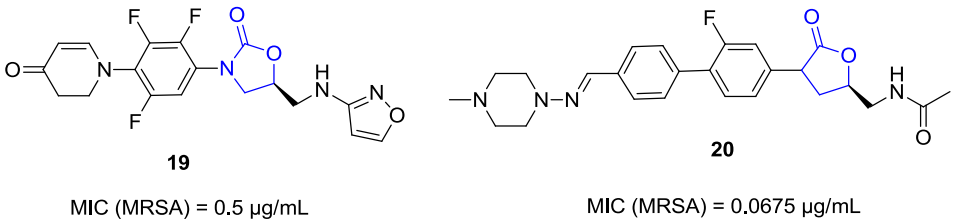


Fig. 6. Some oxazolidinone derivatives with antibacterial activity.

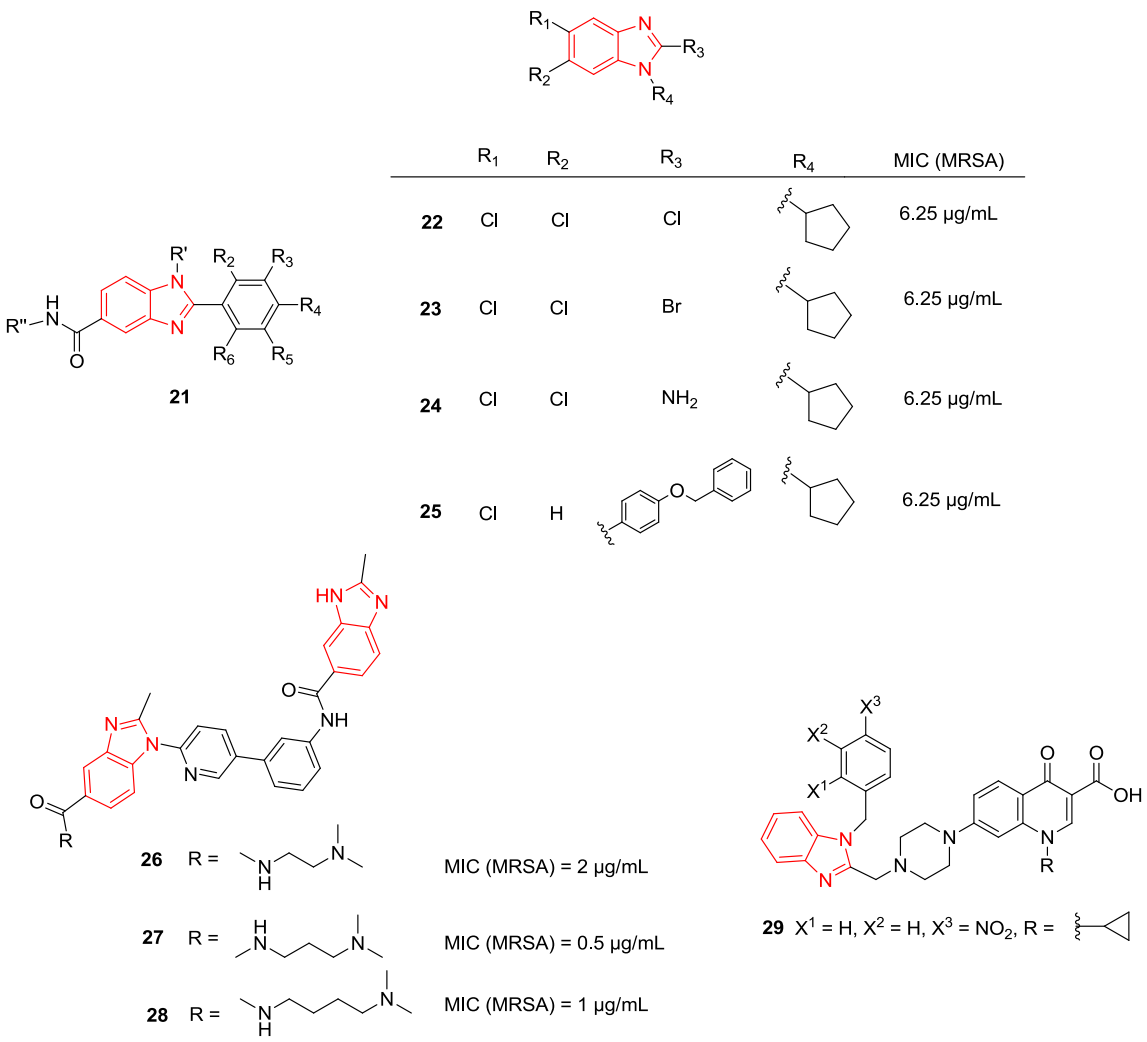


Fig. 7. Some new benzimidazole derivatives with antibacterial activity.

formation model (> 60% survival after 8 days). Ni et al. [51] reported an effective benzocycloalkane derived staphyloxanthin inhibitors against MRSA infections. Derivatives **43** and **44** (Fig. 11) exhibited remarkable pigment inhibitory activities and low hERG inhibition. The broad antibacterial spectra of **43** and **44** were displayed first with normal administration in the liver and heart in mice against Mu50 (vancomycin-intermediate *S. aureus*) and pigmented *S. aureus* Newman, NRS271 (linezolid-resistant *S. aureus*) and were compared with standard drugs linezolid and Vancomycin.

2.6. Quinolone derivatives and variants

Odagiri et al. [52] reported a compound **45** (DS21412020) (Fig. 11) possessing a trans-fused pyranose ring on the pyrrolidine part at the position 7 of the quinolone heterocycle which exhibited potent *in vitro* antibacterial activity against respiratory pathogens including quinolone-resistant (QR-MRSA) and methicillin-resistant *Staphylococcus aureus*. Additionally, compound **45** exhibited good *in vivo* activity, reduction in the hERG inhibition and favourable toxicological and pharmacokinetic studies. Wang et al. [53] evaluated the anti-MRSA activities of series of new ITQs (Isothiazoloquinolones) having structural modifications at the positions 6, 7 and 8. The SAR studies indicated that the most beneficial modification of the ITQ nucleus was addition of a methoxy substituent to position 8, which enhanced anti-MRSA activities. Among the groups attached at position 7, the activities reduced in the order 6-isoquinolinyl > 4-pyridinyl > 5-dihydroisoindolyl > 6-tetrahydroisoquinolinyl against MRSA. Compound **46** (Fig. 11) had an excellent *in vitro* antibacterial activity against a panel of clinical isolates of MRSA (MIC_{90} = 0.5 µg/mL) with good selectivity and desirable cytotoxicity profile. A series of new 7-(3′-substituted)pyrrolidino-8-methoxyisothiazoloquinolone (ITQ) analogues were prepared and their potency against methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin resistant *Staphylococcus aureus*(MRSA) were studied by H.Y. Kim et al. [54] The 7-[(*R*)-3-((*S*)-1-aminoethyl)pyrrolidin-1-yl] analogue (**47**(*R*,*S*)) and the (*R*)-7-[3-(2-aminopropan-2-yl)pyrrolidin-1-yl] analogue (**48**(*R*)) (Fig. 14) were found to be the most potent antibacterial activities. The MICs of these compounds against a panel of clinical MRSA strains were found to have 8- to 16-fold greater potency than standard linezolid. Highly potent compounds **47** (*R*,*S*) (MIC = 0.06 µg/mL) and **48** (*R*) (MIC = 0.09 µg/mL) against MQRSA resurfaced from this study. This activity was due to their inhibition of enzymes topoisomerase IV and DNA gyrase from MRSA isolates. Hong et al. [55] revealed the SAR data of a series of new pyrrolidine substituted quinolone derivatives possessing an alkyloxime substituent in the position 4 and an aminomethyl substituent in the position 3 of the pyrrolidine ring. This structural variations of the pyrrolidine ring allowed proper modulation of the physical properties of the corresponding quinolone derivatives and resulted in improved pharmacokinetic properties and *in vivo* potency. The antibacterial activity against gram positive organisms was swayed by the C-8 substituent in the order F (C5-NH_2) > F (C5-H) > naphthyridine > Cl > OMe > H. The oxime group of the quinolones was preferred to a desoximino

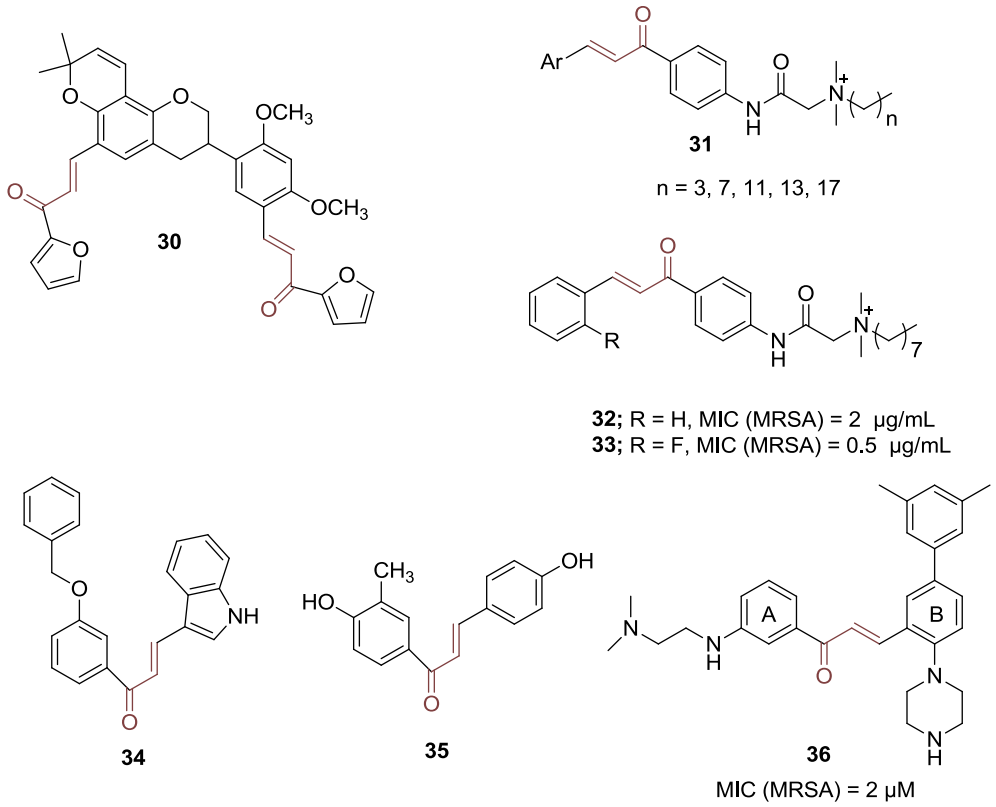
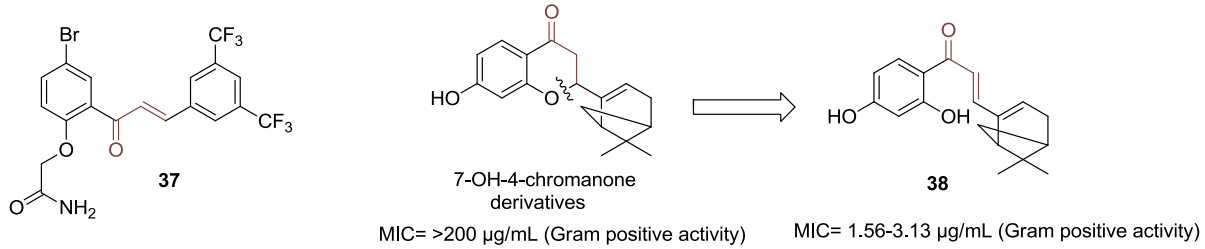


Fig. 8. Some chalcone derivatives with anti-MRSA activity.



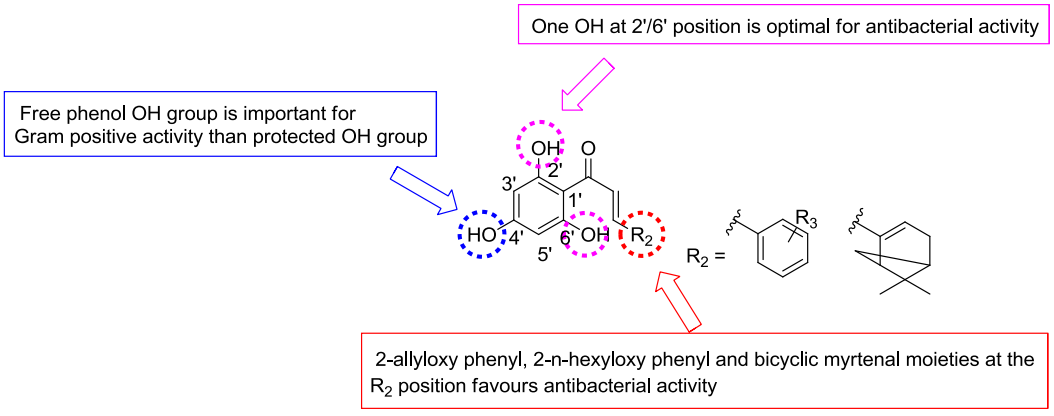


Fig. 9. Some new chalcone derivatives with antibacterial activity.

compound **49,** (Fig. 11) which exhibited lower activity and improved pharmacokinetic parameters. Among the compounds tested, **50** (LB20304) (Fig. 11) exhibited the best *in vivo* efficacy and pharmacokinetic profile. The MIC values of compound **49**, LB20304 **50** and ciprofloxacin against methicillin resistant *S. aureus* 241 was found to be (16, 4 and 128 μg/mL respectively). Ma et al. [56] synthesized

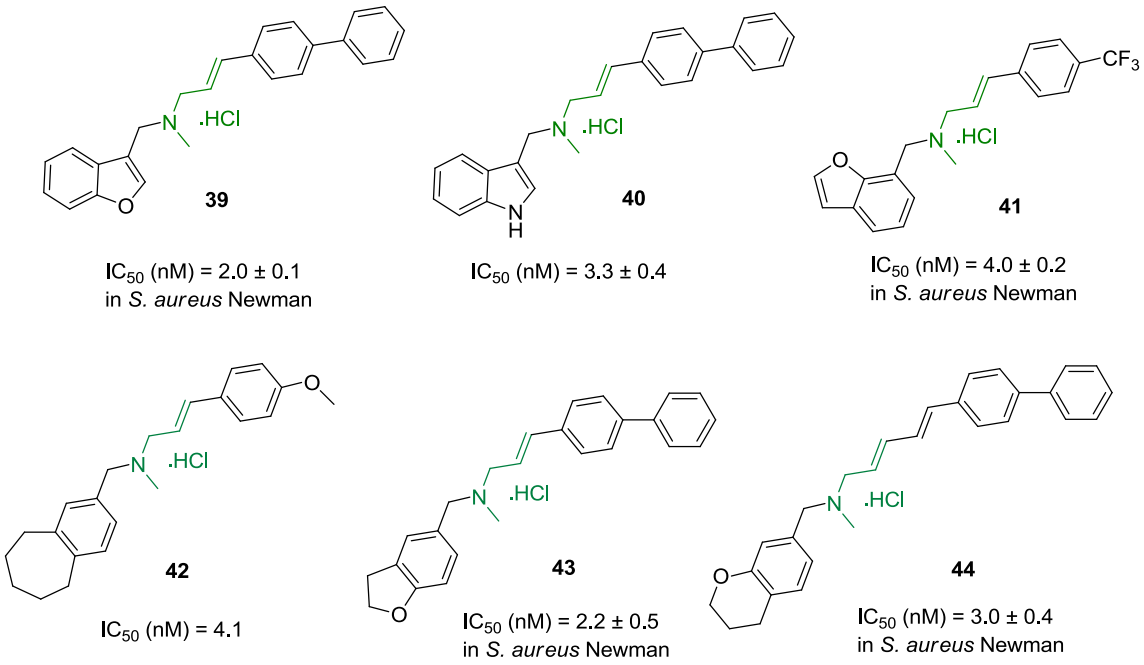


Fig. 10. Some *N*-methylpropenamine hydrochloride derivatives with antibacterial activity.

and examined a series of new oxoquinolizines with various substituents at the position 8, in order to enhance spectrum of activity, tolerability and good pharmacokinetic profile. Most of the compounds tested in this study demonstrated better activity against Gram-positive resistant bacteria than reference compound ciprofloxacin. The oral ED_{50} values for the *cis*-3-amino-4-methylpiperidine analogue **51** (Fig. 11) against *S. aureus* NCTC 10649 M was found to be 0.8 mg/kg. The study revealed that the steric and electronic environment, absolute stereochemistry and C-8 group conformation are paramount to the antibacterial properties. Structural manipulations of the C-8 group gave a advantageous means to improve the antibacterial activities, physicochemical properties and pharmacokinetic profiles. Ellsworth et al. [57] represented a new series of 3-aminoquinzolinediones as antibacterial agents structurally related to the fluoroquinolones. These bacterial gyrase and topoisomerase IV inhibitors demonstrated antibacterial activity against recalcitrant Gram-negative and Gram-positive organisms, including multidrug resistant pathogens. These agents also demonstrated *in vivo* efficacy in murine systemic infection models. The profound utility of the 3-aminoquinazolinediones **52**, **53** (Fig. 11) appeared to be promising against resistant Gram-positive organisms especially MRSA.

2.7. Quinazolinone derivatives

In 2015, Bouley et al. [58] discovered the (*E*)-3-(3-carboxyphenyl)-2-(4-cyanostyryl)quinazolin-4(3*H*)-one **54** (Fig. 12) as a new antimicrobial agent having *in vivo* afficacy against methicillin resistant *Staphylococcus aureus* (MRSA). In 2016, Bouley et al. [59] reported the SAR of the new quinazolinone class of antibacterials. They have examined the final compounds for activity against the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae,*

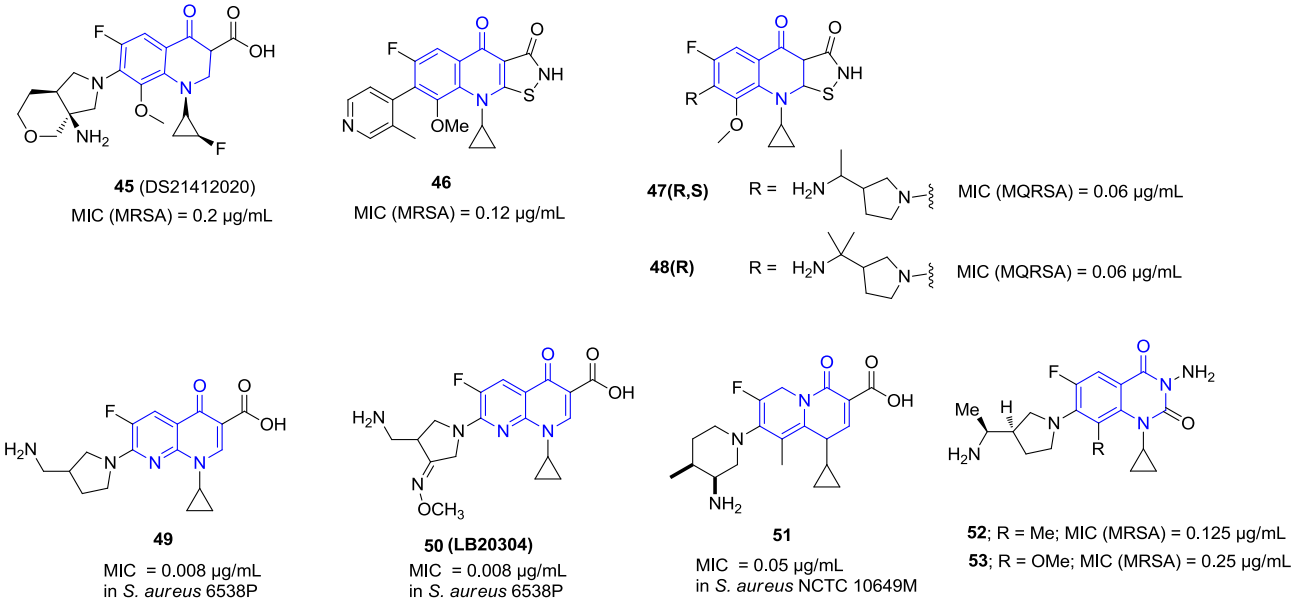


Fig. 11. Some quinolone derivatives with anti-MRSA activity.

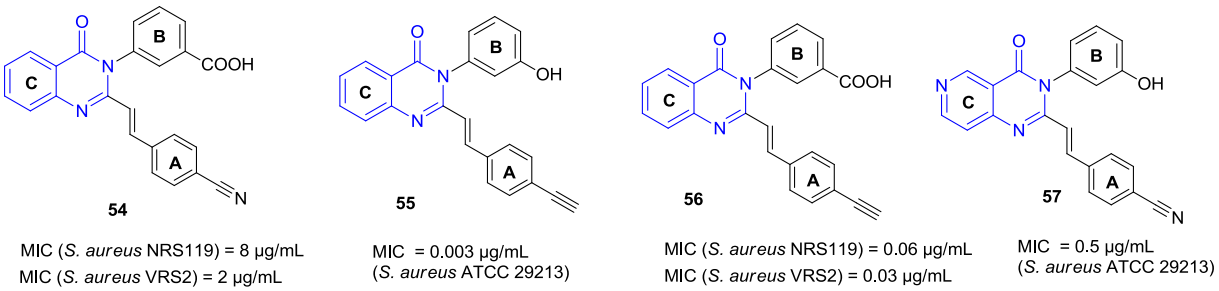


Fig. 12. Some 4(3*H*)-Quinazolinone derivatives with antibacterial activity.

Acetinobacter baumanii, Pseudomonas aeruginosa, and Enterobacter species) pathogen panel. Several changes were made on quinazolinone heterocycle. When ring A was a phenyl, *para* substitution was found to be superior to *meta* or *ortho*. An alkyne at *para* position on ring A (**55**), **(56)** was found to be the most potent substituent *in vitro* with an MIC values of 0.003–0.03 μg/mL (Fig. 12). With ring B as the phenyl group, *meta* and *ortho* substitutions were equally active, but *para* was generally not favoured. Replacing ring C with a pyridine **57** (Fig. 12) was tolerated when ring B was 3-hydroxyphenyl. Substitution at the C-6 and C-7 position of ring C with a bromo or hydroxyl group was not tolerated (Fig. 12). Bouley et al. also reported the *in vivo* data of these compounds.

Recently, Gatadi et al. [60] reported the design and synthesis of a series of new 3-phenylquinazolin-4(3*H*)-one derivatives, and screened for their antibacterial activity against ESKAP (*E. coli*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*) pathogen panel. The *in vitro* data revealed that compounds **58**, **59** and **60** (Fig. 13) were found to be benign to Vero cells (CC_{50} = > 10– > 100 μg/mL) and exhibited reasonable selectivity index (SI = 40– > 200). The compounds **58**, **59** and **60** also showed potent activity against various isolates of MDR-*S. aureus* (Fig. 13). New compounds **61** and **62** were synthesized by Gatadi and team [61] also displayed concentration dependent bactericidal activity and synergized with the drugs tested. Moreover, compound **62** displayed very potent anti-biofilm activity and displayed a PAE of ~2 h at 10X MIC which is comparable to drugs levofloxacin and vancomycin. *In vivo* efficacy in the murine neutropenic thigh infection model, suggested that the compound **62** was equipotently capable of causing reduction in CFU as compared to Vancomycin. In continuation of efforts, Gatadi et al. [62] synthesized and examined several new 4-oxoquinazolin-3(4*H*)-yl)benzoic acid and benzamide derivatives for antibacterial activity against ESKAP pathogens. In the initial screening, compounds were found to be selective and potent activity against *Staphylococcus aureus*. All the compounds were found to be benign against Vero cells, possessing favourable selectivity index (SI > 10). Compounds **63** and **64** (Fig. 13) (SI > 40) were found to exhibit potent activity against multiple clinical strains of multi-drug resistant *S. aureus*. Besides, compound **63** exhibited concentration dependent bactericidal activity and synergized with the drugs tested.

Further, Gatadi and co-workers [63] studied the new series of 1,2,3-triazole linked 4(3*H*)-quinazolinone derivatives and evaluated against ESKAP pathogen panel, compounds exhibited remarkably, selective inhibitory activities towards *Staphylococcus aureus* (MIC = 0.5–4 μg/mL). These compounds were also found to be less cytotoxic to Vero cells and displayed excellent selectivity index (SI = 40 to 80). Furthermore, **65** and **66** (Fig. 14) were found to possess potent inhibitory activity when tested against multidrug-resistant *S. aureus* isolates (MIC values = 0.5 μg/mL).

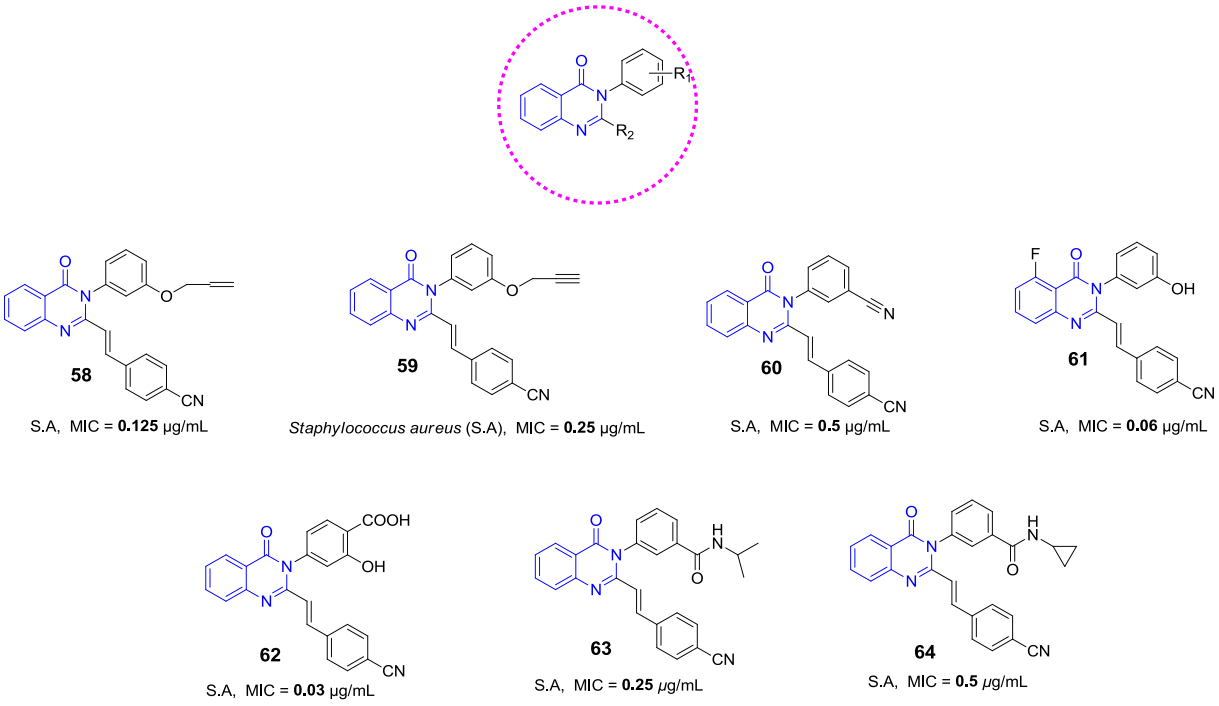


Fig. 13. Some new 4(3*H*)-Quinazolinone derivatives with antibacterial activity.

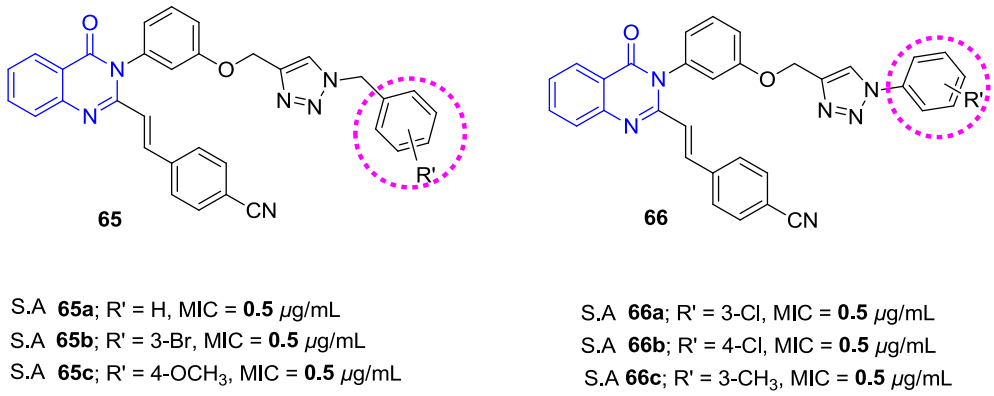


Fig 14. Some new 1,2,3-triazole linked 4(3*H*)-quinazolinone derivatives via ether linker with antibacterial activity.

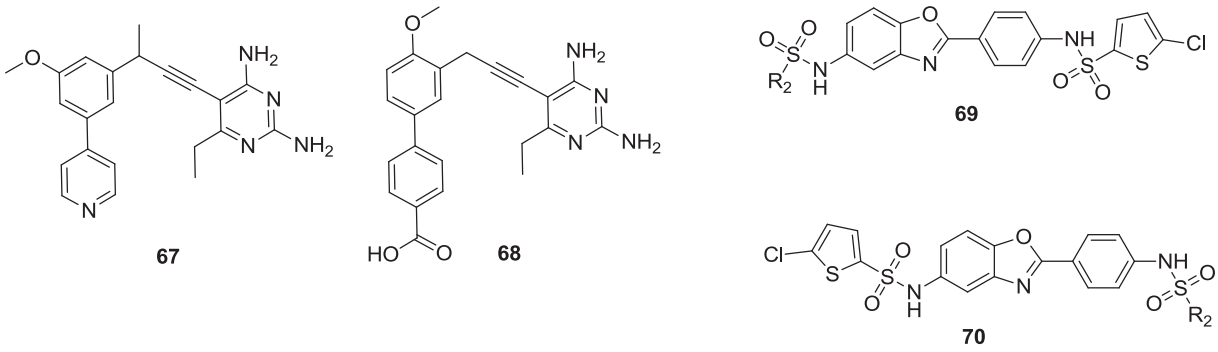


Fig. 15. Some miscellaneous heterocyclic derivatives with anti-MRSA activity.

2.8. Miscellaneous heterocyclic derivatives

Reeve et al. [64] have evaluated Trimethoprim (TMP) and a series of new propargyl-linked antifolates (PLAs) **67**, **68** (Fig. 15) against mutant *S. aureus* strains. The PLAs having a carboxylate moiety exhibited good potency against the mutant enzymes and strains. These carboxylate PLAs also showed good metabolic stability and low cell toxicity which make as promising drug candidates. S. Abdeen et al. [65] published many analogues of sulfonamido-2-arylbenzoxazole GroEL/ES inhibitors **69**, **70** (Fig. 15) as potent antibacterials against MRSA. EC_{50} values of the most potent analogues were in the range of 1–2 μM range. Furthermore, though some derivatives inhibit human HSP60/10 biochemical functions *in vitro*, many of these exhibited moderate to low cytotoxicity to human kidney and hepatic cells (CC_{50} values > 20 μM).

Hu et al. [66] described a facile access to a focused library of new structural class yielding compounds with improved activity in an *in vivo* mouse peritonitis model. The most potent compounds (**71** and **72**) (Fig. 16) exhibited efficacy against MRSA at ED_{50} values of ~1 and ~5 mg/kg respectively and exhibited good *in vitro* activity against VRSA. This research group also investigated the *in vivo* efficacy of the benzothiophene **72**, which showed 80% survival at 3 mg/kg and 60% protection at 1 mg/kg. In this model, compound **72** was compared with vancomycin (ED_{50} = ≈1 mg/kg). Ishiguro et al. [67] conducted molecular modeling and SAR studies and reported that the transpenems lose the strong interaction at the C-2 substituent-binding site of enzyme PBP2a and the carboxylate of the *cis*-penems would be acylated only through the interaction of the C-6 moieties and the carbonyl oxygen of *β*-lactam at the oxyanion hole. The *cis*-penems **73** and **74** (Fig. 16) showed potent activities against a wide variety of bacteria specifically MRSA. Sinko et al. [68] reported the antibacterial potential of new undecaprenyl Diphosphate Synthase Inhibitors. Among the compounds tested, Compound **75** (and its analog **76**) (Fig. 16) inhibited the growth of Gram positive microbes. Activity against *B. anthracis, S. aureus* and a Vancomycin-resistant *Enterococcus* spp. was found with MIC in the range of 0.125–4 μg/mL and exhibited very strong synergy with methicillin.

Spink et al. [69] reported structure-activity relationship (SAR) for the newly discovered oxadiazole class of antibacterial agents. These oxadiazoles **77**, **78**, **79** (Fig. 17) were discovered by *in silico* docking studies against the crystal structure of a penicillin-binding protein. These compounds inhibited cell-wall biosynthesis and exhibited potent activities against the MDR *Staphylococcus aureus*, including MRSA, VRSA and linezolid-resistant *S. aureus*. 5-(1*H*-Indol-5-yl)-3-(4-(4-(trifluoromethyl) phenoxy)phenyl)-1,2,4-oxadiazole **79** was found to be promising candidate in a mouse model of MRSA infection and exhibited a long half-life $t_{1/2}$, a high volume of distribution, and low clearance. Wiles et al. [70] published a series of selenophene analogues which maintained similar anti-staphyloccocal potencies similar to those of thiophenes against a panel of MRSA isolates. Among the tested compounds, selenophene **80** (R) (Fig. 17) demonstrated the lowest potential towards hERG inhibition and the lower cytotoxicity against all the cell lines tested. Compound **80** (*R*) exhibited good MRSA activity, limited hERG inhibition, low cytotoxicity, and high metabolic stability. Niu et al. [71] reported a series of new AMP mimetic dimeric alkylamides of lysine, which were rationally designed and synthesized through dimerization strategy. Among the synthesized compounds, **81** (Fig. 17) displayed very potent and broad spectrum antibacterial activities against Gram positive MRSA, MRSE and VRE strains. **81** could inhibit biofilm formation and did not induce resistance.

A series of *N*-substituted carbazole derivatives having an indole ring were synthesized as anti- MRSA agents from a molecular hybridization approach by Cheng et al. [72] The representative compound **82** (Fig. 18) showed potent activity (MIC = 1 μg/mL) against a panel of MRSA strains and compared with standard drug Vancomycin. In a mouse model with lethal infection of MRSA (4 N216), showed a 75% survival rate after a single dose of **82** was intravenously administered at 20 mg/kg. This data underlined the importance of designed hybrid series for the development of new *N*-substituted carbazoles as

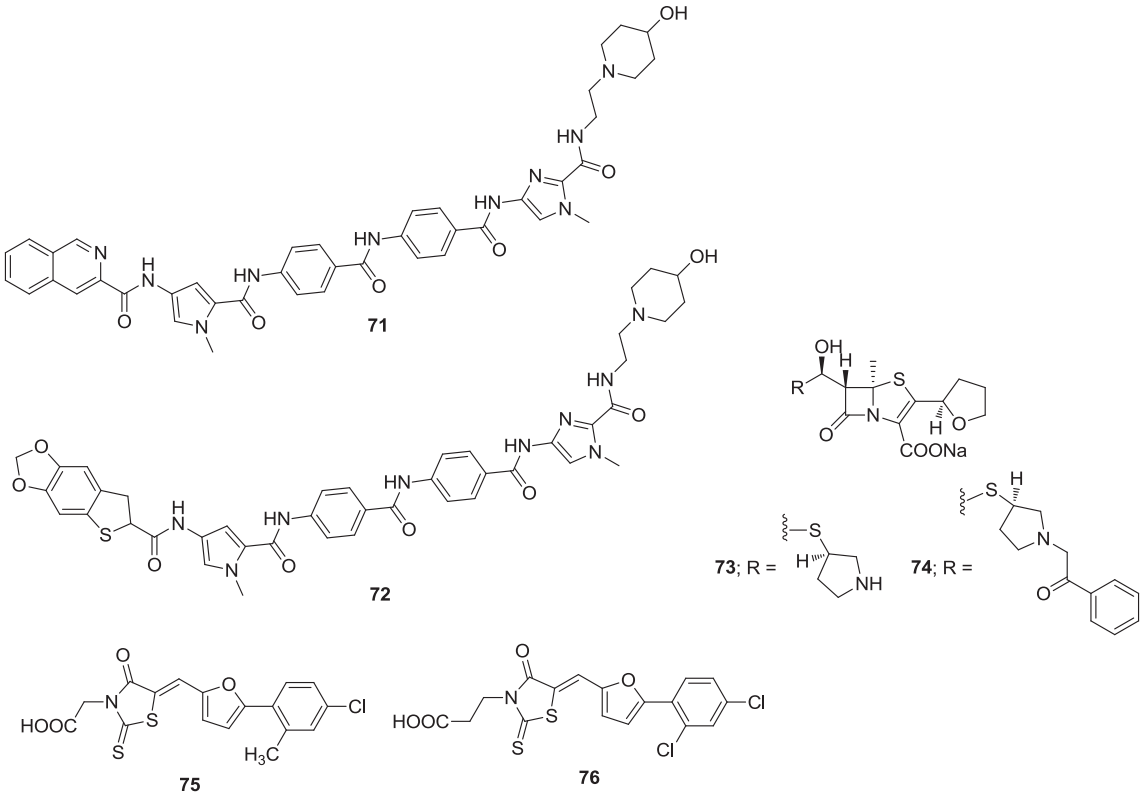


Fig. 16. Some new miscellaneous heterocyclics with anti-MRSA activity.

promising anti-MRSA agents. Khodade et al. [73] reported the synthesis and bio-evaluation of a new series of benzo[*b*]phenanthridine-5,7,12(6*H*)-triones, which were designed based on redox-active natural products strategy. The research group found the *in vitro* inhibitory activity of 6-(prop-2-ynyl)benzo[*b*]phenanthridine5,7,12(6*H*)-trione **83** (Fig. 18) against MRSA, and compared with vancomycin. They also revealed that the new lead compounds generated reactive oxygen species (ROS) in the cell and demonstrated antibacterial activity. Panchaud et al. [74] efforts in screening around the minimal ethyl urea binding motif led to the identification of isoquinoline ethyl urea **84** as an acceptable starting point for fragment evolution. The optimization was guided by structure-based design and focused on antibacterial activity *in vitro* and *in vivo*. Characterization of **85**, and the target lead **86** (Fig. 18) emphasized the potential for treatment of the formidable fluoroquinolone-resistant MRSA, VRE and *S. pneumonia*.

Kaizerman et al. [75] described the lead optimization and structure–activity relationship of new class of DNA minor-groove binders. The optimization was mainly focused on C-terminal amines and *N*-terminal aromatic heterocycles which led to compounds with improved *in vivo* tolerability and excellent *in vitro* antibacterial activity (MIC = 0.031 μg/mL) against methicillin-resistant *Stapylococcus aureus* (MRSA). The compound **87** (Fig. 19) was evaluated and found the *in vivo* efficacy in a mouse peritonitis model against methicillin-sensitive *S. aureus* infection with an ED_{50} value of 30 mg/kg. Vooturi et al. [76] presented the discovery of a new class of benzophenone containing compounds that possess good activity against clinically relevant

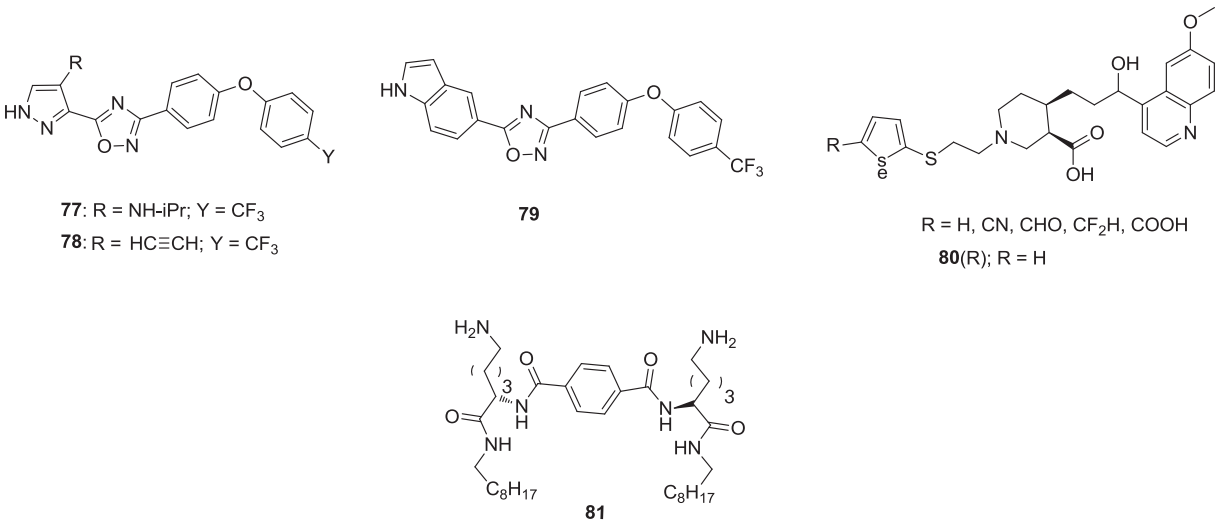


Fig. 17. New miscellaneous heterocyclic compounds with anti-MRSA activity.

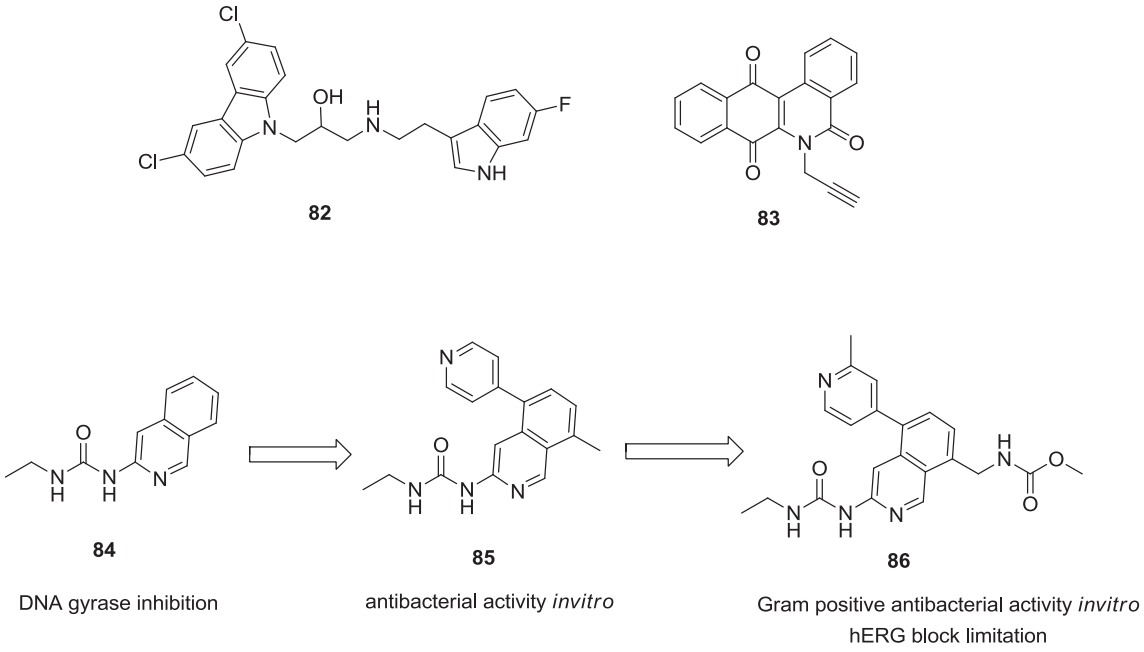


Fig. 18. Miscellaneous heterocyclic compounds with anti-MRSA activity.

multidrug resistant strains. This compound **88** exhibited MIC values in the 0.5–2.0 μg/mL range and was benign to mammalian cells. Structure-activity relationship studies revealed that the presence of a benzophenone and the cationic group was highly essential for antibacterial activity. The research team found that these agents could cause membrane depolarization, indicating that the bacterial membrane was the primary site of action for these agents. Li et al. [77] reported the synthesis and evaluation of new optimized coumarin-based inhibitors with 9-18-fold increase in potency against *Staphylococcus aureus*. Compounds **89** and **90** (Fig. 19) showed the best potency (IC_{50} = 3 and 1 μM respectively), against *S. aureus* helicases without disturbing the single strand DNA stimulated ATPase activity. Selectivity index (SI = CC_{50}/MIC) values against *S. aureus* for compound **89** was 33 and for compound **90** was 20. Furthermore, compounds **89** and **90** showed potent antibacterial activity against multiple ciprofloxacin-resistant MRSA strains (MIC = 0.5 and 4.2 μg/mL respectively). Kawatkar and co-workers [78] employed a structure guided design approach to utilize a previously unexplored region in *Staphylococcus aureus* Thymidylate Kinase (TMK) via new interactions. These efforts resulted in a compound **91**, (Fig. 19) with IC_{50} 3 nM against *S. aureus* TMK and MIC = 2 μg/mL against MRSA.

Surivet et al. [79] reported a series of new tetrahydropyran linked to a bicyclic aromatic moiety via a syn-diol linker, which exhibited potent antibacterial activity against drug resistant Gram-positive bacteria. Among the compounds synthesized, analogue **92** was found to be a potent dual DNA gyrase-topoisomerase IV inhibitor, with broad antibacterial activity, lower resistance and lower hERG K+ channel inhibition. Furthermore, analogue **93** (Fig. 20) displayed modest clearance in rat and good *in vivo* efficacy against *Staphylococcus aureus* in a murine model. Tanitame, et al. [80] have described the synthesis and

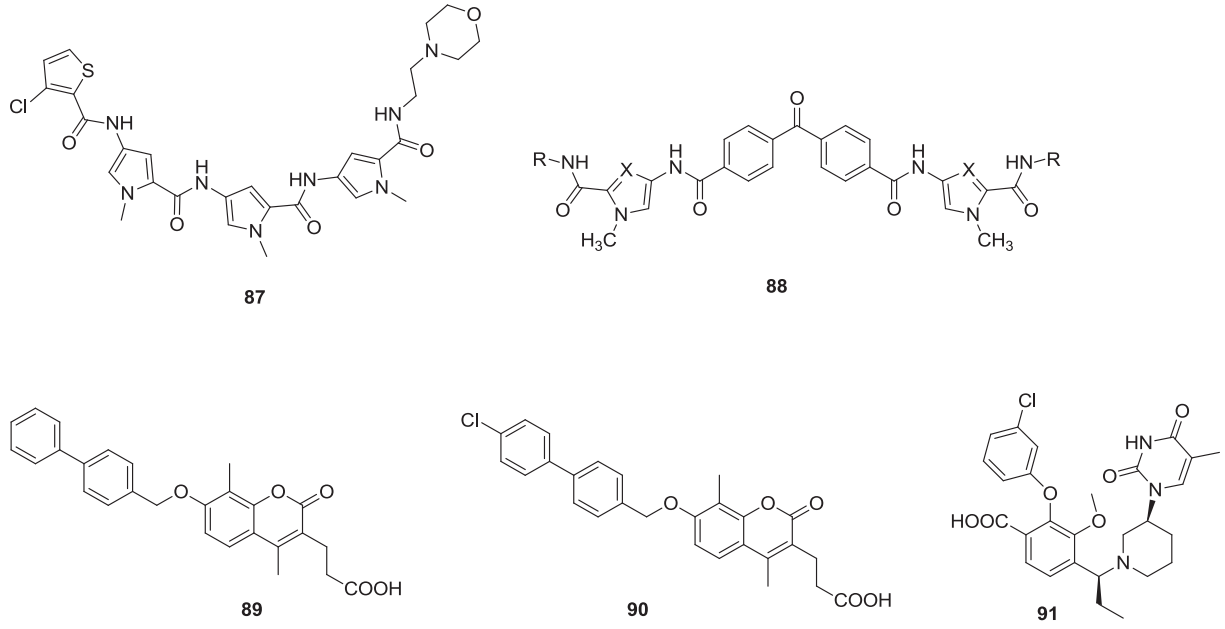


Fig. 19. Some new miscellaneous compounds with anti-MRSA activity.

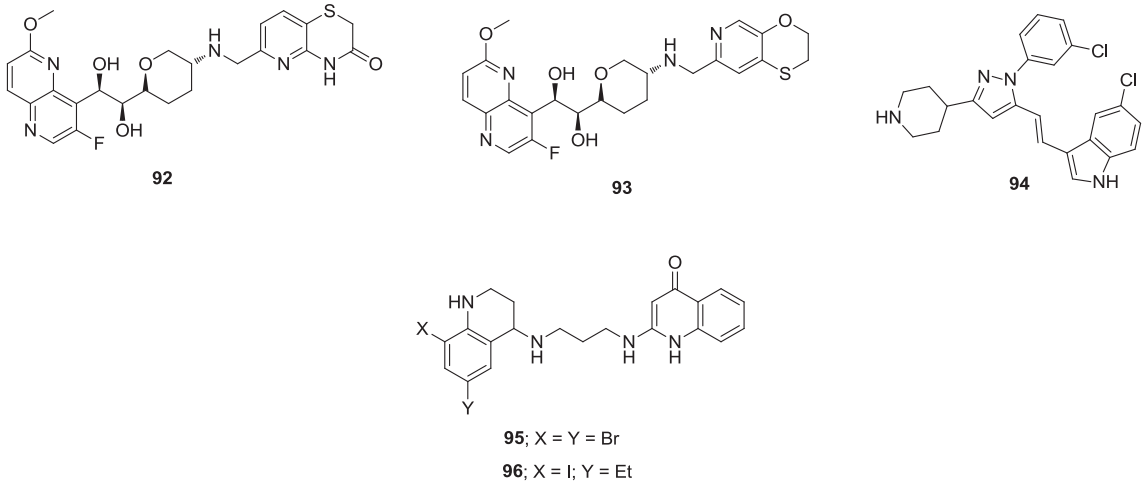


Fig. 20. Some miscellaneous heterocyclic compounds with antibacterial activity.

structure-activity relationships of new pyrazole derivatives. Compound **94** 5-[(*E*)-2-(5-chloroindol-3-yl)vinyl]pyrazole (Fig. 20) was the most active compound among the series, which showed potent antibacterial activity against multidrug-resistant isolates. Besides, **94** showed a more potent antibacterial activity against quinolone- and coumarin-resistant Gram-positive pathogens than sparfloxacin and novobiocin, respectively. Potent nanomolar inhibitors of *Staphylococcus aureus* methionyl tRNA synthetase have been reported by Jarvest et al. [81] Optimized compounds **95, 96** (Fig. 20) showed potent antibacterial activity against staphylococcal and enterococcal microorganisms. Compound **95** exhibited *in vivo* efficacy in an *S. aureus* rat abscess infection model.

Zha et al. [82] have designed, synthesized and tested a series of diverse (hetero)aryl fluorosulfonyl analogues as antibacterial agents against Staphylococcal species. Compounds **97**, **98** and **99** (Fig. 21) were found to possess potent *in vitro* antibacterial activity among the series of sulfonyl fluorides (MIC = 0.818, 0.840 and 0.811 μg/mL respectively). The analogues **97**, **98** and **99** exhibited excellent anti-biofilm properties compared to other antibiotics. The research group studied the intracellular redox activities via changing cyclic voltametric (CV) method. The analogues **97**, **98** and **99** possessed great potential for discovery and development of anti-staphylococcal leads to treat the MRSA infections. Diaryltriazene derivatives were synthesized and evaluated for their antimicrobial properties by Vajs et al. [83] Primary experiments revealed that, some of these compounds **100**, **101** (Fig. 21) showed activity against MRSA with MIC value of 0.02 μg/mL. Those compounds with potent anti-staphylococcal activity were found to be non toxic to mammalian cell lines and lower prone to resistance. Vermote et al.[84] performed several practical pathways towards the synthesis of new HAM derivatives with an alternative central scaffold. The resulting compounds were examined for their calibre to potentiate the activity of vancomycin in *S. aureus* biofilms *in vitro*. The 2,5-anhydro-D-allitol derivative **102** and dioxane derivative **103** showed comparable activity to that of lead compound **104** (Fig. 21) in the setup of combination treatment.

Matys et al. [85] reported a new series of piperazine derivatives of 5-arylideneimidazolidine-2,4-dione **105** and primary amines of 5-naphthyl-5-methylimidazolidine-2,4-diones **106** (Fig. 22) which were examined against *Staphylococcus aureus* ATCC 25923 (a reference strain) and MRSA HEMSA 5 (a resistant clinical isolate). The naphthalene derivative **107** was the most potent when used in combination with *β*-lactam antibiotics against the clinically relevant resistant strains. Molecular modeling studies were performed with the use of crystal structures of a penicillin binding protein (PBP2a) and MecR1 in order to explain the mechanism of action of the compounds **107** and **108** (Fig. 22). Their results indicated that the most possible mechanism of action of the potent compounds was the strong interaction with MecR1. Zhua et al. [86] reported the discovery, antibiotic profiling, and structure-activity relationships of a new class of RMAs, tetracyclic indoline derivatives, which selectively potentiated *β*-lactam antibiotics in methicillin-resistant *Staphylococcus aureus* (MRSA). Among the synthesized derivatives, **109** (Fig. 22) showed strong potentiation of amoxicillin/clavulanic acid in a variety of nosocomial and community-acquired MRSA strains with low cytotoxicity.

Hardej et al. [87] reported the synthesis and anti-MRSA activity against a series of new rhodanine compounds containing various substituents at the positions N-3 and C-5. The anti-MRSA activity of

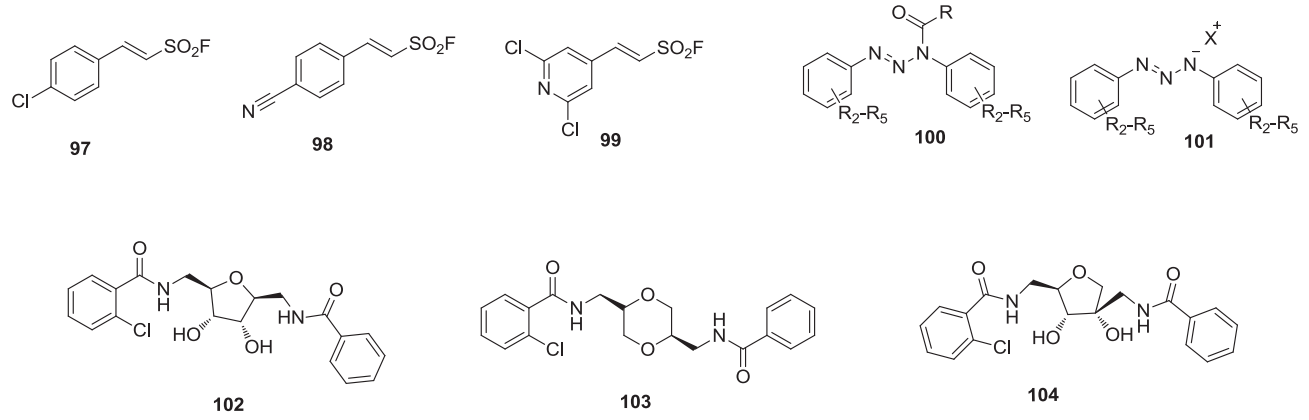


Fig. 21. Some new heterocyclic compounds with antibacterial activity.

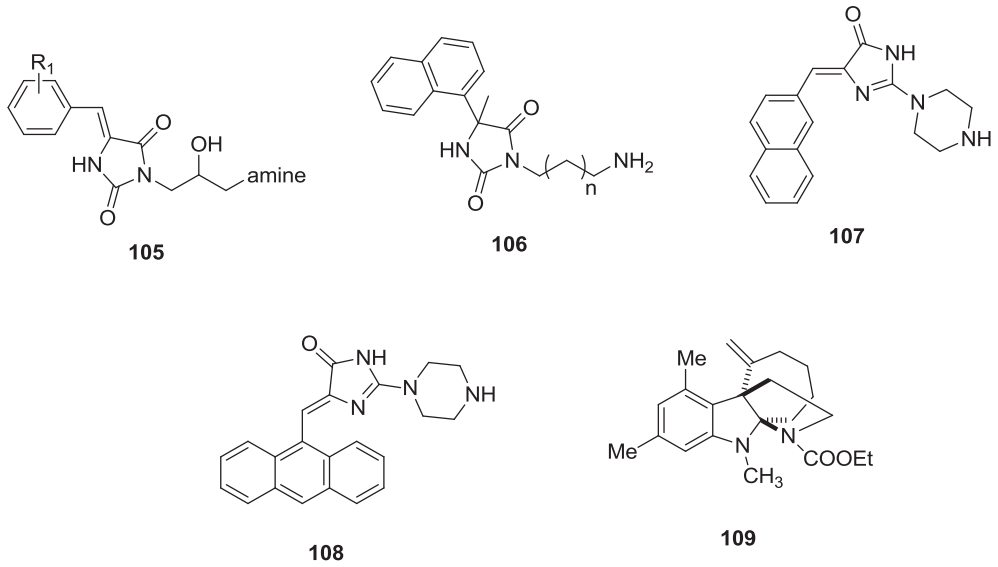


Fig. 22. Some new heterocyclic compounds with anti-MRSA activity.

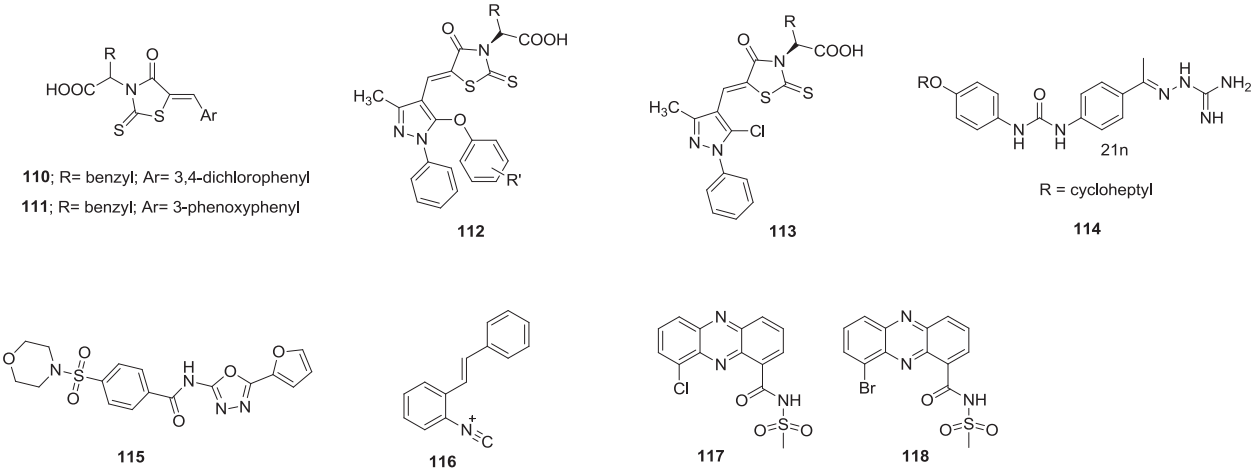


Fig. 23. Some novel heterocyclic compounds with antibacterial activity.

compounds **110** (MIC = 3.9 μg/mL, MBC = 7.8 μg/mL) and **111** (MIC = 1.95 μg/mL, MBC = 7.8 μg/mL) was remarkably greater than that of the lead compounds and reference antibiotics. Compounds **110** and **111** (Fig. 23) were found to be bactericidal at only 2-4-fold higher than their MIC concentrations. Song et al. [88] synthesized new series of rhodanine derivatives and examined them for antibacterial and cytotoxic activities. Compound **112** and **113** (Fig. 23) displayed the potent activity (MIC = 1 or 2 μg/mL) against selected MRSA and QRSA isolates. Hassan et al. [89] reported a new class of diphenylurea as a broad spectrum antibacterial agents. Several analogues were prepared by harmonizing key structural features of lead compound that carries an aminoguanidine and *n*-butyl functionality. The SARs at the lipophilic side chain were examined and led to the discovery of the cycloheptyloxyl analogue **114** (Fig. 23) as a potential drug-candidate. Furthermore, the potent anti-MRSA activity of **114** was confirmed *in vivo* using a *Caenorhabditis elegans* animal model by the research group. Temeng et al. [90] reported the potent compounds, **115** (Fig. 23) which inhibited the growth of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin intermediate and Vancomycin-resistant *S. aureus* at concentrations ranged from 1 to 2 μg/mL. Resistance experiments revealed that MRSA could develop resistance to the antibiotic ciprofloxacin but not to compound **115**. In a mouse skin wound infection model, **115** was equipotent to the drug fusidic acid in reducing MRSA load. Davis et al. [91] published a new class of compounds featuring an aryl isonitrile moiety **116** that exhibited potent inhibitory activity against several clinically relevant MRSA and VRSA isolates. The SAR studies were conducted and the aryl isonitrile group was identified as crucial for antibacterial activity. Sheridan et al. [92] identified and reported two promising lead compounds **117** (MIC = 2 μg/mL) and **118** (Fig. 23) (MIC = 4 μg/mL) containing an *N*-(methylsulfonyl)amide substituent with MICs comparable to standard Vancomycin. The novel endophenazine G and other phenazines were evaluated for their anti-MRSA potency.

A series of new 2,4-disubstituted-6-thiophenyl-pyrimidine derivatives were synthesized and their antibacterial potencies against clinically relevent pathogens were investigated by Fanga et al. [93] The antibacterial activity of compound **119** (Fig. 24) against MRSA and VREs (MIC values = 2 μg/mL) was stronger than that of methicillin and vancomycin. *In vitro* and *in vivo* data, revealed that **119** was found to inhibit GTPase activity, FtsZ polymerization and imparts low resistance. Yang et al. [94] reported a series of new bromo-substituted indolizinoquinoline-5,12-dione derivatives and evaluated against clinical MRSA strains. The most potent compound **120** (Fig. 24) exhibited strong activity against clinical MRSA strains with both MIC_{50} and MIC_{90} values lower than 7.8 ng/mL. Compound **121** (Fig. 24) had strong activity against clinical MRSA strains with MIC_{50} value of 63 ng/mL,

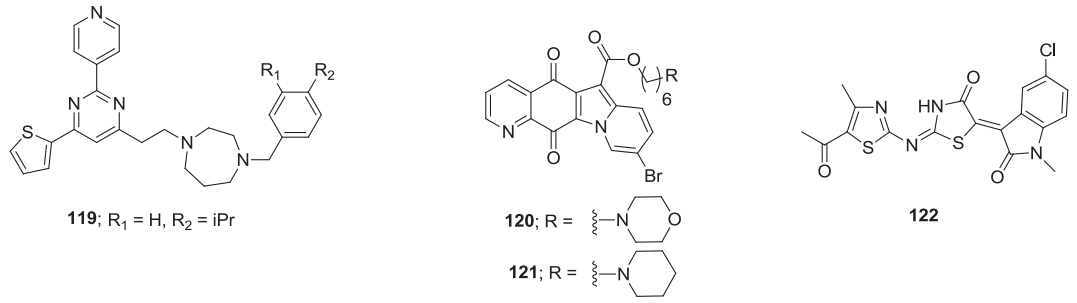


Fig. 24. Some new heterocyclic derivatives with anti-MRSA activity.

which is 16 times higher than that of Vancomycin. Ashour et al. [95] reported the design and synthesis of two different sets of indole-thiazolidinone conjugates. The target compounds were screened for their *in vitro* antibacterial activity against MRSA and other pathogens. Compound **122** (Fig. 24) exhibited potent broad spectrum antibacterial activity (MIC = 0.39–0.98 μg/mL) with good selectivity index. Moreover, compound **122** exhibited promising inhibitory activity towards MRSA and VRE (MIC = 3.90 and 7.81 μg/mL, respectively).

Dive et al. [96] have synthesized a series of new bis-2-oxo-azetidinyl macrocycles as potential antibacterials. Compound **123** (Fig. 25) was buried into the largest ring (32 atoms) and exhibited inhibitory activity similar to ceftobiprole. Molecular modeling studies of PBP2a cavity allowed to propose a novel pharmacophore, i.e. the 3-(*S*)-acylamino-1-acyl-2-azetidinone ring, with the syn-conformation of the imide function and a pliable macrocycle favouring the opening of the active site. Liu and co-workers [97] reported a series of new diamidines with *N*-substituents on an amidine *N*-atom and evaluated for their *in vitro* antibacterial activity against clinically relevant Gram-positive bacterial strains. The SAR data revealed that a shorter carbon chain on the amidine *N*-atom and *N*-substituents with a branched chain exhibited higher activity against MDR-gram-positive bacteria. Compound **124** (Fig. 25) showed greater efficacy than levofloxacin against most drug-resistant Gram-positive bacteria and exhibited broad-spectrum antibacterial activity against Gram-negative bacteria (MIC = 2–16 μg/mL. Effective antibacterial activity of **125** (Fig. 25) was also shown *in vivo* in a mouse model of MRSA strain with an ED_{50} value of 2.62 mg/kg. Zhang et al. [98] identified the new series of isatin *β*-thiosemicarbazones (IBTs) **126** that could inhibit the growth of MRSA and VRE. Most of the synthesized compounds showed minimum inhibitory concentration (MIC) data ranging from 0.39 to 0.78 μg/mL against a clinical isolated MRSA strain and compared with vancomycin. Su, et al. [99] synthesized a variety of 4,5-disubstituted-2-aminoimidazole–-triazole conjugates via Weinreb amide approach. The antibiofilm activities of these compounds were examined and the compounds **127**, **128** and **129** (Fig. 25) were noticed as the most active. Growth-curve and colony-count analyses clearly suggested that lead compounds inhibit biofilm formation via a non-microbicidal mechanism.

Jarvest et al. [81] reported a series of new potent nanomolar inhibitors of *Staphylococcus aureus* methionyl tRNA synthetase enzyme, which showed excellent antibacterial potency against strains resistant to clinical antibiotics. Compound **130**, **131** (Fig. 26) demonstrated excellent *in vivo* efficacy in a *S. aureus* rat abscess infection model. Chang et al. [100] synthesized a number of structural derivatives of tricyclic indoline Resistance-Modifying Agent (RMA) and examined for their ability to potentiate *β*-lactam antibiotics (amoxicillin/clavulanic acid, meropenem and cefazoline) in MRSA and for their cytotoxicity in mammalian cells. SAR analysis data revealed that the sulfonamide group on the side chain was vital for the RMA activity. Modifications of both aromatic systems could tune the RMA activity and the mammalian toxicity. This research group found that adding fluorine to the position-7 of the indoline enhances RMA activity of the compound. The most potent analogue of **132** was compound **133** (Fig. 26), with reduced mammalian toxicity, low hemolytic activity and exhibited synergy with antibiotics tested. Sabatini et al. [101] have identified the 3-(4-chlorophenyl)-1-(4-nitrophenyl)-1,4-dihydropyrazolo[4,3-c]-[1,2]benzothiazine-5,5-dioxide **134** (Fig. 26), which showed modest intrinsic anti-staphylococcal activity. SAR data suggested that the presence of an *N*-4 unalkylated in the benzothiazine ring was preferred to the NMe, whereas in the phenyl ring linked at the pyrazole scaffold a strong electron-withdrawing nitro group was preferred to bulkier groups and to the *meta*- or *para*-fluorine. Inspite of, the Efflux Pump Inhibitors (*EPI*) activity of derivative **135** (Fig. 26) in the EtBr efflux inhibition assay was lower than that of reserpine, its synergistic activity with CPX was similar or slightly better than the reference against the norA-over-expressing strain SA-1199B.

2.9. Pleuromutilin derivatives

Pleuromutilins are tricyclic diterpenoid antibacterial agents that selectively inhibit bacterial translation which derived its name from the fungus *Pleurotus mutilus*. Several chemists reported the antibacterial properties of natural and semisynthetic pleuromutilin derivatives. C. Ling et al. [102] synthesized a series of new pleuromutilin analogues. Among the compounds tested, compounds **136** and **137** (Fig. 27) exhibited the most potent antibacterial activity. Scrupulous optimization on the physicochemical properties of compound **137** resulted in compounds **138**, **139**, **140** and **141** (Fig. 27) possessing notable antibacterial activity and enhanced hydrophilicity. Compound **141**, displayed a moderate Pharmacokinetic profile and exhibited good *in vivo* efficacy. The phosphate prodrug of compound **136** was also prepared

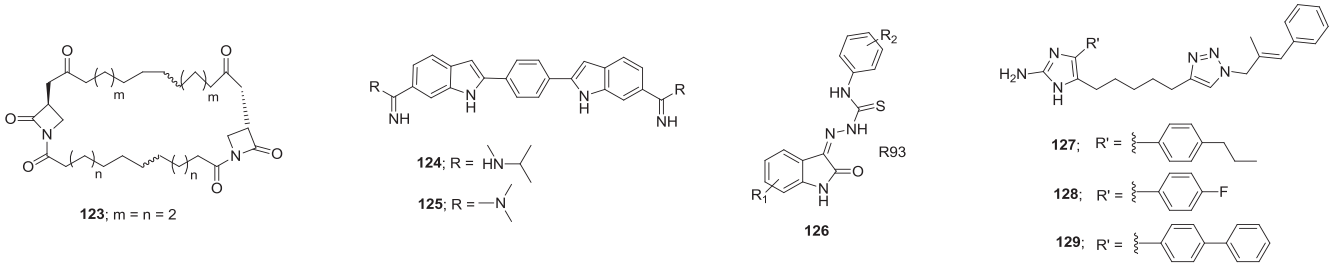


Fig. 25. New heterocyclic compounds with anti-MRSA activity.

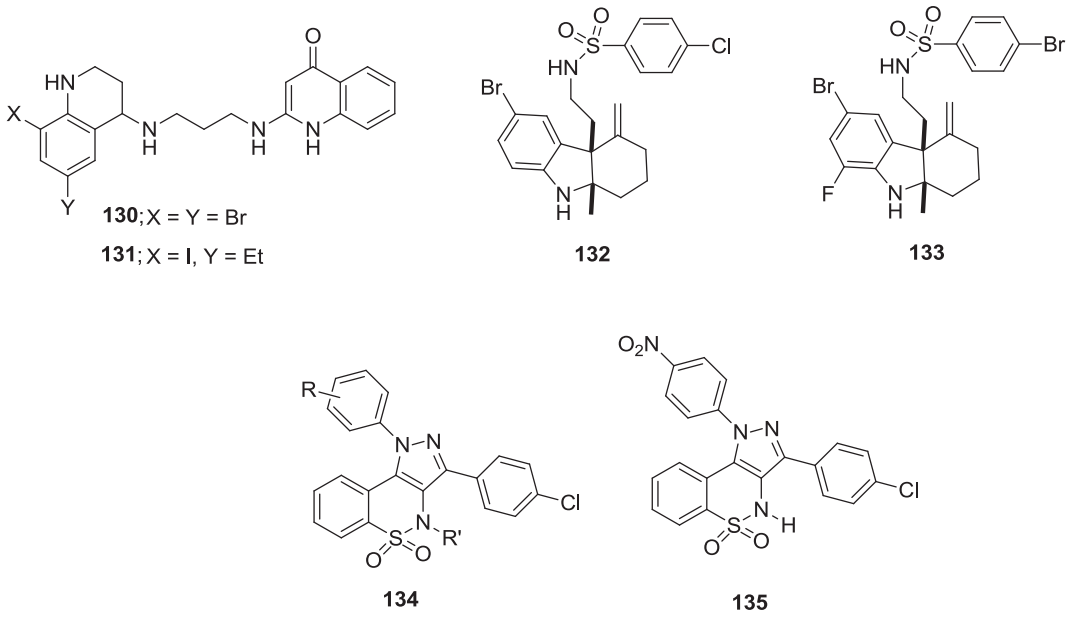


Fig. 26. Some new heterocyclic derivatives with antibacterial activity.

and examined. Shang et al. [103] reported a new series of novel pleuromutilin analogues containing thiadiazole moieties, which were prepared by acylation under mild conditions. These new derivatives were screened for their antibacterial properties *in vitro* against MRSA. The obtained MICs and antibacterial activities revealed that the compounds **142**, **143** and **144** (Fig. 27) were the most active antibacterial agents against MRSA and other resistant strains.

Hirokawa et al. [104] identified and designed a series of new thioether pleuromutilin analogues having a purine ring as a promising pleuromutilin analogue **145** (Fig. 28) with good water solubility (~50 mg/mL) and better *in vivo* efficacy. Compound **145** exhibited promising *in vitro* and *in vivo* antimicrobial activity against clinically relevant drug resistant isolates. Gao et al. [105] reported a series of new pleuromutilin derivatives possessing piperazine ring. The *in vitro* antibacterial activities of the pleuromutilin analogues against MRSA (ATCC 43300) and resistant strains were screened by the broth dilution method. Among the compounds tested, compounds **146**, **147** and **148** (Fig. 28) were found to be the most active antibacterial derivatives against MRSA (MIC = 0.015 μg/mL). Compound **146** was further examined in MRSA systemic infection model and exhibited superior *in vivo* efficacy to that of standard tiamulin.

2.10. Other natural product derivatives

2.10.1. Flavones

Lin et al. [106] reported a series of new natural icaritin derived semisynthetic flavone-based small molecules mimicking AMPs (Antimicrobial peptides). Compound **149** (Fig. 29) was found to possess enhanced antimicrobial properties with MICs of 1.56–3.13 μg/mL. Among all the flavone derivatives tested, only compound **149** was found to be water-soluble. Compound **149** was tested against twelve gram-positive bacterial strains, including MRSA with MICs in the range of 1.56–3.13 μg/mL and was compared with vancomycin (MICs = 0.78–1.56 μg/mL). In this study, the *in vivo* efficacy of compound **149** was examined topically by using an infected mouse keratitis model. Compound **149** showed good safety profile and potent *in vivo* antibacterial activity in the *S. aureus* 29213-infected mouse keratitis model and compared with the levofloxacin as a positive control [107].

2.10.2. Teixobactin derivatives

Parmar et al.[108] designed and synthesized a series of new derivatives of teixobactin by selective replacement of D-Gln4, Ser3 and Ala9 residues by D- and L-arginines in Leu10-teixobactin and Ile10-teixobactin. Many of these teixobactin derivatives showed potent inhibitory activities against *S. aureus*, MRSA and VRE and compared to Ile10-teixobactin and Leu10-teixobactin. The teixobactin-based peptide derivative **150** (Fig. 29) was found to be benign both *in vitro* and *in vivo*. In a mouse model of infectious keratitis, the topical instillation of **150** resulted in > 99.0% reduction in the bacterial load, and the efficacy was compared with standard moxifloxacin.

2.10.3. Glycosides

Ibrahim et al. [109] published the three new potent, selective and benign anti-MRSA metabolites, kaempferol 3-*O*-R-L-(2″-*Z*-*p*-coumaroyl-3″-*E*-*p*-coumaroyl)rhamnoside **151** (IC_{50} 0.7 μg/mL), kaempferol 3-*O*-R-L-(2″-*E*-*p*-coumaroyl-3″-*Z*-*p*-coumaroyl)rhamnoside **152** (IC_{50} 0.8 μg/mL), and kaempferol 3-*O*-R-L-(2″,3″-di-*Z*-*p*-coumaroyl)rhamnoside **153** (Fig. 29) (IC_{50} 0.4 μg/mL), were seperated from the common American sycamore, *Platanus occidentalis*. Due to the virtue of unusual selectivity, potency and safety, the semipure glycoside mixture represented a potential class of anti-MRSA inhibitors. The number of MRSA colonies recovered after treatment with these new compounds at 3 and 15 mg/kg was 2.6×10^7 and 1.8×10^7, respectively, which indicated the reduction of 67% and 78% as compared to control. These results suggested that the test compound was as active as Vancomycin (3.0 mg/kg) against MRSA. Hossion et al. [110] used a structure-guided molecular design approach to optimize quercetin diacylglycoside derivatives that inhibit bacterial DNA gyrase and topoisomerase IV. New 3,7-diacylquercetin, quercetin 6″-acylgalactoside and quercetin 2″, 6″- diacylgalactoside derivatives of lead compound were synthesized and found to exhibit pronounced inhibition (MIC = 0.13 to 128 μg/mL) toward the growth of multidrug-resistant clinically relevant strains. Structure activity relationship data revealed that the acyl moiety was crucial for activity against Gram-positive multidrug-resistant strains. The most active compound **154** (Fig. 29) was 512-fold more potent than vancomycin and showed very low acute toxicity in mice.

2.10.4. Cycloberberine derivatives

Fan et al. [111] identified 8-acetoxycycloberberine which showed potent activity against Gram-positive bacteria MRSA partly through catalyzing the cleavage of bacterial DNA with MIC values of 1–8 μg/mL. The research team designed a series of new 8-substituted

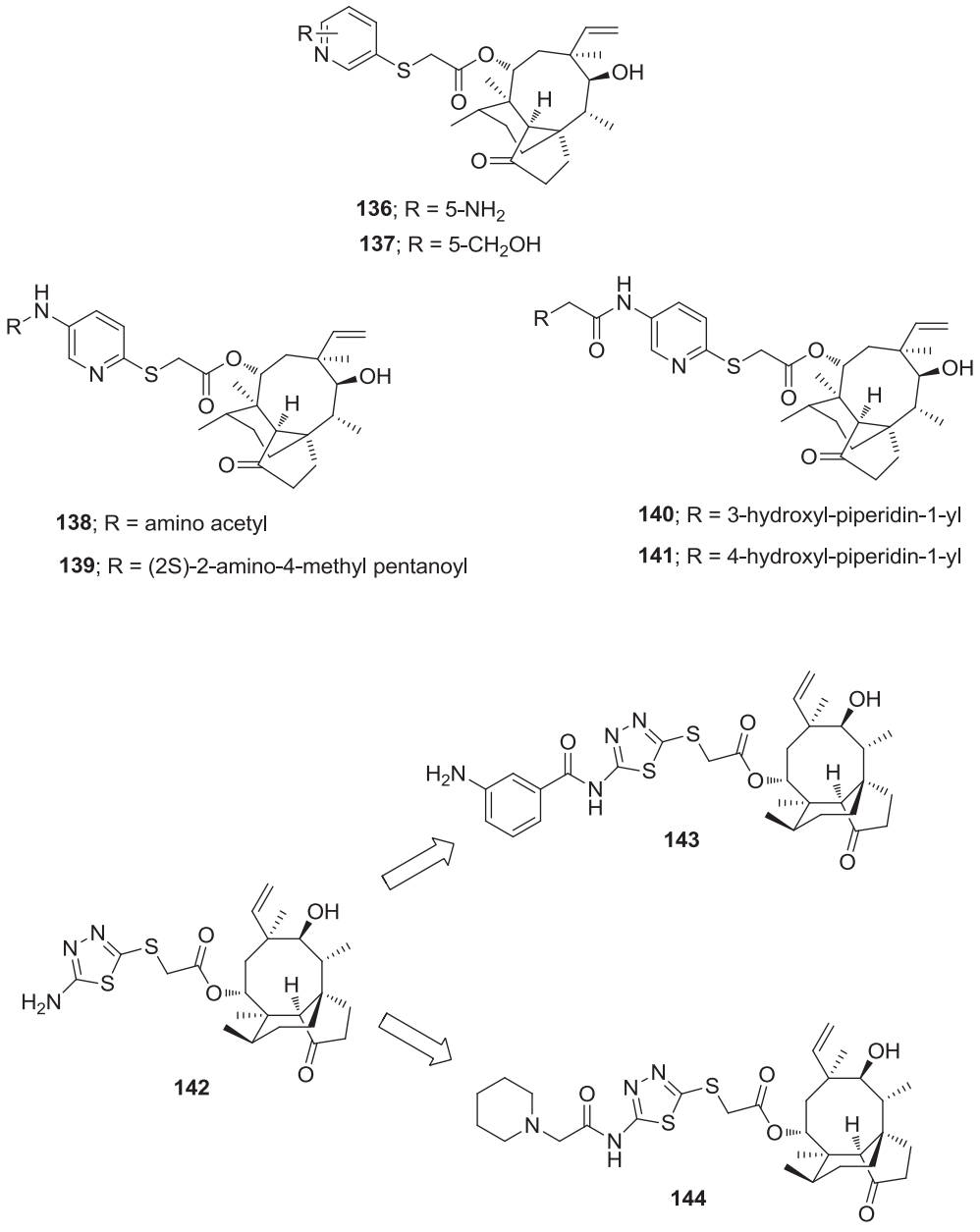


Fig. 27. Some new pleuromutilin derivatives with antibacterial activity.

cycloberberine (CBBR) analogues including ether, amine and amide and were synthesized and examined for their antibacterial potency. SAR studies revealed that the incorporation of a suitable substituent at the position 8 could greatly increase the activity against MRSA. Among all, compounds **155** and **156** (Fig. 30) exhibited equally effective anti-MRSA activity as lead compound, with stable pharmacokinetic characteristics. Fan et al. [112] synthesized and screened a series of new cycloberberine (CBBR) derivatives against Gram-positive bacteria taking CBBR as the lead compound. SAR analysis revealed that the introduction of a electron-donating group at the 13-position in CBBR could be advantageous for the antibacterial activity. Among the tested compounds, **157** and **158** (Fig. 30) showed high potency against clinically relevant resistant isolates with MICs of 1–4 μg/mL. Both of these compounds **157** and **158** showed good *in vivo* safety profile with LD_{50} values of 65.6 and 41.2 mg/kg in intravenous (i.v.) route respectively.

2.10.5. Bionectins

Zheng et al. [113] reported a series of new epidithiodioxopiperazine compounds, bionectins **159** and **160** (Fig. 30) which were derived from the fermentation cultures of the fungus *Bionectra byssicola* F120. Compounds **159** and **160** possessed with a dioxopiperazine moiety and a disulfide bridge. SAR studies indicated that incorporating a dioxopiperazine ring with two methylsulfanyl groups led to loss of activity. Compounds **159** and **160** exhibited antibacterial activity against methicillin resistant *S. aureus* (MRSA) and quinolone-resistant *S. aureus* (QRSA) with MIC values ranged from 10 to 30 μg/mL.

2.10.6. Azaphilones and penicilones

Chen et al. [114] have isolated new azaphilones and penicilones from the mangrove rhizosphere soil-derived fungus *Penicillium janthinellum* HK1-6. Compound **161** and **162** (Fig. 30) had the opposite configuration at position C-7 compared to the closer chloro analogues **163** and **164** (Fig. 30). Ester hydrolysis of **162** and **164** yielded their parental penicilones. Penicilones **162–164** exhibited potent anti-MRSA

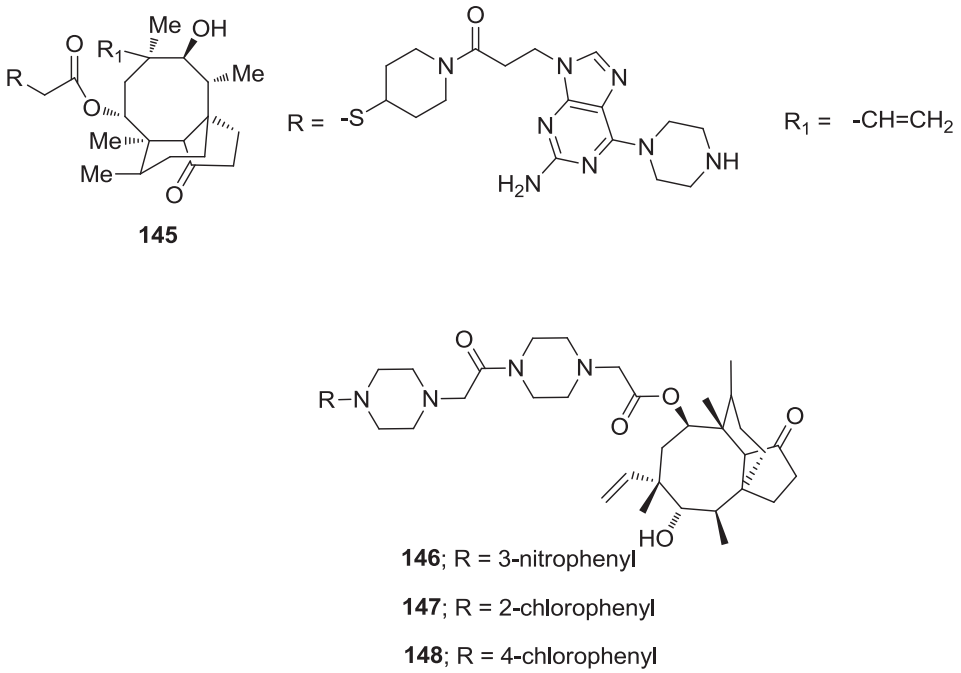


Fig. 28. Some new pleuromutilin derivatives with anti-MRSA activity.

(*S. aureus* ATCC 33591, ATCC 43300) activities (MIC = 3.13 to 6.25 μg/mL).

2.10.7. Miscellaneous

Matarlo et al. [115] published a new series of 4-oxo-4-phenyl-but-2-enoates as MenB, the 1,4-dihydroxyl-2-naphthoyl-CoA synthase inhibitors which meddles with bacterial menaquinone (MK) biosynthesis pathway, by forming an coenzyme A (CoA) adduct complex. Methyl butenoates displayed potent MIC values < 0.35–0.75 μg/mL against drug sensitive and resistant strains of *Staphylococcus aureus*. Mechanism studies on the most active compound, methyl 4-(4-chlorophenyl)-4-oxobut-2-enoate **165** indicated that **165** was converted into the corresponding CoA adduct **166** (Fig. 31) in *S. aureus* cells and binded to the *S. aureus* enzyme MenB with a K_d value of 2 μM. The research team examined the *in vivo* efficacy of **165** using two mouse models of MRSA infection. Compound **165** enhanced survival in a systemic infection model and resulted in a dose-dependent reduction in bacterial burden in a thigh infection model.

Kurosu et al. [116] reported a new series of 1,4-dihydroxy-2-naphthoate prenyltransferase (MenA) inhibitors namely,

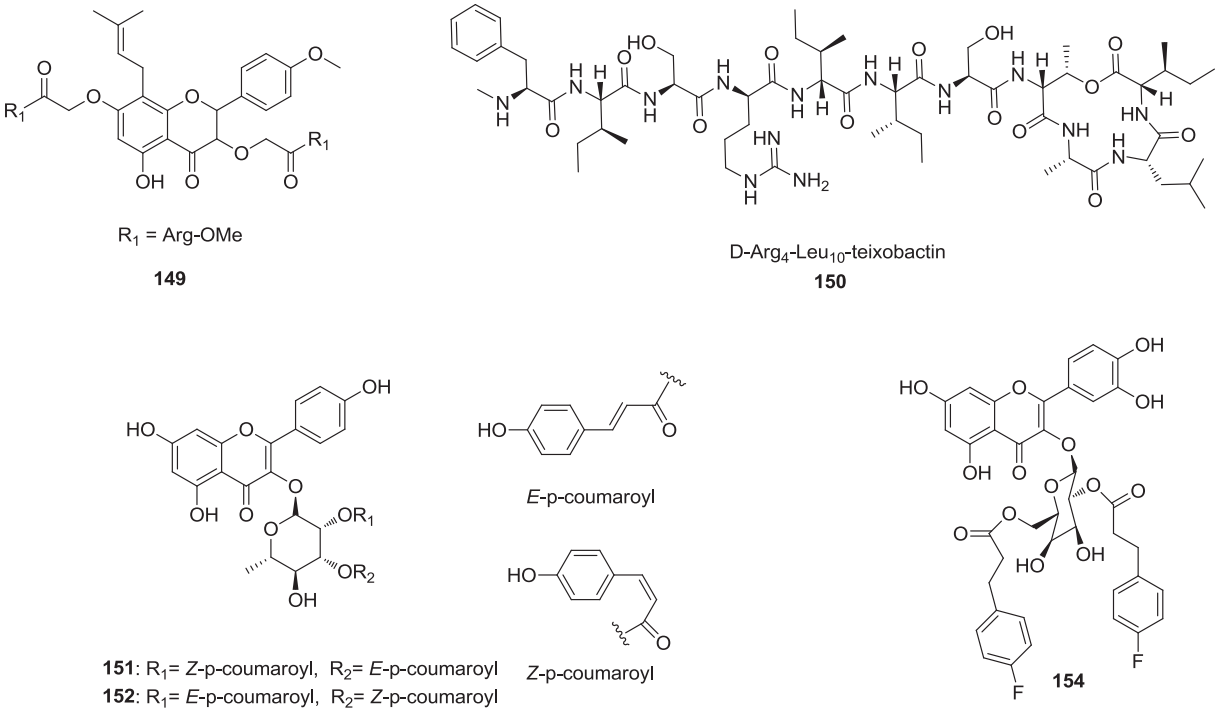


Fig. 29. New natural product derivatives with anti-MRSA activity.

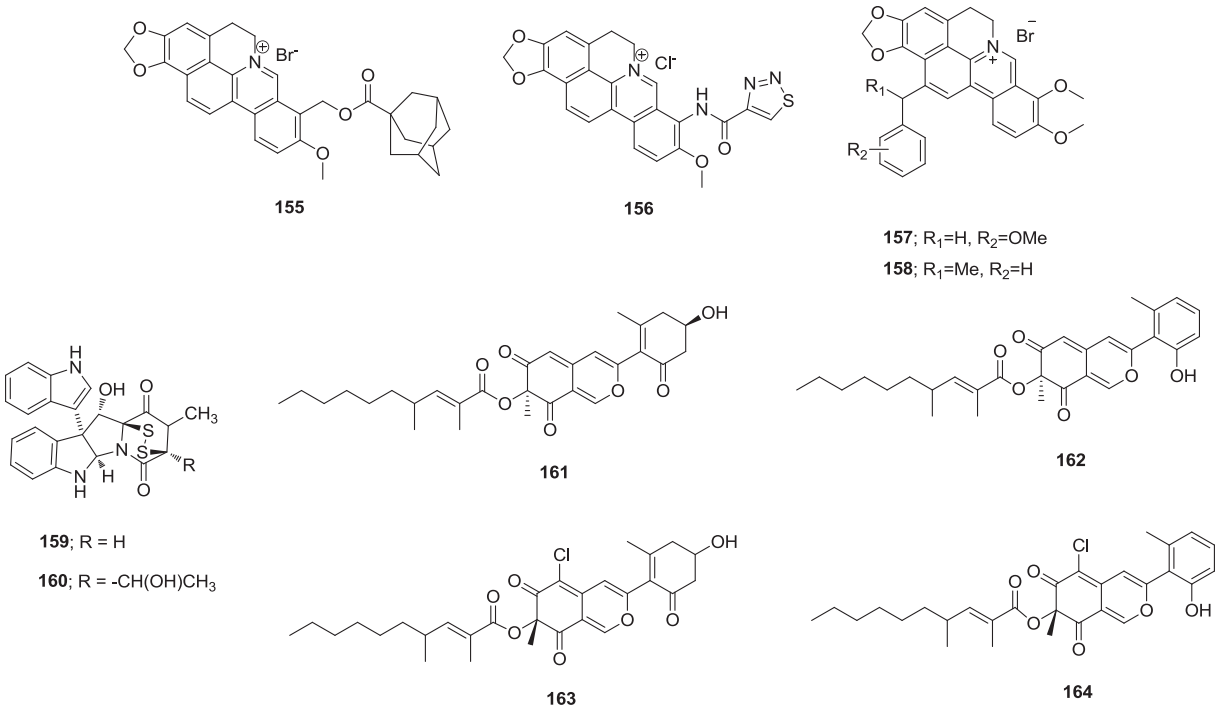


Fig. 30. Some natural product derivatives with anti-MRSA activity.

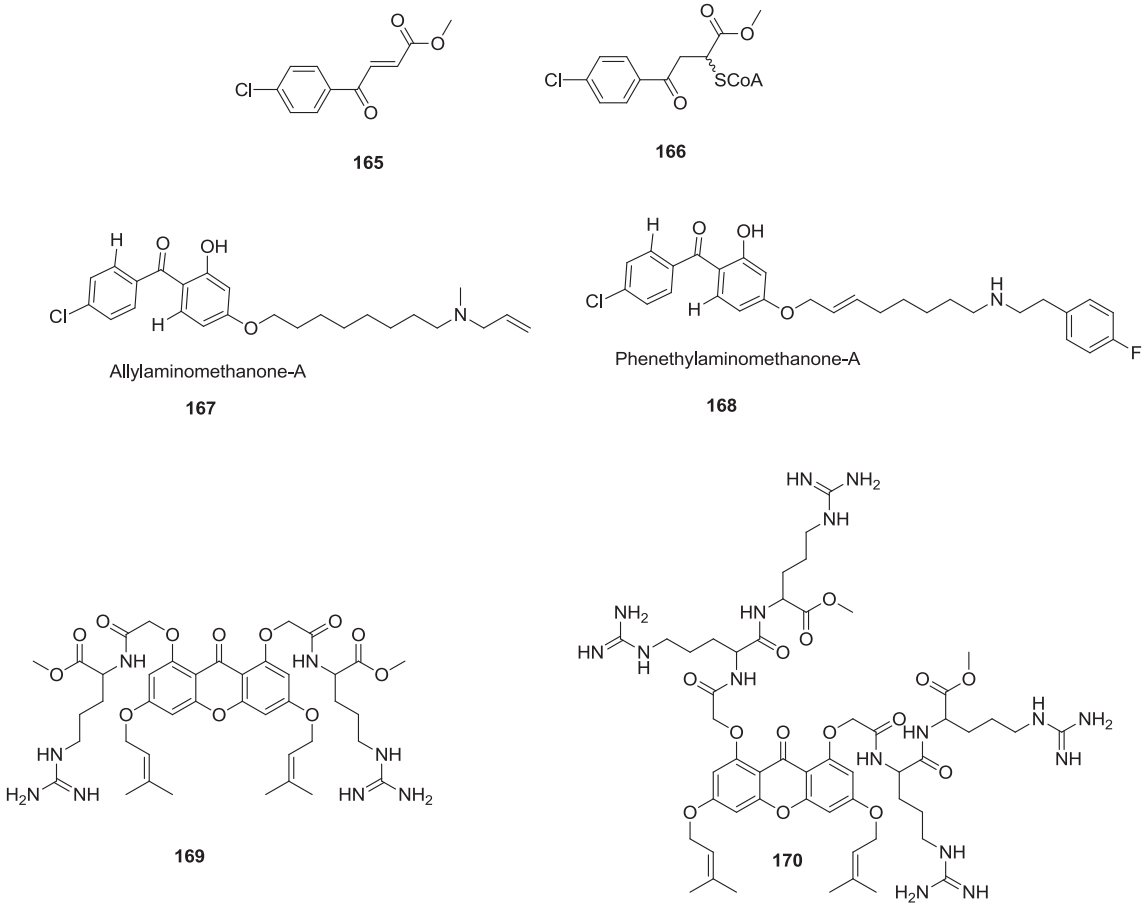


Fig. 31. Some new natural product compounds with anti-MRSA activity.

allylaminomethanone-A **167** and phenethylaminomethanone-A **168,** (Fig. 31) as selective antibacterial agents against methicillin-resistant *Stapylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE). Lin et al. [117] demonstrated a total synthesis method to design and synthesize a new series of symmetrically substituted amphiphilic xanthones. Fine tuning of the cationic and hydrophobic moieties, led to two

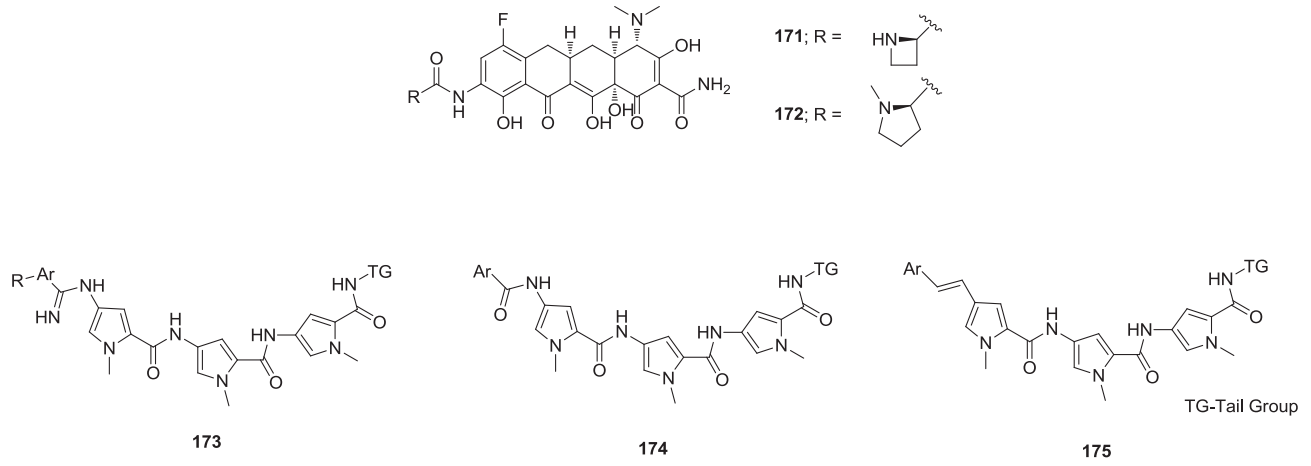


Fig. 32. Natural product derivatives with anti-MRSA activity.

optimized water-soluble compounds **169** and **170** (Fig. 31), which were found to exhibit high membrane selectivity and excellent antibacterial potency. The mechanistic studies clearly suggested that the electrostatic discrimination in favour of the negatively charged bacterial membranes over the zwitterionic mammalian membranes, which enhanced the compounds ability to rapidly infiltrate the bacterial membrane.

Clark et al. [118] widened the chemical space at the position 9 of the fluorocyclines. The research team demonstrated the ability to optimize compounds for antibacterial activity, via subduing both efflux and Tet(M)-mediated ribosomal protection tetracycline-resistance modes. They identified two compounds **171** and **172** (Fig. 32) which displayed superior potency against respiratory pathogen panel. Anthony et al. [119] described the synthesis and features of short minor groove binders **173, 174** and **175** (Fig. 32) related to distamycin and the thiazotropsins. They placed hydrophobic aromatic head groups and of alkenes as linkers, which showed potent antibacterial activity with MIC values ranged from 0.1 to 5 μg/mL against multi drug resistant pathogens, which was compared with the current antibiotics.

Story et al. [120] published the synthesis of new pyrene-neomycin B (PYR-NEO) conjugates **176** and **177** (Fig. 33). pyrene-neomycin B conjugation notably alters the affinities of neomycin B for bacterial A-site targets. The conjugation of PYR to NEO greatly augmented the resistance of NEO to AME modification. Especially, PYR-NEO conjugates displayed broad-spectrum activity towards NEOresistant methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. Twenty-one natural product-based acylphloroglucinol congeners were synthesized, which possessed various side chains by Tan et al. [121]. Antibacterial screening results revealed that acyl moiety tailoring is paramount for the antibacterial activity. Compound **178** (Fig. 33) exerted profound *in vitro* antibacterial activity against the MRSA strain (JCSC 2172) and its MIC was 3–4 fold lower than that of vancomycin. An initial mode of action study of compound **178** unveiled that the mechanism underlying its anti-MRSA activity included membrane depolarization and some extent membrane disruption and cell lysis.

Khan et al. [122] explored the biofilm inhibiting properties of the diterpenoids and new lactone derivatives of **179** against methicillin resistant *Staphylococcus aureus* (MRSA). Compounds **179** and **180** (Fig. 33) at 10–20 μg/mL were found to be bacteriostatic and greatly reduced the biofilm formation. Florescence and scanning electron microscopy affirmed the biofilm inhibiting activities of compounds **179** and **180** and exhibited disrupted biofilms at MIC and sub MIC concentration levels. Besides, the observed anti-virulence properties and delayed bacterial growth after stipulated time of exposure to the test compounds **179** and **180** made them a promising drug leads. Sheppard et al. [123] published a new library of pyridyl disulfides that reflect the chemical reactivity of allicin (garlic) and were screened for

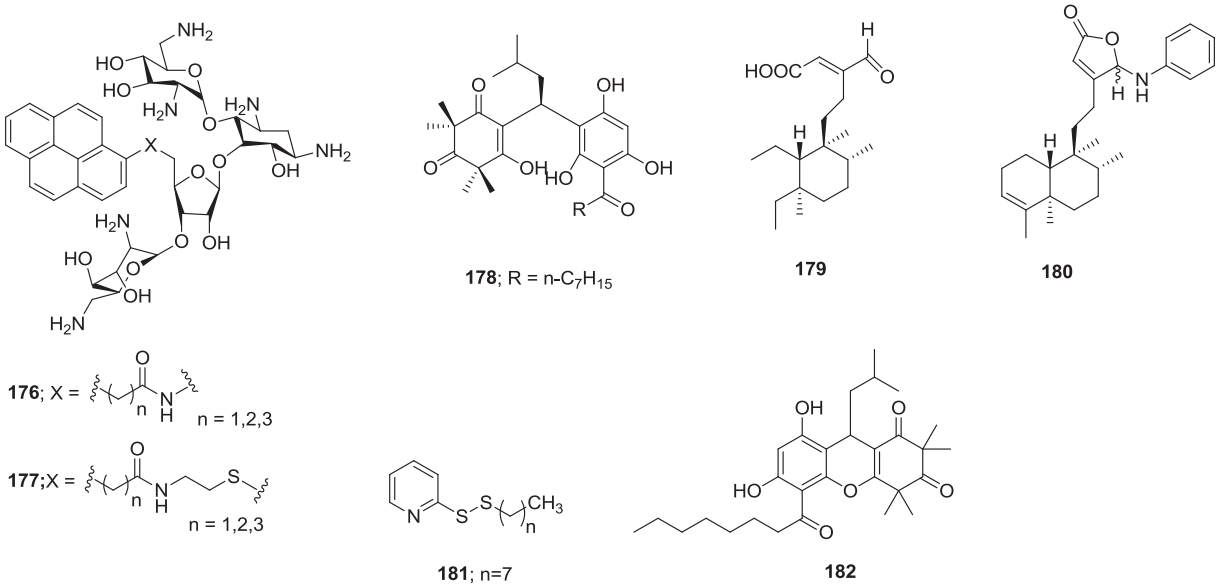


Fig. 33. Some new natural product derivatives with antibacterial activity.

antimicrobial activity against a clinically relevant resistant strain panel. The study demonstrated that analogues with *S*-alkyl chains of 7 to 9 carbons in length imparted high level of susceptibility. The most potent compound among the series was found to be **181** (Fig. 33). Furthermore, biological data unveiled that the disulfides showed excellent synergy with vancomycin against VRSA, exhibited low Cytotoxicity, caused dispersal of *S. aureus* biofilms and decelerated metabolism. Zhao et al. [124] published the structure–activity relationship studies against various MRSA strains and indicated that a suitable hydrophobic acyl tail in the phloroglucinol moiety was found to be prerequisite for antibacterial activity. Analogue **182** (Fig. 33) was identified as a potential lead compound with significant *in vitro* and *in vivo* antibacterial activities against a clinical relevant MRSA strain panel. Besides, compound **182** possessed broad antibacterial spectrum, fast bactericidal action, and excellent membrane selectivity. Further mechanistic study of compound **182** at the biophysical and morphology levels disclosed that **182** exerted its MRSA bactericidal action by superpolarization which resulted in cell breakage and layer disruption.

3. Conclusions

Emergence of multidrug resistant *Staphylococcus aureus* infections has created a critical medical emergency globally. Thus, new antibiotics with new mode of action are greatly sought, and exploration for the anti-bacterial agents has been conducted widely. In this review we have presented various new multidrug resistant *Staphylococcus aureus* active antibacterials such as natural products, phenyl thiazoles, oxazolidinones, benzimidazoles, chalcones, quinazolinones and miscellaneous derivatives which exhibited significant *in vitro* and *in vivo* activity. Various classes of molecules exhibited antibacterial activity by different mechanisms. The phenyl thiazole derivatives mainly act by interfering with the cell wall biosynthesis through inhibiting undecaprenyl diphosphate synthase and undecaprenyl diphosphate phosphatase enzymes. Oxazolidinones are protein synthesis inhibitors which bind to 50S subunit and target an early step involving the binding of *N*-formylmethionyl-tRNA to the ribosome. The new classes of benzimidazoles exhibited a bactericidal activity by inhibiting of bacterial gyrase and topoisomerase IV enzymes. The *N*-methylpropenamine hydrochloride derivatives act by inhibiting Diapophytoene Desaturase (CrtN) and Virulence Factor Staphyloxanthin. The mechanism of action of Quinoline class of compounds is through inhibition of topoisomerase IV and DNA gyrase whereas Quinazolin-4(3*H*)-one derivatives interferes with cellwall synthesis by inhibiting Pencillin Binding Protein 2a (PBP2a). Chalcones act by unselective disruption of cell membranes and also damage the cell walls of *S. aureus*. The natural product pleuromutilin derivatives inhibit protein synthesis by binding to the peptidyl transferase component of the 50S subunit of ribosomes. The other natural products like flavones (disrupting the bacterial membrane), cycloberberine (catalyzing the cleavage of bacterial DNA), 4-oxo-4-phenyl-but-2-enoates (Inhibits MenB in the Menaquinone biosynthesis), Teixobactin derivatives (binds to lipid II and lipid III, precursors of peptidoglycan and teichoic acid respectively) exhibit inhibitory activity against multidrug resistant *Staphylococcus aureus* in a unique manner. However, mechanism of action of some natural products are not well understood. This review covers the recent reports on new antibacterial agents with potent activity against multidrug resistant *Staphylococcus aureus* and the corresponding SAR is also discussed. The variety of antibacterial agents with SAR may lead to further development with a new mode of action to evade the emergence drug resistance.

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Declaration of Competing Interest

The authors declare no competing financial interests.

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