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Chalcone derivatives and their antibacterial activities: Current development

Man Xu, Piye Wu, Fan Shen, Jiayou Ji, K.P. Rakesh*

Engineering Research Center of Environmental Materials and Membrane Technology of Hubei Province, School of Materials Science and Engineering, Wuhan Institute of Technology, Wuhan 430205, PR China

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ABSTRACT

The increase in antibiotic resistance due to various factors has encouraged the look for novel compounds which are active against multidrug-resistant pathogens. In this framework, chalcone-based compounds showed a diversity of pharmacological properties, and its derivatives possess a high degree of structural diversity, and it is helpful for the discovery of new therapeutic agents. The growing resistance to antibiotics worldwide has endangered their efficacy. This has led to a surging interest in the discovery of new antibacterial agents. Thus, there is an urgent need for new antibacterial drug candidates with increased strength, new targets, low cost, superior pharmacokinetic properties, and minimum side effects. The present review concluded and focuses on the recent developments in the area of medicinal chemistry to explore the diverse chemical structures of potent antibacterial agents and also describes its structure-activity relationships studies. The various synthetic structures leading to this class of neutral protective compound is common and additional structural optimization is promising for potential drug discovery and development.

1. Introduction

The damage of bacterial and fungal infections has increased hugely in recent years [1]. Infectious diseases caused by bacterial pathogens have become a main public health problem due to the extensive occurrence of drug resistance. Resistance to antimicrobial agents has increased health concerns and resulted in mortality and morbidity from treatment failures [2,3]. Several bacterial strains causing infectious diseases which seemed to be in control are once again causing death every year due to the absence of suitable antibiotic drug [4]. Regrettably, the development of new antibiotics has failed to keep pace with the development of drug-resistance over the past few decades [5]. Thus, there is a critical global healthcare crisis, which requires the urgent development of more effective antibiotics. In particular, attention has focused on the Gram positive organism *Staphylococcus aureus* because many strains of this organism are now resistant against clinically useful antibiotics like methicillin and vancomycin [6].

The occurrence of multi-drug resistant bacteria becomes a severe medical setback in hospital and community settings [2]. Among them, MRSA (methicillin-resistant *Staphylococcus aureus),* penicillin resistant *Streptococcus pneumoniae* (PRSP), and vancomycin resistant *Enterococci* (VRE) are leading concerns. In addition, this can be caused due to routine dealing of non-bacterial infections antibiotics and insufficient completion with the system for drug intake. In this position, the new therapeutic molecule is very significant to be introduced as antibiotic for the treatment of multi-drug resistance MRSA [7,8]. Even though the MRSA presence in the human flora of skin and especially nasal mucosa, it is an opportunistic pathogen frequently found in nosocomial infections that may lead to severe infections, including septicemias [9].

S. aureus is one of the main human pathogen cause's soft external infections to harsh life-threatening persistent infections to the human world ensuing in important morbidity and mortality [10–16]. The *S. aureus* growing on living or inert surfaces as biofilms, which is community having closely packed *S. aureus* cells bounded with self-secreted matrix [17]. The biofilm play an important role in antibiotic drug resistance which leads to public hazard worldwide [18]. In the past few decades, the number of efforts has been made in the medicinal chemistry through synthetic tailoring in a combinatorial fashion, to generate a large set of analogues as core scaffolds. While the tremendous approaches have been successful, no new major class of antibiotics were invented between 1962 and 2000 [19]. Therefore, to come up with new effective therapeutic agents, there is a need for aggressive efforts and it is imperative to discover novel synthetic entities for the microbial target is a big challenge to the medicinal chemistry [20,21]. The overall clinical experiences reveal that the single-targeted drugs will not be effective agents to the biological system even if they have good inhibitory activity against specific target [22,23].

Chalcones is an open-chain flavonoid with α,β-unsaturated carbonyl

* Corresponding author.
E-mail address: rakeshasg@gmail.com (K.P. Rakesh).

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group and is one of the important compound groups of flavonoid derived from nature and synthetic compounds belonging to the flavonoid family which remain a fascination among researchers in the 21st century due to their simple chemistry, ease of synthesis, large number of replaceable hydrogens to yield a variety of derivatives. Due to their abundance in plants and ease of synthesis, this class of compounds has generated great interest for possible therapeutic uses [24]. Thousands of chalcone derivatives are synthesized in chemical laboratories, up to date. Chalcones containing several functional groups showed a wide spectrum of biological activities such as antimicrobial [25–28], antimalarial [29,30], anticancer [31,32], anti-inflammatory [33,34], antiprotozoal [35], anti-HIV [36], antioxidant [37] and antiulcer [38] activities. Chalcones and their derivatives have also been found to display antioxidant [39], antimicrobial [40], anticancer [41], anti-malarial [42], anti-inflammatory [43], antiulcer [44], antileishmanial [45] and anti-HIV [46] properties.

We believe, this review article will be useful for inspiring the design, structural-activity relationship and developments of less toxic, low cost and powerful chalcone-based drugs against the various types of bacterial infectious diseases.

2. Antibacterial properties of chalcone derivatives

2.1. Antibacterial activity of fluorinated chalcones

Fluorine has become an important tool in drug discovery, since incorporation of fluorine atom or fluorinated group into drugs or drug lead allows simultaneous modulations of electronic, liphophilic, steric parameters all of which can critically influence both the pharamcokinatics and pharmacodynamic properties of drugs [47,48]. Thus, integration of fluorinated chalcone-1,2,3-triazole hybrids might exhibit synergetic effect in enhancing the bio-activity of these derivatives. Based on the above consideration, a novel series of fluorinated chalcone-1,2,3-triazole hybrids were designed, synthesized and tested for *in vitro* antibacterial activities against *S. epidermidis*, *B. subtilis*, *E. coli* and *P. aeruginosa* [49]. Compound **1** (Fig. 1) with 4-nitro group was found to be more active than the standard with minimum inhibitory concentration (MIC) value of 0.0032 μmol/mL against *E. coli* and *S. epidermidis*, which was better than the standard drug Ciprofloxacin (MIC: 0.0047 μmol/mL). The structure-activity relationship (SAR) suggested that the antibacterial activity was influenced largely by fluorinated triazoles exhibited good results than the non-fluorinated compound **2** (Fig. 1) [50]. The introduction of C-2 position of fluorine containing chalcone analogues played an important role for the antibacterial activity of hybrids **3** (MIC: 1 μg/mL against *S. aureus*, 0.5 μg/mL against MRSA) and **4** (MIC: 0.5 μg/mL against *S. aureus*, 0.25 μg/mL against MRSA; Fig. 1) showed good bactericidal activity against both Gram-positive and Gram-negative bacteria, including the drug-resistant species MRSA, *Klebsiella pneumoniae* Carbapenemase (KPC) and New Delhi metallo-lactamase-1 (NDM-1) [51]. The incorporation of methyl or methoxy groups at phenyl ring causes the loss of antibacterial activity. The SAR revealed that the antibacterial activity depends on the positive correlation with the length of the alkyl chain, and medium alkyl chain length (n = 7) hydrids were more active than long alkyl chain length hybrids. However, the antibacterial activities of the cationic molecules were found to vary significantly because of the different hydrophobicity of the alkyl chain. The antibacterial activity of compounds decreased with increasing spacer length. This decrease in the antibacterial activity may be caused by the aggregation tendency because of the long hydrophobic chain.

Selvakumar et al. described a systematic SAR study on synthesized chalcone-oxazolidinone derivatives [52]. Although both of the regioisomeric hybrid molecules were inactive, the introduction of pyridineinstead of an aromatic ring led to new derivatives possessing moderate *in vitro* activity. Further modifications involving the conversion of the acetamide group to the corresponding thiocarbamate led to the generation of compound **5** (Fig. 1). Recently, triazolyl bearing chalcone **6** (Fig. 1) was synthesized and evaluated [53] against a panel of bacterial (MRSA, *S. aureus*, *B. subtilis*, *M. luteus*, *E. coli*, *B. typhi*, *P. aeruginosa*, and *B. proteus*) strains. The most active compound **6** displayed maximum activity against MRSA (MIC: 4 μg/mL), *M. luteus* (MIC: 4 μg/mL) and *C. mycoderma* (MIC: 8 μg/mL) comparable or better than the control drugs (**Chloromycin** and **Norfloxacin**).

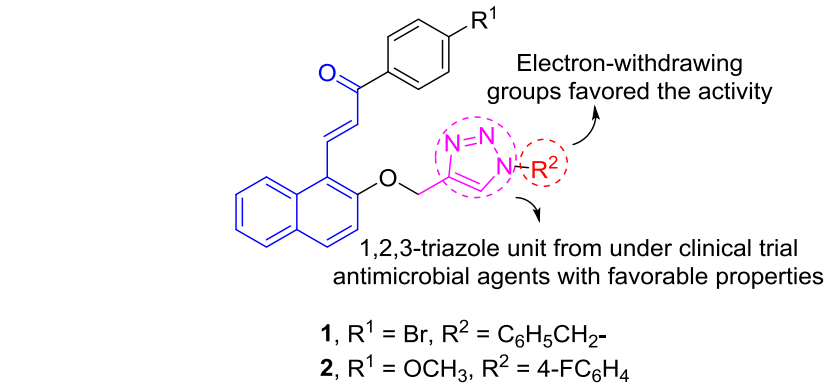
2.2. Antibacterial activity of chlorinated chalcones

The SAR of 2-((5*E*)-5-(4-((*E*)-3-(2,4-dichlorophenyl)-3-oxoprop-1-enyl)benzylidene)-4-oxo-2-thioxothiazolidin-3-yl)acetic acid hybrid **7** (Fig. 2) was found to be most potent antibacterial activity against *S. aureus* with MIC value of 2 μg/mL, which was better than the standard drug (norfloxacin; but less active than oxacillin) indicated that the introduction of strong electron-withdrawing chloro groups at 2 and 4-position of phenyl ring increased the anti bacterial activity. While the incorporation of electron-donating (*p*-CH_3, 2,4-$(CH_3)_2$, *m*-OCH_3, *p*-OCH_3, *m*-OCH_2OCH_3, *p*-OCH_2OCH_3) groups on the phenyl ring reduced the antibacterial activity. Comparing the derivatives with different chloro-substitution positions on the phenyl ring, their activity order was 2,4-Cl_2 > *p*-Cl > *m*-Cl > *o*-Cl [54]. This suggests that the introduction of two atoms of the halogens to the hybrid compound may have played an important part in increasing anti-bacterial properties, for which more compounds using **7** as the lead compound need to be designed and synthesized for further investigation.

The electron-withdrawing substituents (−NO_2) on benzene ring displayed superior activity than electron-donating (−OH and −OMe) groups [55]. The substituent at R position of quinazolinone-chalcone hybrids played an important role in antibacterial activity of hybrid **8** (Fig. 2; IC_{50} = 0.125 mg/mL against *S. aureus* and *S. pyogenes*) showed excellent antibacterial activities and which is more potent than standard antibacterial drug **Ciprofloxacin** (IC_{50} = 0.5–1.0 mg/mL). The SAR revealed that the position of bromine atom on the benzene ring is highly favoured for antibacterial activity. On the other hand, replacing the bromo by chloro, and methoxy at 4-position of phenyl ring decreases in antibacterial activity. This may be attributed to the greater hydrophobic effect of bromo group, than chloro, and methoxy at 4-position. In general, the contribution order of the R group was Br > Cl > OMe [56].

The β-chloro vinyl chalcones **9–13** (Fig. 3**)** was found to be most sensitive against *E. coli* (NCIM 2065), *S. aureus* (NCIM 2120) and *K. pneumoniae* (NCIM 5082) was 25–100 μg/mL [57]. Interestingly, derivatives with electron-withdrawing (−Cl, −F and −Br) substituents at 2 and 4-position on phenyl ring showed more active compared to electron-donating (−Me and −OMe) substituents on phenyl ring. The most active compound **13** (25 μg/mL) were slightly similar potent than standard drug **Penicillin** (25 μg/mL), and could act as a starting points for further optimization. In the continuous searching for potent antibiotics, Li et al. [58] synthesized a library of cinnamaldehyde based chalcone derivatives and tested for their *in vitro* antibacterial activity against a variety of Gram-positive and Gram-negative bacteria. Several compounds exhibited MIC values of 0.25–4 μg/mL against *S. aureus* ATCC25923. Cinnamaldehyde derivatives containing a 2-methyl-benzimidazolyl substitution at 1-position and 3-chlorophenyl, 2,4-dichlorophenyl,4-clorophenyl,4-fluorophenyl, or 4-nitro-phenyl at the 3-position exhibited the best activity (Compounds **14** and **15;** Fig. 3).

In order to reduce the toxicity and increase the antibacterial activity, Gawande and co-workers [59] have synthesized a novel class of β-chlorovinyl chalcones (**16–20;** Fig. 3) and evaluated for *in vitro* antibacterial activity against *E. coli*, *P. vulgaris*, *K. pneumoniae*, *S. aureus*, and *B. subtilis* bacterial pathogens using agar diffusion method [60,61]. All the synthesized hybrids **16–20** showed promising antibacterial activity with MIC values range between 10 and 18 μg/mL, and structure-cytotoxicity relationship indicated that the introduction of −OMe at R^1 and R^2 position reduced the cytotoxicity against CCK-8 cell lines, while



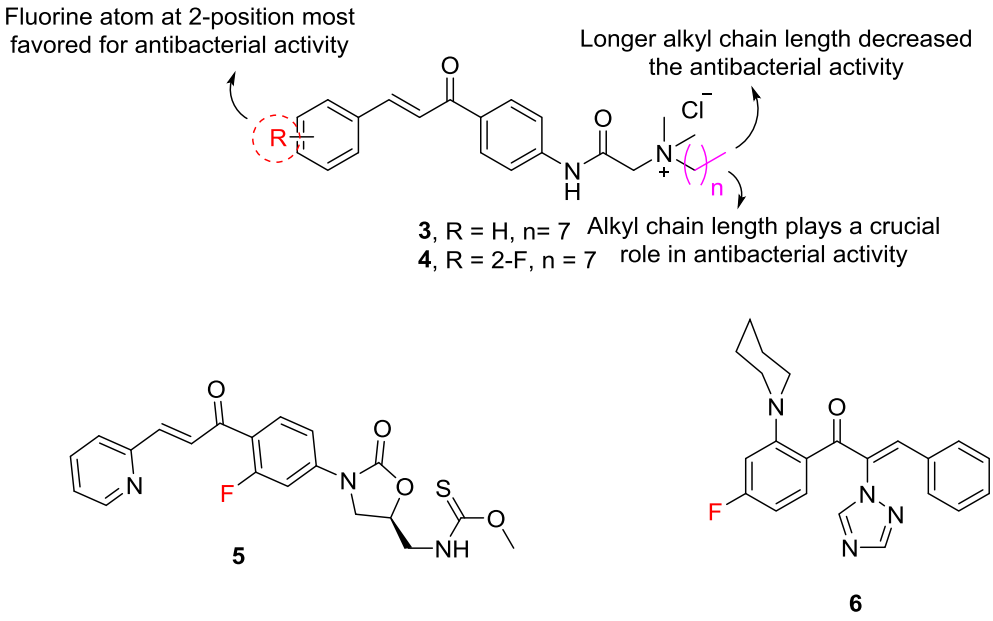


Fig. 1. Fluorinated chalcone based hybrids (**1–6**) showed potent antibacterial activities.

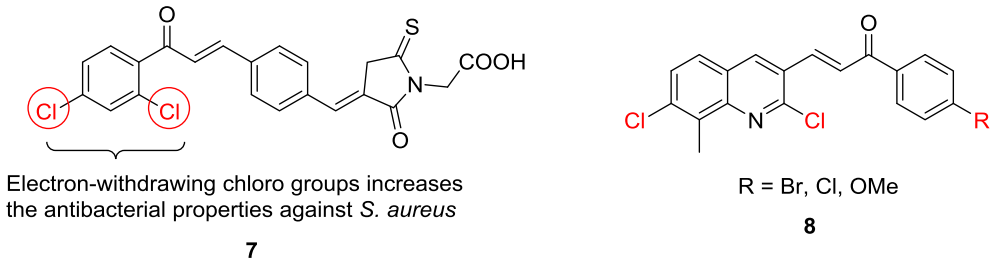


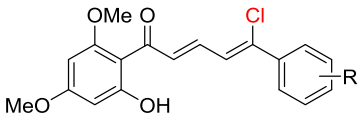
Fig. 2. Chlorinated chalcone based hybrids (**7** and **8**) showed potent antibacterial activities.

the introduction of electron-withdrawing (−Cl and −Br) groups at R^4 and R^5 positions were increases the cytotoxicity level of tested compounds. Compounds **16** (MIC: 17 μg/mL against *E. coli*), **17** (MIC: 17 μg/mL against *P. vulgaris*) were more active than standard antibacterial drug **Tetracycline** (MIC: 15 μg/mL against *E. coli*, and MIC: 16 μg/mL against *P. vulgaris*). That it could act as a lead for further investigations.

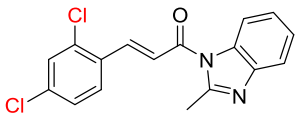
2.3. Antibacterial activity of ferrocene-chalcone derivatives

Organometallic chemistry is of growing interest especially in the recent decades due to its wide applications in the biological and medicinal field, this application leads to a new area called bioorganometallic chemistry. Ferrocene moiety is used in bioorganometallic chemistry due to its stability, biological activity and application in organic synthesis to prepare new compounds. Also, metal complexes are used in bioorganometallic chemistry since they exhibit a wide range of biological activities against various diseases [62]. Many ferrocene compounds display interesting antibacterial [63], antifungal [64], antimalarial [65], antitumor [66], antioxidant [67] and cytotoxic [68] activities. Also, ferrocene compounds appeared promising in biological activities.

Vipan Kumar et al. [69] have synthesized a series of novel isatin-ferrocenyl chalcone conjugates and evaluated for antimicrobial inhibitory activity against *T. vaginalis*. Introduction of electron-withdrawing substituents, viz., fluoro and chloro compounds improved the



9, R = 4-Br; **10**, R = 2-Cl
11, R = 4-Cl; **12**, R = 2,4-Cl
13, R = 4-F



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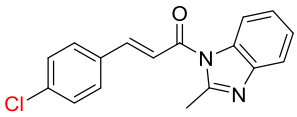

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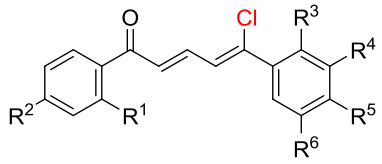


Com. No	R^1	R^2	R^3	R^4	R^5	R^6
16	H	OMe	H	H	OMe	H
17	OMe	OMe	H	H	OMe	H
18	OMe	OMe	H	H	Br	H
19	OMe	OMe	H	H	Cl	H
20	OMe	OMe	H	Cl	H	H

Fig. 3. Chlorinated chalcone based hybrids (**9**–**20**) showed potent antibacterial activities.

growth inhibition activity against *T. vaginalis* irrespective of the length of the alkyl chain linker. The conjugates, viz., **21** (R = F, n = 4) and **22** (R = Cl, n = 2) (Fig. 4**)** with an optimal combination of electron-withdrawing substituents at the C-5 position of the isatin ring and short alkyl chain length proved to be the most potent among the test compounds with 100% growth inhibition. All the synthesized compounds showed an interesting SAR with activity being dependent upon the nature of substituent at the C-5 position of the isatin ring as well as the length of the alkyl chain, introduced as a linker. Quinoline-appended ferrocenyl chalcones synthesized by Prasath et al. [70] exhibited promising anti-microbial potential when evaluated against bacterial strains such as *E. coli*, *P. aeruginosa* and *S. aureus* using agar cup-plate method. Compound **23** (Fig. 4**)** showed significant activity against all bacterial strains studied with inhibition zone (IZ) ranging between 17.6 mm against *E. coli* and 22.3 mm against *S. aureus*.

A novel series of ferrocene based chalcone linked triazole coupled organosilatranes were synthesized and evaluated for *in vitro* antimicrobial activities by Singh et al. [71]. The synthesised multi-component motifs were evaluated against six strains of bacterial strains and compared with the standard antibacterial drug Rifampicin. Compound **24** and **25** (Fig. 4**)** showed promising antibacterial activity against *E. coli* (MIC: 125 μM) and *E. faecalis* (MIC: 125 μM) respectively. The SAR indicated that the structural modifications like the introduction of new substituents at the chalcone or the ferrocene ring that can highly enhance their antibacterial potency of synthesized ferrocene based chalcone derivatives.

Muškinja et al. [72] have developed novel series of ferrocenyl chalcones with *O*-alkylated vanillins analogues and screened for their *in vitro* antibacterial activities against *S. aureus* (ATCC 25923), *B. subtilis* (ATCC 6633), *B. cereus* (ATCC 10987), *E. coli* (ATCC 25922), and *Proteus mirabilis* (ATCC 12453). Among all the synthesized compounds, compounds **26** (Fig. 4**)** showed promising antibacterial activity against *E. coli* with the MIC values of 1.25 mg/mL. Compound **27** (Fig. 4**)** showed potent antibacterial activity against *S. aureus* with the MIC values of 0.625 mg/mL. A diversity of various novel series of ferrocenyl based chalcone sulfones and bis-sulfones were synthesized and evaluated for *in vitro* antibacterial activity by Ahmed et al. [73]. Many compounds exhibited high and broad-range bactericidal activity. Among them, compounds **28** (MIC: 100 μg/mL against *C. neoformans*) and **29** (MIC: 3.90 μg/mL against *A. niger*, Fig. 4**)** displayed excellent antibacterial activity, which was better than the standard drug ampicillin (MIC: 250 μg/mL). The SAR revealed that the presence of electron-donating groups (OCH_3 and CH_3) on the phenyl ring highly enhances the antibacterial properties and presence of sulfone groups also contributed to improve the antibacterial activity.

2.4. Antibacterial activity of steroidal-chalcone derivatives

In 2013, Kakati and co-workers [74] have developed a novel series of steroidal chalcones and evaluated for their antibacterial activities against *B. subtilis* and *E. coli*. Some of the compounds showed excellent inhibitory activity against the tested bacterial strains. Compound **30** (Fig. 5, ZoI: 26 mm against *E. coli*) was found to be the most promising having both bactericidal and fungicidal activity with MIC values 150 μg/mL. The presence of the α,β-unsaturated carbonyl moiety in the synthesized compounds was found to be essential for the activity and epoxidation of the double bond decreases in antibacterial properties. Abood and Ibraheem [75] were synthesized progesterone based chalcone hybrids and tested for *in vitro* antimicrobial activities. Some of the tested compounds showed potent antibacterial activities against the antibacterial standard drug Ampicillin. Compound **31** (Fig. 5, ZoI: 30 mm against *S. pneumonia*; ZoI: 24 mm against *S. aureus*) showed excellent antibacterial activities, which is better than the standard drug Ampicillin.

A series of oximes of steroidal chalcones were synthesized and screened for their *in vitro* antimicrobial activities by Lone et al. [76]. Among the oxime derivatives, compound **32** (Fig. 5**)** was found to be more potent against *B. subtilis* with the MIC values of 64 μg/mL. The SAR revealed that the incorporation of oxime group (=NOH) in the core molecule of steroidal chalcone to enhance its antibacterial properties. Presence and position of different substituents on the benzene ring of the chalconyl pendent had a marked effect on the activity of the compounds. Both electron donating and electron withdrawing groups on the aromatic nucleus had no remarkable effect on the antimicrobial properties of oximes. Banday and co-workers [77] have synthesized chalconyl pregnenolone derivatives and evaluated for *in vitro* antimicrobial activities against different bacterial pathogens. Among all the synthesized compounds, compound **33** (Fig. 5**)** showed promising

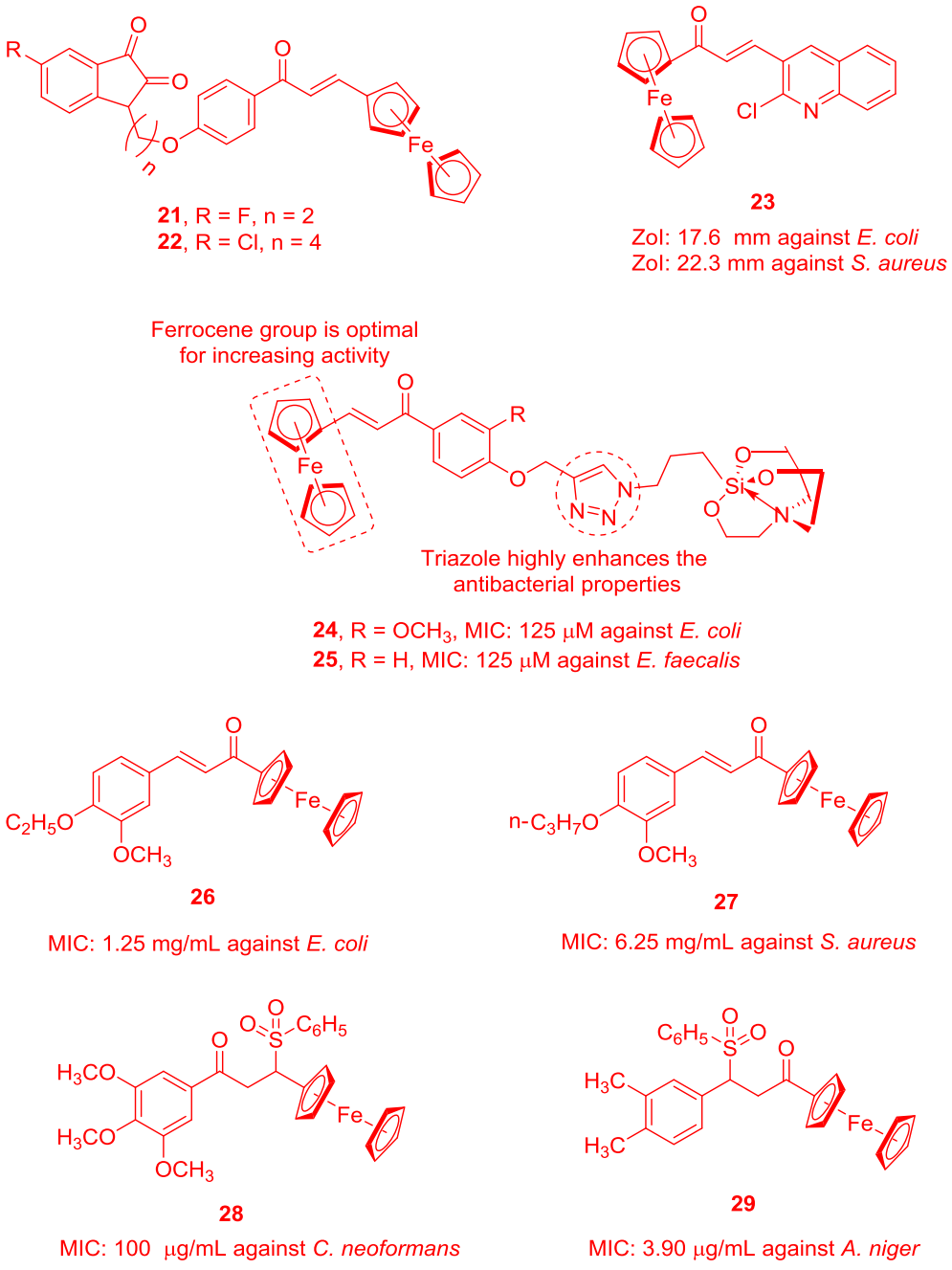


Fig. 4. Ferrocene-chalcone hybrids (**21–29**) showed potent antibacterial activities.

antibacterial activity against *B. subtilis* (MTCC619) with the zone of inhibition value of 20 mm. The SAR revealed that even the position of substituent on the aromatic ring influences the relative activity which can be attributed to their differences in either the bioavailability or the protein binding properties. The presence of furan ring highly enhances the antibacterial activity against *B. subtilis* (MTCC619).

2.5. Antibacterial activity of other chalcone based derivatives

Bavachalcone **34** (Fig. 6; MIC: 4 μg/mL against *B. subtilis*), and broussochalcone B (**35,** MIC: 8 μg/mL against *S. epidermidis*) were active compounds against Gram-positive bacteria. Antibacterial activity against Gram-positive bacteria between prenylated chalcones, such as 4-hydroxyl (**34**, and **35**), group on the B-ring is found to enhance antibacterial activity. The 3′-prenylchalcones showed significant activity, but chalcones with no prenyl group, showed very weak activity. The prenyl moiety on the A-ring is revealed to contribute an increase in bacterial activity. The methoxy group at 4′-position on the A-ring slightly influence on the activity [78].

The antibacterial activity of **39** (Fig. 6; MIC: 4 μg/Ml) against clinical isolates of Gram-positive bacterial strain *S. mutans* 3289 by Zhang and co-workers [79]. The SAR indicated that the electron-withdrawing (−Cl) substituents at 2 and 4-position on phenyl ring most favourable for increasing antibacterial properties. Interestingly, the other electron-withdrawing properties of halogens such as phenyl ring (**36**) 4-F (**37**) and 2-Br (**38**, Fig. 6) hybrids were not influenced the antibacterial activity against *S. mutans*. While the presence of electron-donating (2-OMe, 3-OMe and CH_3) groups at various position on the phenyl ring was not favoured for increasing antibacterial activities. The most hybrid compound **39** showed no toxicity (IC_{50} = 45.05 μmol/L) against human normal liver cell (L02), may serve as new potential antibacterial candidate in near future.

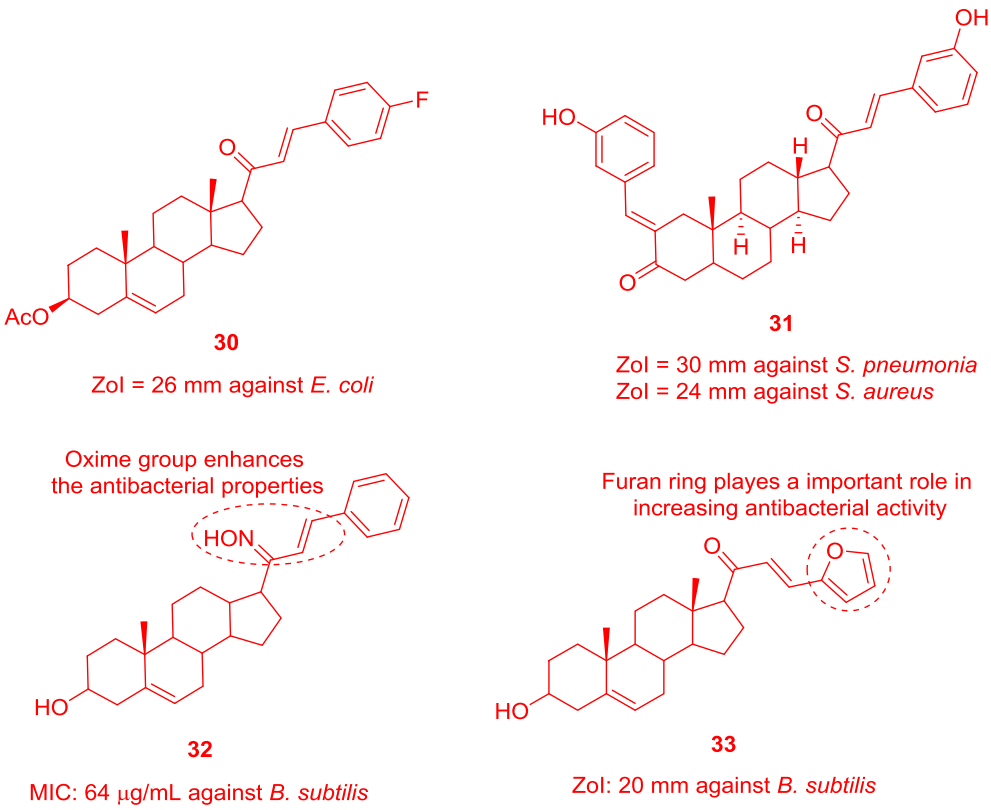


Fig. 5. Antibacterial properties of steroidal-chalcone hybrids (**30–33**).

A library of novel series of chalcone hybrids (**40–45,** Fig. 6) were synthesized and tested for *in vitro* antibacterial activities against drug sensitive strain of *S. aureus* by Liu and co-workers [80]. Among them, compound **40** and **41** showed good antibacterial activities with MIC values of 6.25 and 6.25 μM, respectively against the *S. aureus*. The SAR suggested that 3-Cl and 4-CH_3 at R position boost up the antibacterial activity, and the electron-withdrawing groups such as 4-F (**42**), 3-OMe (**43**), 4-CN (**44**) and 4-CF_3 (**45**) decreased the antibacterial activity.

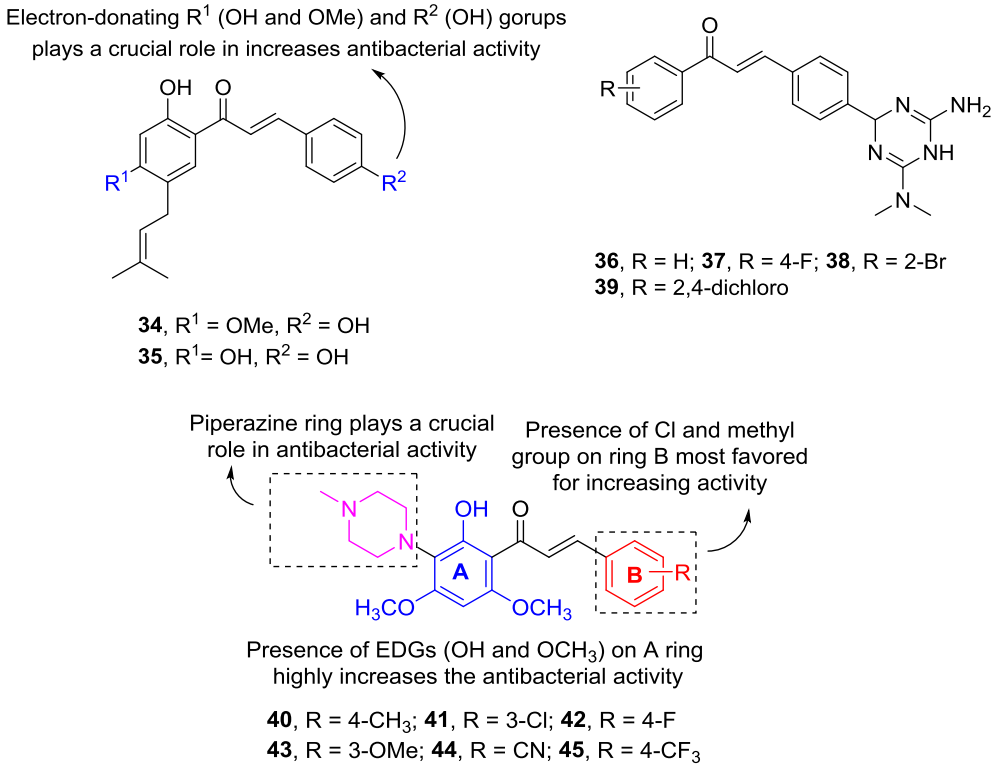


Fig. 6. Chalcone based derivatives (**34–45**) showed promising antibacterial activities.

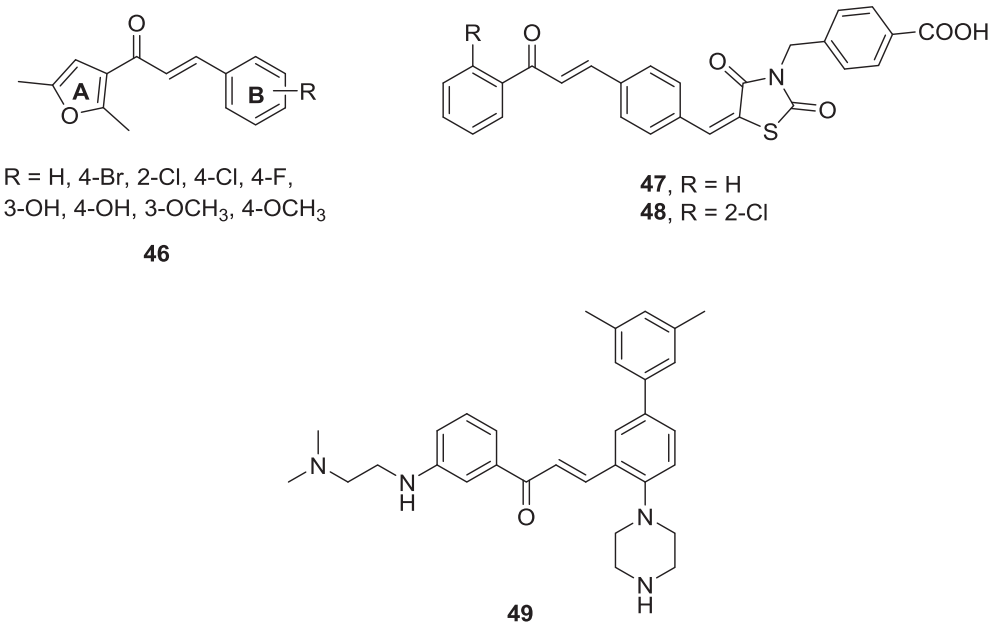


Fig. 7. Chalcone based hybrids (**46–49**) showed good antibacterial activities.

Microwave assisted synthesis of 2,5-dimethyl-3-furyl chalcones [2E-1-(2,5-dimethyl-3-furyl)-3-(substitutedphenyl)-2-propen-1-ones] and their testing for antibacterial and antifungal strains using Kirbye Bauer disc diffusion method, has recently been reported [81]. It was inferred that the chalcone **46** (Fig. 7) possessing hydroxyl functionality at C-3 of ring B was active against all gram positive (*B. subtilis* and *M. luteus*), except *S. aureus*, and gram-negative bacterial strains (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) with Zone of Inhibition values between 6 and 11 mm and 6–9 mm, respectively.

A series of novel chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties were synthesized by Liu et al. [82] and evaluated for their anti-bacterial activities against Gram-positive and Gram-negative bacteria. Compounds **47** and **48** (Fig. 7) showed potent anti-bacterial activity (MIC: 1 μg/mL) against Gram-positive strains (*S. aureus* RN 4220 and *S. aureus* KCTC 503), which was comparable to the control drugs, **Norfloxacin** (MIC: 2 μg/mL) and **Oxacillin** (MIC: 1 μg/mL). The test compounds did not exhibit any activity against Gram-negative strains (*E. coli* 1356 and *E. coli* 1682) at 64 μg/mL. Compound **47**, with a MIC of 1 μg/mL and 0.5 μg/mL against MRSA CCARM 3167 and 3506 respectively, showed eight-fold more potency than Norfloxacin (MIC: 8 μg/mL and 4 μg/mL) and 64-fold more activity than Oxacillin (MIC > 64 μg/mL). Furthermore, the results suggested that the carboxyl group seemed to be necessary for the anti-bacterial activity against Gram-positive strains.

Nielsen et al. [83] described the bioisosteric replacement of the essential 4′-hydroxy group in the hydroxy chalcones with bioisosters of varied degrees of acidity and found that more acidic 4′-hydroxy analogues (e.g., 3′-fluoro- or 3′,5′-difluoro-) were almost inactive compounds where as exchanging the hydroxy group with a carboxy groupresulted in a potent compound with high aqueous solubility. They also studied a class of chalcones having “cationic” aliphatic amino substituents and found that the compound **49** (Fig. 7) showed MIC values of 2 μM against MRSA and also active against *E. faecium* and *E. coli* with MIC: 5 μM [84].

Licochalcone A (**50**) and Licochalcone C (**51**, Fig. 8) were isolated from liquorice and evaluated for *in vitro* antibacterial activity against *B. subtilis*, *S. aureus* and *M. luteus* displayed excellent antibacterial properties with MIC values range between 3.13 and 12.5 μg/mL [85]. Compound **50** showed good antibacterial effect on the MRSA strains (OM481, OM505) with MIC values of 16 μg/mL and MRSA strains (K3 and ST28) with MIC: 6.25 μg/mL [86]. The analogues of **50** were tested against *S. aureus* and showed that the free hydroxyl group at 4-position in ring A was necessary for the antibacterial activity. When the lipophilic prenyl group is removed, a total loss of activity is also observed. If the prenyl group is exchanged by a propyl group, a moderate antibacterial effect is observed. The introduction of the longer hexyl group results in chalcone **52** (Fig. 8) that was more potent than **50**. ClogP study showed that the strong lipophilic character of the molecule played an essential role in the antibacterial effect [87].

A series of 1,2,3-triazole linked chalcones (**53–55;** Fig. 9) hybrids were evaluated for *in vitro* antimicrobial and cytotoxicity by Rama Kant and co-workers [88]. Although compound **53** showed good antibacterial activities against Gram-neagative bacterial pathogens *S. aureus* (ATCC 25323) and *E. faecalis* (ATCC 29212) with MIC of 6.25 μg/mL, which is similar to the reference drug **Ciprofloxacin** (MIC: 6.25 μg/mL). The other hybrids **54** (MIC: 12.5 μg/mL) and **55** (MIC: 12.5 μg/mL) showed promising antibacterial activity. Compound **54** (MIC: 6.25 μg/mL) and **55** (MIC: 6.25 μg/mL) were showed good antibacterial activity against clinically isolated Gram-negative *S. boydii* strain. Further study indicated that, the introduction of electron-withdrawing groups such as −Cl, −F and also their combination has strong effects in rendering the antibacterial activity. Moreover, the positions of these groups in benzene ring also play a critical role towards activity. The presence of −F group on the phenyl ring was optimal for increasing antibacterial activity, which was superior to −Cl group. All the potent compounds are not toxic to a cellular carcinoma cell line (Huh-7) at the highest test concentration (100 μg/mL).

Some of the 2,5-dimethyl-3-thienyl chalcones **56–59** (Fig. 9**)** were exhibited promising anti-*E. colil* activities with the Zone of inhibition values range between 8 and 10 mm and most of them are comparable or better than standard drug **Ampicillin** (ZoI: 8 mm) [89]. The SAR indicated that the incorporation of strong electron-withdrawing groups (−Cl and $-NO_2$) on the phenyl ring exhibited superior antibacterial activity against Gram-negative *E. coli*. While the introduction of fluorine group at C-4 position of chalcone moiety significantly loss the antibacterial activity.

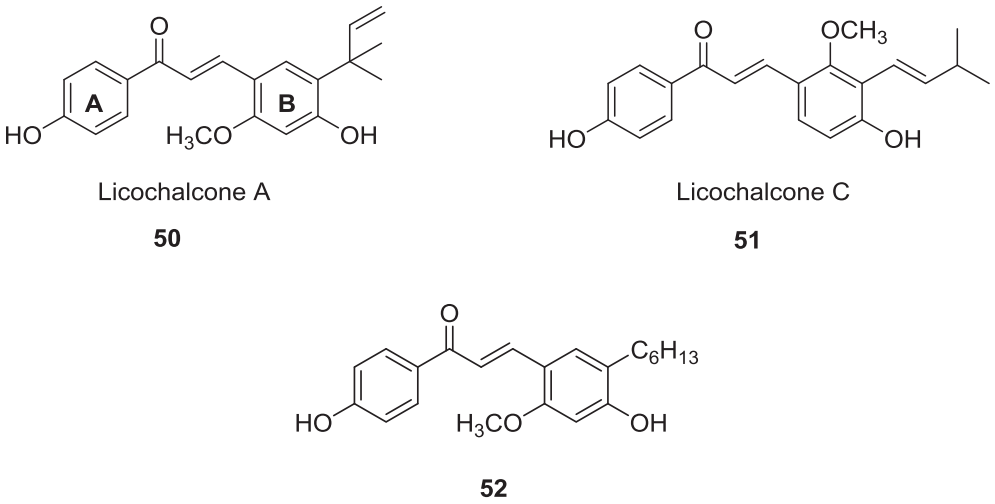


Fig. 8. Licochalcones showed promising antibacterial activity.

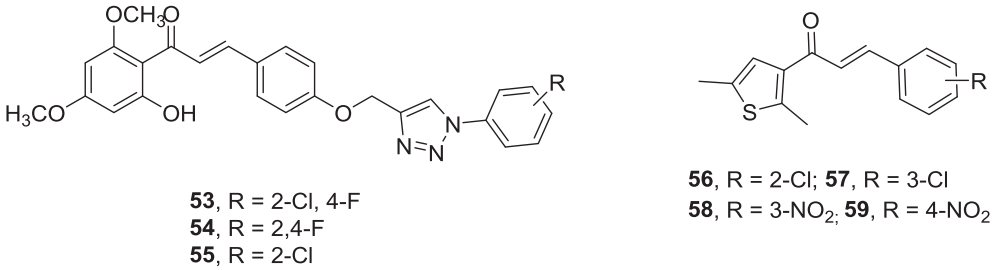
To explore more active candidates of 3-(pyridin-4-yl)-1*H*-pyrazole-5-carboxamide hybrids (**60–63,** Fig. 10) were screened for *in vitro* antibacterial activities against both Gram-positive and Gram-negative bacterial pathogens [90]. The SAR indicated that di-chloro (**63**) counterparts showed excellent activities against Gram-positive bacterial strains *S. pyogenes* (ZoI: 15.5 mm) and *S. aureus* (ZoI: 17.5 mm) respectively, compared with mono-chlorinated chalcone hybrid **62** (ZoI: 15.3 mm against *S. pyogenes* and ZoI: 12.3 mm against *S. aureus*). In particular, C-4 substituted nitro compound **61** (ZoI: 19.3 mm against *S. pyogenes* and ZoI: 20.2 mm against *S. aureus*) was found to possess potent *in vitro* antibacterial activity, which was better than the compounds **62** and **63**. Thus it could acts as a lead for further investigations.

All dehydroacetic acid-chalcone-1,2,3-triazole hybrids **64–66** (Fig. 10**)** displayed promising antibacterial activities against *E. coli*, *B. subtilis* and *S. epidermidis*. Among them compound **65** was found to possess excellent antibacterial activities against all the tested three bacterial strains with MIC of 0.0034 μM/mL, which is more potent than **Ciprofloxacin** (MIC: 0.0047 μM/mL) [91]. The SAR revealed that the synergistic effect of biological activity depends on the combination of two pharmacophoric units, i.e. chalcone and 1,2,3-triazole are conjugated [92]. The introduction of different electronic properties of two functional (−Br and −OMe) groups on phenyl ring exhibited superior antibacterial activity against most of the tested bacterial strains [55]. *Para*-methoxy group was optimal for C-4 position against all the tested bacterial strains and was found to be more potent than Ciprofloxacin [93]. Indeed, compound **65** was a promising candidate for the development of new antibacterial agents in future.

A series of new pyrazolyl chalcones **67** (Fig. 10**)** were evaluated for *in vitro* antibacterial activity against *S. pyogenes*, MRSA, *P. aeruginosa*, *K. pneumoniae* and *E. coli* species [94]. All hybrids showed significant activities against Gram-positive *S. pyogenes* (MIC: 12.5–50 μg/mL) and MRSA (MIC: 12.5–50 μg/mL) but less or nearly same potent than the standard drug **Ciprofloxacin** (MIC: 12.5 μg/mL). The importance of such kind of work lies in the possibility that the new compounds might be more effective against microbes for which a thorough further study regarding the structure-activity relationship, toxicity and their biological effects would be helpful in designing more potent antibacterial agents in future.

Libraries of thirty chalcones were synthesized via a base catalyzed Claisen Schmidt condensation [95] and evaluation for their *in vitro* antibacterial activity against MRSA strain by Tran and co-workers [96]. The combinations of ciprofloxacin with **68** and **69** (Fig. 11**)**, respectively were produced considerably synergism against MRSA with very low MICs (0.0625 μg/mL) for Ciprofloxacin in both combinations. The rates in increasing susceptibility of MRSA with ciprofloxacin were eight-fold. The SAR revealed that a free hydroxyl group in position(s) 2 and/or 4 of B ring appears to be very important to anti-MRSA activity alone or in combination with antibiotics (**68** and **69**). In other hand, electron-withdrawing groups are unfavoured for anti-MRSA activity. Recently, numerous studies confirm that the activity against MRSA of flavonoid derivatives is generally weak, but when they are in combinations with some antibiotics, they could contribute to increase antibacterial activity of antibiotics used together or to restore the effect of separate invalid antibiotics. This result shows significant contributions of chalcones to increasing or recovering the effectiveness of specific antibiotics [97–102].

The structural modifications were carried out involving the substitution of the carboxyl moiety at the *N*-3 position of the rhodanine with a phenylpropionic acid to synthesize the L-phenylalanine-derived C-5-substituted rhodanines **70** (Fig. 11**;** MIC: 2 μg/mL) exhibited very promising antibacterial activity against *S. aureus* RN4220, and which is superior to standard antibacterial drug **Norfloxacin** (MIC: 2 μg/mL).



53, R = 2-Cl, 4-F
54, R = 2,4-F
55, R = 2-Cl

56, R = 2-Cl; **57**, R = 3-Cl
58, R = 3-NO_2; **59**, R = 4-NO_2

Fig. 9. Chalcone analogues (**53–59**) showed promising antibacterial activities.

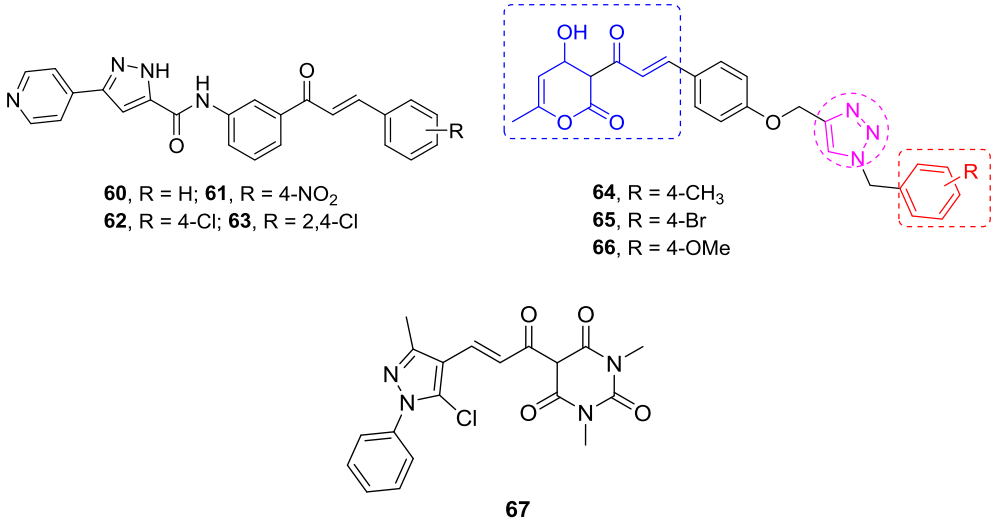


Fig. 10. Chalcone based hybrids (**60–67**) showed significant antibacterial activities.

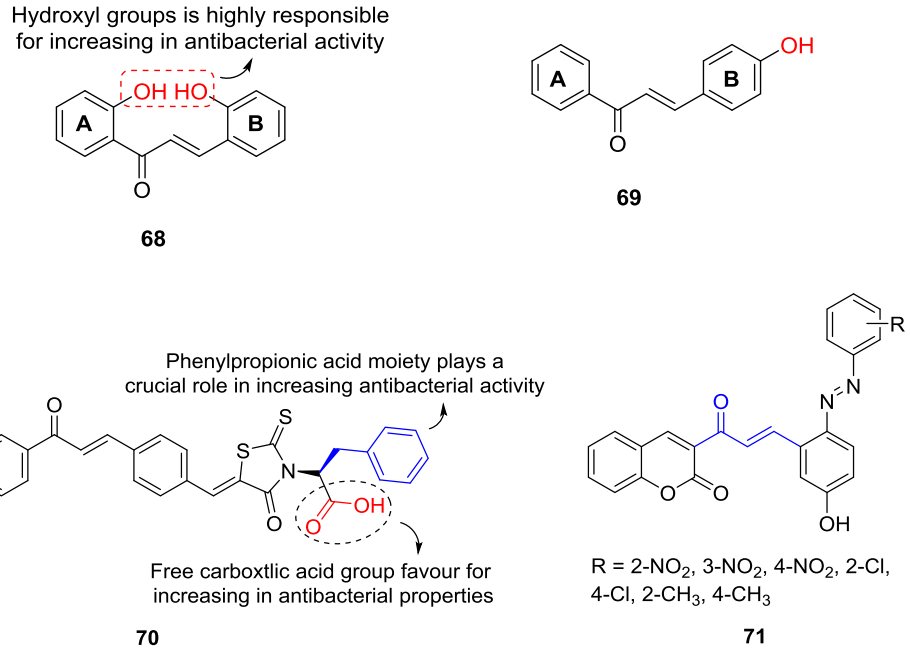


Fig. 11. Chalcone hybrids (**68–71**) displayed significant antibacterial activities.

But, unfortunately here not clear SAR were observed, indicating that the antibacterial activity was not significantly affected by the position or physicochemical properties of the different substituents on the phenyl ring. The results suggest that the hybrid compounds bearing a phenylpropionic acid moiety (which plays an important role in increasing the antimicrobial properties) at the N-3 position of the heterocycle represent promising leads for the development of novel antibacterial agents [103].

Deshpande and co-workers [104] reported a series of coumarin-chalcone hybrids **71** (Fig. 11) containing an azo-linkage and their antibacterial activity was screened against five human pathogens including two Gram positive bacteria of *B. subtilis* and *S. aureus* and three Gram negative bacteria of *E. coli, P. vulgaris* and *K. pneumonia*. In the agar diffusion test, compound **71** possessing a *p*-Cl substitution on the benzoyl ring was proven to be the most potent agent against all three Gram positive bacteria (Zone of Inhibition > 17 mm). Therefore, compound **71** could be employed as a promising agent for anti-Gram positive bacteria.

The anthracene-based chalcone derivatives (**ANNP (72)**, **ANPL (73)**, **ANID (74)** and **ANPT (75)** (Fig. 12) showed great antibacterial potency against both Gram-positive and Gram-negative bacterial strains using a resazurin reduction assay method [105] by Prakash and co-workers [106]. All the hybrids showed promising antibacterial activities with MIC values in the range between 3.12 and 12.5 μg/mL. Among them, **ANNP (72)** (MIC: 3.12 μg/mL) chalcone displayed an excellent antibacterial activity against Gram-positive *B. cereus*, which was similar to the standard antibiotic streptomycin (MIC: 3.12 μg/mL), and it also showed good antibacterial potency against *S. aureus* with an MIC value of 6.25 μg/mL. **ANPT** (MIC: 3.12 μg/mL) was active against the Gram-positive *S. aureus* bacteria [107].

In 2015, Gour and co-workers [108] studied *in vitro* and *in vivo* synergistic interaction of substituted chalcone hybrids with norfloxacin

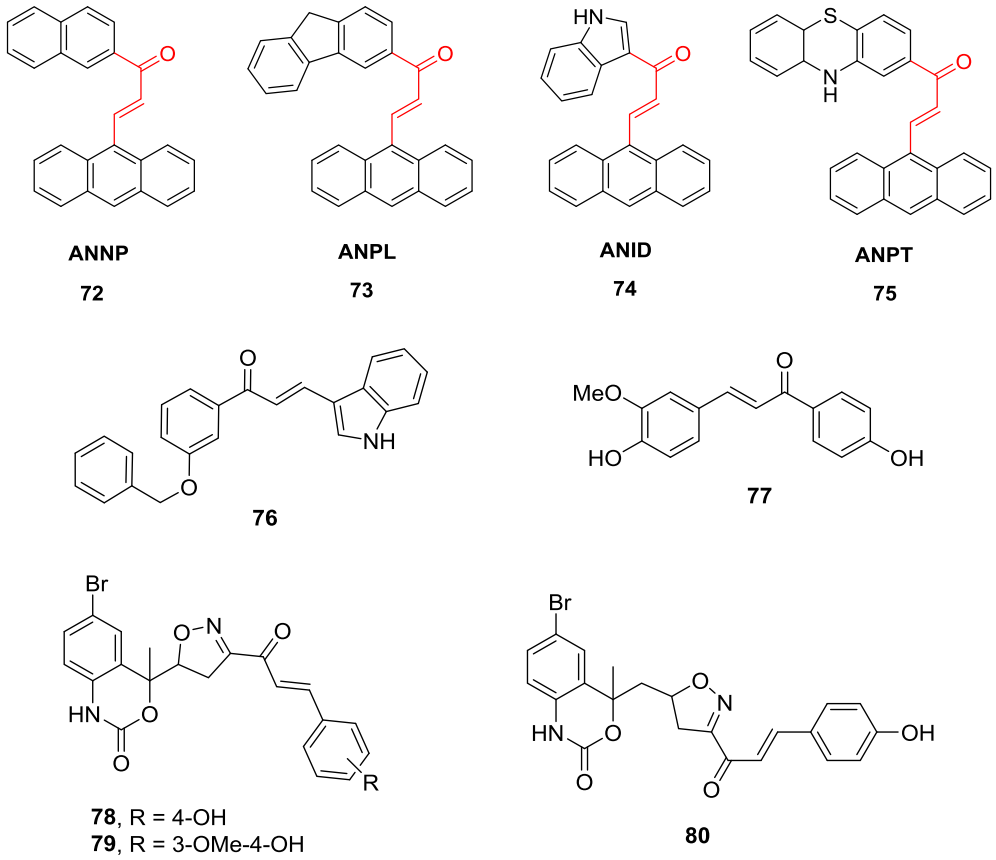


Fig. 12. Chalcone based derivatives (**72–80**) showed potent antibacterial activities.

against methicillin resistant *S. aureus* bacterial strains. Compounds **76** and **77** (Fig. 12**)** showed good antibacterial properties with MIC values of 12.5–50 μg/mL against all clinically isolates of *S. aureus* (MRSA). The combination of norfloxacin with compound **76** showed synergistic interaction (2–16 fold loss of MIC of norfloxacin) against five clinical isolates (MRSA-ST1745, ST2071, P8029, ST5457 and ST10760) with FICI ranging from 0.312 to 0.50 μg/mL. Related to the antibacterial mechanisms, synthesized chalcones **76** and **77** could effect on clinical isolates of *S. aureus* (MRSA) by modulating the bacterial efflux pump. In systemically infected Swiss albino mice model, both the compounds significantly ($P < 0.001$, $P < 0.01$) lowered the systemic bacterial load in blood, liver, kidney, lung and spleen tissues. These results may be of immense helpful in development of anti-MRSA drug combinations from economical and non toxic product in future.

In order to increase the antibacterial activity, a series of novel class of heterocyclic analogues of chalcone containing isoxazole hybrids **78–80** (Fig. 12**)** with −OMe at C-3 and −OH at C-4 position on phenyl ring were evaluated for *in vitro* antibacterial activity by Verma and co-workers [109]. Among them, the hydroxyl group substituted compounds **78** and **80** showed excellent (MIC: 0.34 μg/mL) to good (MIC: 1.78 μg/mL) antibacterial activity against *S. aureus* and *B. subtilis*. Compounds **78–80** exhibited the highest antibacterial activity towards Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria with MIC values of 0.34, 0.59 and 0.74 μg/mL respectively, which was more superior than the standard drug **Ampicillin** (MIC: 0.78–1.56 μg/mL). The SAR suggested that the introduction of −OMe and −OH groups at C-3 and C-4 position of phenyl ring could boost up the antibacterial activity. Hydroxyl group was optimal for *para*-position on phenyl ring.

A series of (E)-3-aryl-1-(3-alkyl-2-pyrazinyl)-2-propenone hybrids **81–83** (Fig. 13**)** were screened for their *in vitro* antibacterial activity against *S. aureus* and *E. coli* using broth tube dilution method [110] by Kitawat and co-workers [111]. All the hybrids showed significant MIC of 32–256 μg/mL against *S. aureus*, and synthesized hybrids showed less potent against *E. coli* (MIC: > 512 μg/mL). Compounds **81–83** displayed excellent antibacterial activity with MIC values of 32–64 μg/mL against Gram-positive *S. aureus*. In particular, the most active **83** (MIC: 32 μg/mL) was found non-toxic against MCF-7 ($LC_{50} \geq 100$ μM/mL). The SAR suggested that compounds having methyl substitution on pyrazine and electron-withdrawing groups such as -F, -Cl, -Br and $–NO_2$ on the *para*-position of the phenyl ring are more sensitive against gram-positive strains, while the electron-donating groups reduced the antibacterial properties. The relationship between structural and biological properties has been explored and could be helpful in designing more potent compounds for biomedical uses in future.

A series of luorine-substituted benzofuran chalcones **84–86** (Fig. 3**)** were synthesized and screened for their *in vitro* antibacterial activities, and the results were compared with standard drugs **Ampicillin** and **Griseofulvin**. All the developed hybrids (**84–86**) were showed promising antibacterial activities against Gram-positive and Gram-negative bacteria with MIC value range between 62.5 and 250 μg/mL. Compound **84** displayed good activity with an MIC of 62.5 μg/mL against *S. typhi* and *S. pyogenes*, whereas compounds **85** (MIC: 100 μg/mL) showed similar antibacterial activity to the reference drug **Ampicillin** (MIC: 100 μg/mL) warrant further investigation [112]. The SAR revealed that the substituents appear to be an important factor in their antibacterial activities, and the electron-withdrawing (mainly −F)

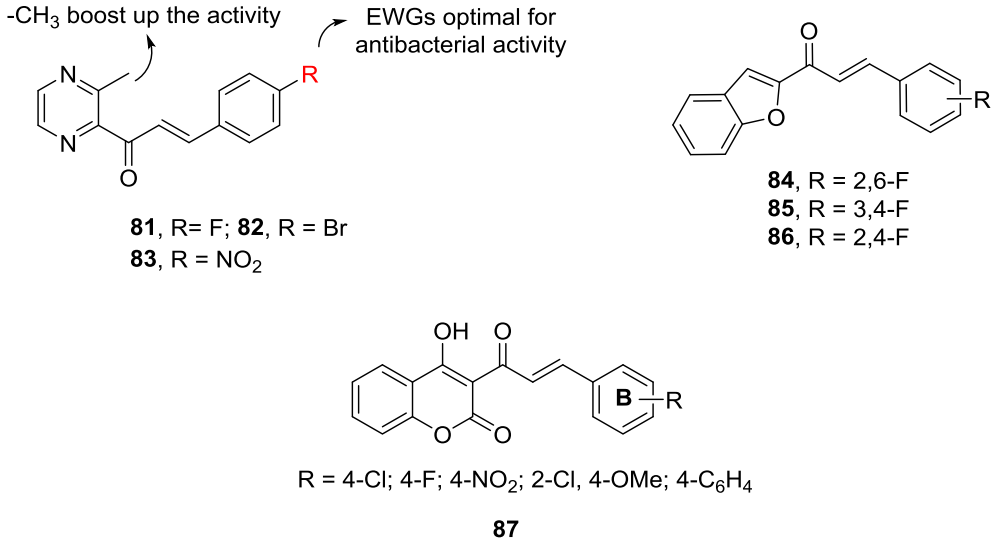


Fig. 13. Chalcone hybrids (**81–87**) showed promising antibacterial activities against tested bacterial pathogens.

groups in the phenyl ring are important for improved the antibacterial activities. Thus these two (**84** and **85**) derivatives would be promising leads for further development of antibacterial agents in near future.

Libraries of coumarin-chalcone hybrids (**87;** Fig. 13) containing substituted B-ring with different electron-donating or electron-withdrawing groups were reported by Hamdi et al. [113] through the similar synthetic route, Trivedi and co-workers [114] synthesized a novel series of coumarin based chalcone derivatives and evaluated for *in vitro* antimicrobial activities using disc diffusion method. All the synthesized analogues displayed promising antibacterial activity with

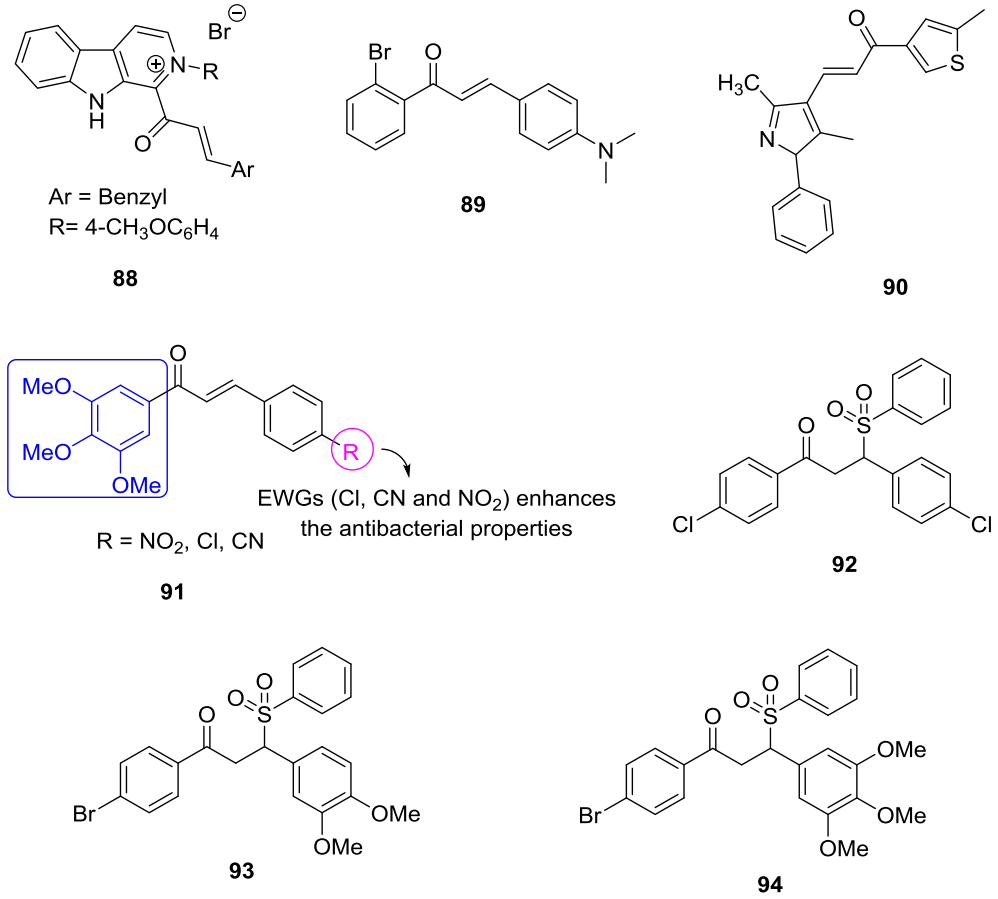


Fig. 14. Some of the chalcone containing analogues displayed excellent antibacterial activity against tested both Gram-positive and Gram-negative bacterial strains.

Zone of inhibition range between 8 and 16 mm against tested bacterial pathogen *S. aureus* (NCTC-7447), and near to same or superior than antibacterial standard drug **Gentamycin** (ZoI = 15–20 mm).

Very recently, Dalip Kumar and co-workers [115] have developed a novel series of β-carboline chalcones and screened for their *in vitro* antibacterial activities against Gram positive and Gram negative bacterial strains. Among all the compounds, carboline derivative **88** (Fig. 14) was found to be most potent analogue against Gram-positive bacterial stain (*S. aureus*) with 15 mm of ZoI and MIC value of 440 μg/mL and less cytotoxic.

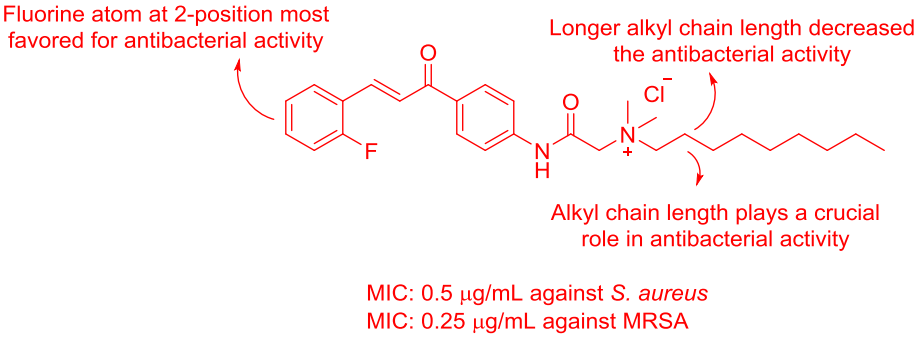
In 2018, Rao et al. [116] synthesized a known chalcone derivatives using the Claisen-Schmidt condensation and evaluated for *in vitro* antibacterial activity *in silico* and consequently confirmed *in vitro* to confirm the findings. Among them, compound 4-NDM-20-HC **89** (Fig. 14) showed excellent *in vitro* antibacterial activity with an IC_{90} value of 0.43 mg/mL against *Vibrio cholerae* as compared to commercially available antibiotic Gentamicin as the standard. The SAR revealed that the bromo chalcone had lesser activity than the hydroxyl chalcone **89** indicating that the hydroxyl group was responsible for better activity, may be due to its better electron pumping nature, i.e., better + R effect and also due to possible hydrogen bonding with the receptor. Above observation reinforce the fact that presence of a strong electron pumping group at the aldehyde side of the chalcone is required for better activity.

Khan and co-workers [117] have prepared for the new series of chalcone analogues as potent antibacterial agents. The anti-bacterial activity of these compounds were first tested *in vitro* by the disk diffusion assay [118] against two Gram-positive and two Gram-negative bacteria, and then the minimum inhibitory concentration (MIC) was determined with the reference of standard drug Chloramphenicol. The antibacterial results presented that compound **90** (Fig. 14; MIC: 16 μg/mL against *S. typhimurium*, and MIC: 16 μg/mL against *E. coli*) is a better inhibitor of both types of the bacteria (Gram-positive and Gram-negative) as compared to **Chloramphenicol** (MIC: 32 μg/mL). A large series of chalcones were synthesized and evaluated for their *in vitro* antibacterial activity against *S. aureus* and *E. coli* by Batovska and co-workers [119].

Among all the synthesized compounds, compounds **91** (Fig. 14; MIC: 62.5 μg·mL against *S. aureus* and *E. coli*) showed excellent antibacterial properties. The SAR suggested that the presence of hydroxyl group in ring B was not a determinant factor for the anti-staphylococcal activity, but the lipophilicity of ring A of the hydroxyl chalcones was of importance. Additionally, electronic effect of the *p*-substituent in ring B is of great importance. *para*-substituted electron withdrawing (−Cl, −CN and $-NO_2$) groups is favourable because it will increase the electrophilicity of C-β and thus facilitate the nucleophilic attack of the cellular thiol groups.

Konduru and co-workers [120] have synthesized a series of novel chalcone based sulfones and bisulfones hybrids and tested for their *in vitro* antibacterial activities against Gram positive and Gram negative bacterial strains. Compound **92** (Fig. 14; MIC: 16.62 μg/mL) has shown slightly better antibacterial activity against *B. subtilis* and compounds **93** (Fig. 14; MIC: 1.95 μg/mL) and **94** (Fig. 14; MIC: 1.95 μg/mL) have shown excellent antibacterial activity against *S. typhimurium* in compare to reference drugs **Ampicillin** (MIC: 125 μg/mL) and **Kanamycin** (MIC: 15.62 μg/mL). The SAR suggested that the electron releasing groups (−OMe or −Me) substitution sulfones have shown excellent (MIC: 1.95 μg/mL) antibacterial activity against *S. typhimurium*. Sulfones having both electron withdrawing groups (−Cl, −Br,- and $-NO_2$) and electron-donating groups (−OMe) on aromatic ring have shown excellent antibacterial activity (MIC: 62.50 μg/mL) against *S. typhimurium*.

3. Some of the most significant findings of SAR studies of potent structures



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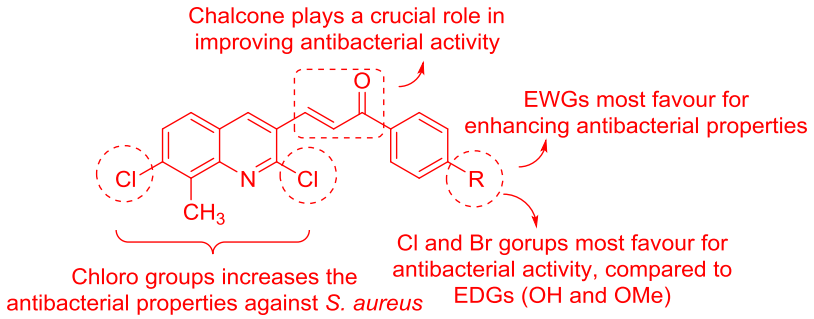

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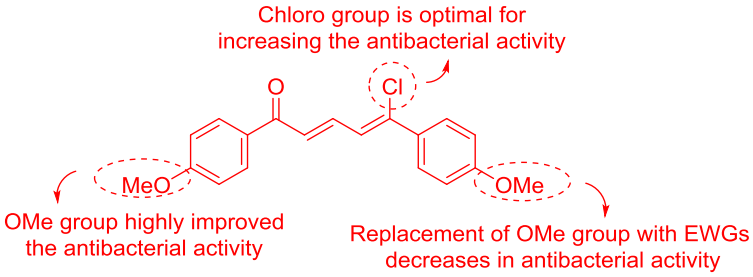
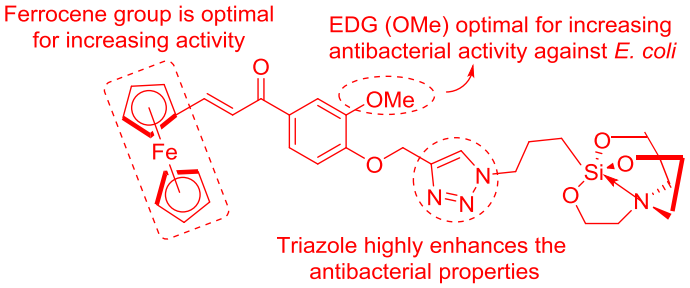


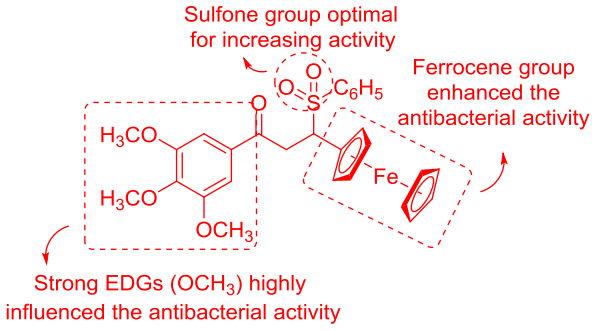
MIC: 17 μg/mL against *E. coli*

16



MIC: 125 μM against *E. coli*

24



MIC: 100 μg/mL against *C. neoformans*

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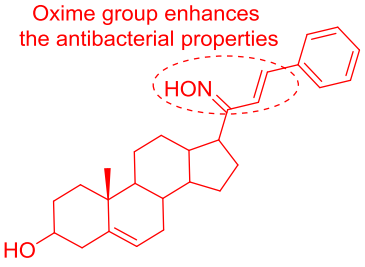
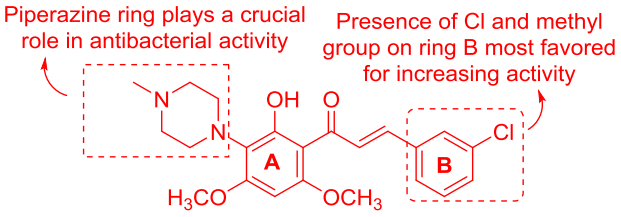


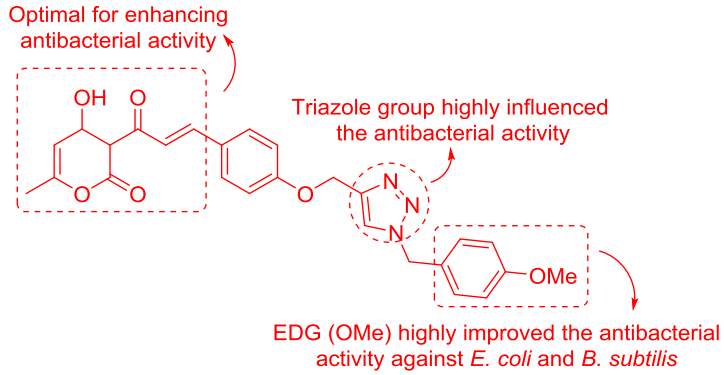
MIC: 64 μg/mL against *B. subtilis*

32



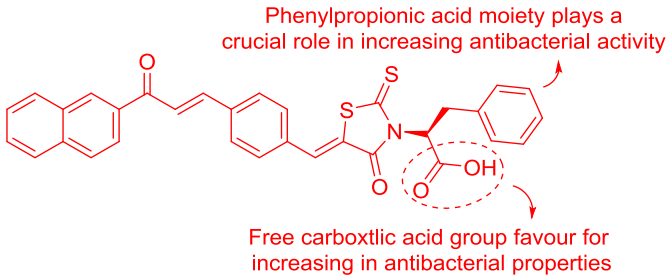
MIC: 6.25 μM against *S. aureus*

41



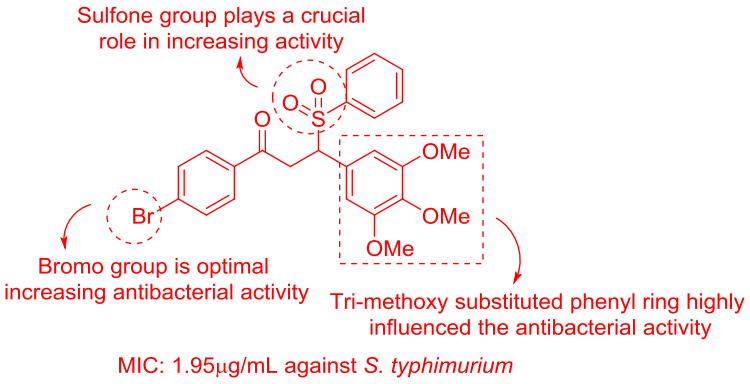
MIC: 0.0034 μM/mL against *E.coli* and *B. subtilis*

65



MIC: 2 μg/mL against *S. aureus*

70



MIC: 1.95μg/mL against *S. typhimurium*

94

4. Author's opinion on this review topic to importance of medicinal chemistry community

Emergence of drug resistance to currently used antibiotics and antimicrobials drugs, especially multidrug resistance, is an imminent danger to human health. Chalcones and its derivatives are not only excellent analogs for synthetic manipulation but also possess multiple biological and medicinal properties such as antimicrobial, anti-inflammatory, antioxidant, antiulcer, anticancer, anti-malarial, COX inhibitors, antileishmanial, anti-HIV and so on.

As described above, a variety of chalcones and their hybrids, as well as synthetic ferrocene or steroidal based chalcones have been investigated and several classes of compounds have been found effective against various Gram positive and Gram negative bacterial pathogens, including MRSA, VRE, as well as *B. subtilis*, *S. aureus*, and *E. coli* and some of the compounds showed potent resistance to tested Gram positive and Gram negative bacterial strains. This review paper deals with SAR investigation on the influence of the substitution pattern, involving electron-donating (OH and OCH_3), electron-withdrawing (Cl, Br, F, and NO_2) groups as well as other heterocyclic substituents of chalcones on their antibacterial activity against human pathogenic microorganisms.

As discussed above, chalcone and its derivatives have proven to be an excellent for discovery and development of antibacterial drug and there have been extensive studies on the discovery and development of next-generation antibacterial agents. Hence, it appears likely that a good number of clinical candidates will be developed in the near future.

5. Conclusion

The development of new antibiotics has been regarded as a potential

therapeutic approach, and a significant number of diverse structures have been reported to inhibit microbial growth in recent years. At present, huge numbers of compounds are undergoing clinical trials as antibiotics. The present review focuses on the recent developments in the area of medicinal chemistry to explore the diverse chemical structures of potent antibacterial agents and also describes its structure-activity relationships studies. The various synthetic structures leading to this class of neutral protective compound is common and additional structural optimization is promising for potential drug discovery and development.

Acknowledgement

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103133.

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