Review Article

Exploring the role of chalcones to treat microbial infections: A mini-review

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ABSTRACT

Chalcones, also known as α, β-unsaturated ketones, are present in some natural products as a major constituent. Chalcones and their derivatives are biologically active molecules that have been an area of great interest from a medicinal view of point in current years. Synthetic manipulations of chalcones or their isolation from natural sources are being looked over worldwide for the expansion of more potent and effective drugs for the treatment of several dreadful diseases including cancer, diabetes, HIV, tuberculosis, and malaria. In previous years, a large volume of research papers and review articles highlighting the biological activity of chalcone derivatives has been compiled in the literature. Chalcones possessed a wide array of biological activity. Few of these biological activities include anti-cancer, anti-aggregation, anti-microbial, and so on. In this review, we have discussed chalcones as antimicrobial agents and also we have highlighted a detailed structure-activity relationship study along with *in vitro* activity.

Keywords: Anti-microbial activity, chalcones, Claisen-Schmidt condensation, structure-activity relationship

INTRODUCTION

Chalcones are aromatic ketone and an enone that forms the central moiety for a broad spectrum of biological activity that is known as chalconoids. Chalcones are a group of molecules with different substitution patterns on the two aryl positions. Chalcones constitute a predominant class of natural products belonging to the flavonoid family and are reported to possess a wide spectrum of biological activities, including anti-bacterial, anti-inflammatory, insect antifeedant, antifungal, analgesic, anti-tumor, anti-mutagenic,[1-3] antitubercular,[4] antiulcerative,[5] antiplatelet,[6] immunomodulatory,[7] anti-viral,[8] anti-malarial,[9] anti-cancer,[10] antihyperglycemic,[11] antileishmanial,[12] antioxidant,[13] inhibition of aldose reductase,[14] inhibition of leukotriene B4,[15] inhibition of tyrosinase,[16] and inhibition of chemical mediators release[17] activities. The presence of a reactive α, β-unsaturated ketone function in chalcones was investigated to be responsible for their antimicrobial activity.

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Chemically, they contain open-chain flavonoids that have two aromatic rings are connected by a three-carbon α, β-unsaturated carbonyl system. Chalcone consists of α, β-unsaturated keto function group that is responsible for antimicrobial activity. In previous years, a variety of chalcones have been investigated for their cytotoxic, anticancer chemo preventive, and mutagenic as well as antiviral, insecticidal, and enzyme inhibitory properties.[18,19]

There are many strategies available for the synthesis of α, β-unsaturated keto function, that is, chalcone. Among them, the direct aldol condensation and Claisen-Schmidt condensation still occupy prominent positions. Both of them the Claisen-Schmidt condensation method is most widely used for the synthesis of chalcone. The Claisen-Schmidt condensation takes place in the presence of aqueous alkaline bases,[20] Ba(OH)2,[21] and LiOH microwave irradiation and ultrasound irradiation.[22] They are also formed through Suzuki reaction,[23] witting reaction, Friedel-Crafts acylation with cinnamoyl chloride, or photo-Fries rearrangement of phenyl cinnamates. An aldol condensation, the preparation of chalcones needs at least two-steps aldol formation and dehydration. Since aldol addition is reversible, Mukaiyama, or Claisen-Schmidt condensation approach of using enol ether has come out as another pathway.

Anti-microbial activity of chalcones

Bhale *et al.* reported the synthesis and biological evaluation of chalcones clubbed imidazo [1,2-a] pyridine scaffolds [Figure 1, **1a-g**] as anti-microbial agents through cup-plate agar diffusion method against *Bacillus coccus*, *Staphylococcus aureus*, *Aerogenes*, and *Pseudomonas aeruginosa* along with anti-fungal activity (*Aspergillus niger*). Results of *in vitro* assay revealed that compound **1b** and **1d** possessed more potent anti-microbial potential toward *S. aureus* (inhibition zone [IZ] = 19 mm) and *Aerogenes* (IZ = 19 mm), respectively, while compound **1f** was more active toward *B. coccus* (IZ = 19 mm) and *A. niger* (IZ = 20 mm).[24]

Yin *et al.* described the design and synthesis of new series α-triazolyl chalcones derivatives [Figure 2, **2a-j, 3a-c,** and **4a-c**] and evaluated them for anti-microbial activity. Among the series, compounds **3a-c** and **4a-c** were exhibited promising anti-microbial potential against a panel of bacterial strains (*MRSA*, *S. aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Bacillus typhi*, *P. aeruginosa*, *Bacillus proteus*) and fungal strains (*Candida albicans*, *Candida mycoderma*). Compound **3a** was found to be more potent toward *MRSA* (MIC = 4 mg/mL), *M. luteus* (MIC = 4 mg/mL), and *C. mycoderma* (MIC = 8 mg/mL), respectively, than that of standard drugs (chloromycin, norfloxacin, and fluconazole). Moreover, compound **3a** forms a complex with calf thymus DNA then inhibited the DNA replication as well as showed interactions with human serum albumin.[25]

Mohammad *et al.* reported the synthesis of 1-(2',4'-Dichlorophenyl)-3-(substituted aryl)-2-propene-1ones derivatives through Claisen-Schmidt condensation reaction, and biological evaluation using the agar diffusion method as anti-microbial agents. Compound **5** exhibited higher anti-microbial potential toward *E. coli* (IZ = 15 mm) followed by *B. subtilis* (IZ = 13 mm) and *Bacillus pumilus* (IZ = 8 mm) at concentration 50 mg/mL. Moreover, compound **6** was found to be most active toward *A. niger* (IZ = 12 mm) as an antifungal agent at the same concentration. Furthermore, structure-activity relationship studies revealed that compounds containing electron releasing groups (methyl, naphthyl) exhibited better antibacterial activity [Figure 3].[26]

Jin *et al.* reported the synthesized the novel series of L-phenylalanine-derived C_5-substituted rhodanine and chalcone congeners bearing thiobarbituric acid or 2-thioxo-4-thiazolidinone

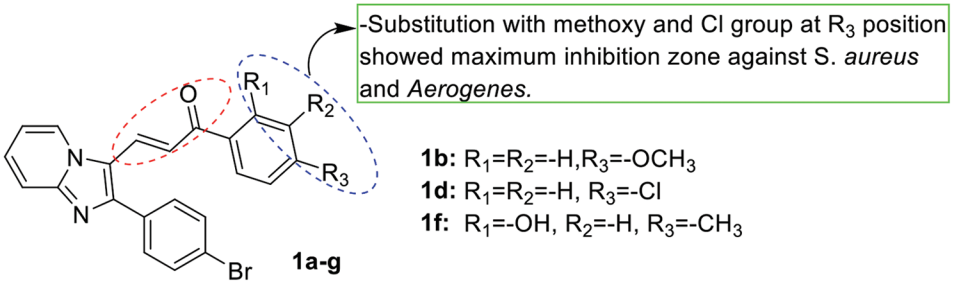

Figure 1: Chalcones clubbed imidazo [1,2-a] pyridine derivatives as anti-microbial agents

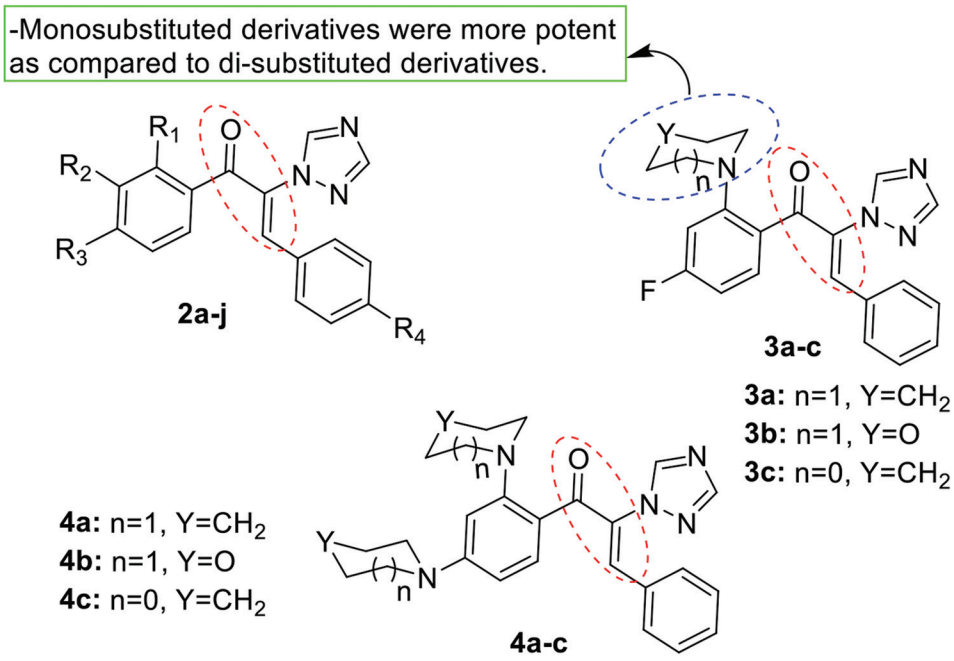

Figure 2: α-Triazolyl chalcones derivatives as anti-microbial agents

[Figure 4, **7a-q**, **8a-j**, **9a-e,** and **10a-e**] and evaluated them as anti-microbial agents toward the Gram-positive bacteria (*S. aureus* RN4220, *S. aureus* KCTC 503 and *S. aureus* KCTC 209) and Gram-negative bacteria (*E. coli* 1356). Among the series, compounds bearing thiazolidine moiety were found to be more active against gram-positive bacteria as well as against the several multi-drug resistant strains having MIC values ranging from 2 to 16 mg/mL, whereas showed less inhibitory potential toward Gram-negative bacteria. Moreover, compound **7q** was found to excellent anti-microbial candidate toward *S. aureus* RN4220 having a MIC value of 2 mg/mL, which bearing a naphthalene ring.[27]

Design, synthesis, and biological evaluation of thiazole clubbed chalcones derivatives [Figure 5, **11a-j**] as anti-microbial agents disclosed by Liaras *et al*. All synthesized compounds were evaluated for their *in vitro* assay toward Gram-negative bacteria such as *E. coli*, *P. aeruginosa*, *Salmonella typhimurium*, and *Enterococcus faecalis* as well as Gram-positive bacteria including *Bacillus cereus*, *Micrococcus flavus*, *Leishmania monocytogenes*, and *S. aureus* and fungi such as *Aspergillus ochraceus*, *Aspergillus fumigatus*, and *A. niger*, *Aspergillus versicolor*, *Penicillium funiculosum*, *Penicillium ochrochloron*, *Trichoderma viride*, and *Fusarium sporotrichioides* as fungi. Results of *in vitro* assay revealed that almost all compounds exhibited promising anti-microbial activity toward the tested strains, followed by more activity toward *E. faecalis* and less against *L. monocytogenes*. Among the series, compound **11g** containing 4-OCH_3 phenyl moiety was found to be most potent against *M. flavus* (MIC = 8.54 µM/mL) and *E. faecalis* (MIC = 17.09 µM/mL), respectively, as compared to standard drug ampicillin (MIC = 24.79 µM/mL). All the synthesized derivatives possessed moderate antifungal activity toward the tested fungal species.[28]

Quinoline clubbed ferrocenyl chalcones congeners [Figure 6, **12a-f,** and **13a-f**] synthesized, and their biological evaluation as anti-microbial agents was reported by Prasath *et al*. All the synthesized derivatives were evaluated for anti-microbial potency through agar cup-plate method toward bacterial strains (*E. coli*, *P. aeruginosa*, and *S. aureus*) and fungal strains (*C. albicans* and *A. niger*) revealed that compound **12a** and **12c** exhibited maximum inhibitory activity toward the tested bacterial strains having IZ values between 17.6 and 22.3 mm as well as showed antifungal activity toward the fungal strains having IZ values ranging from 19.0 to 22.4 mm, as compared to positive control drug.[29]

Subramanian *et al*. reported the synthesis of a new series of 2,5-dimethyl-3-furyl chalcones derivatives [Figure 7, **14a-k**] and

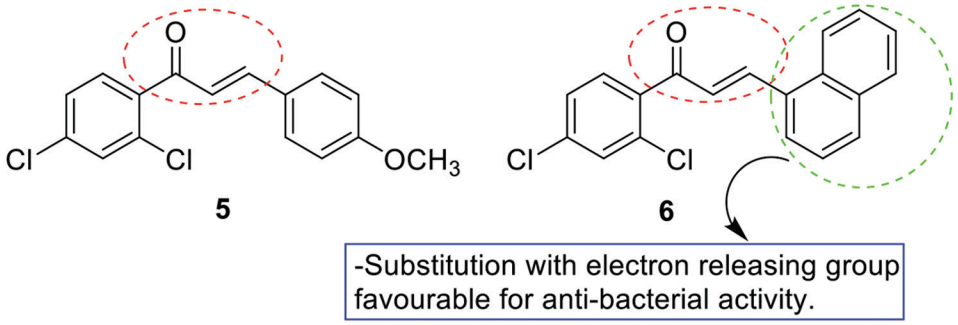

Figure 3: 1-(2',4'-Dichlorophenyl)-3-(substituted aryl)-2-propene-1ones as anti-microbial agents

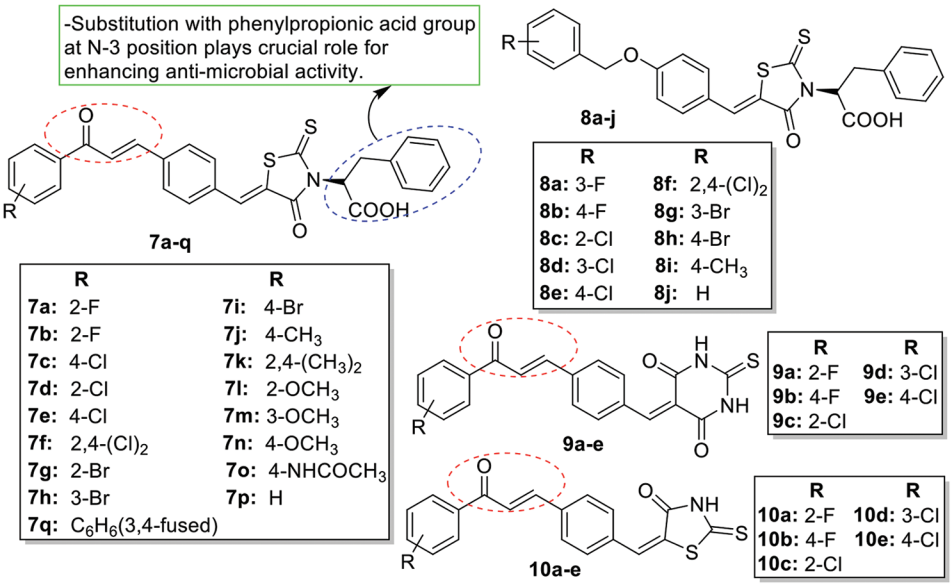

Figure 4: L-phenylalanine-derived C5-substituted rhodanine and substituted chalcones derivatives as anti-microbial agents

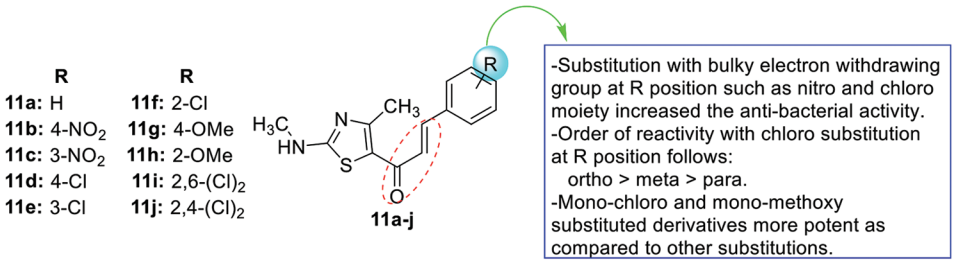

Figure 5: Thiazole substituted chalcones derivatives as anti-microbial agents

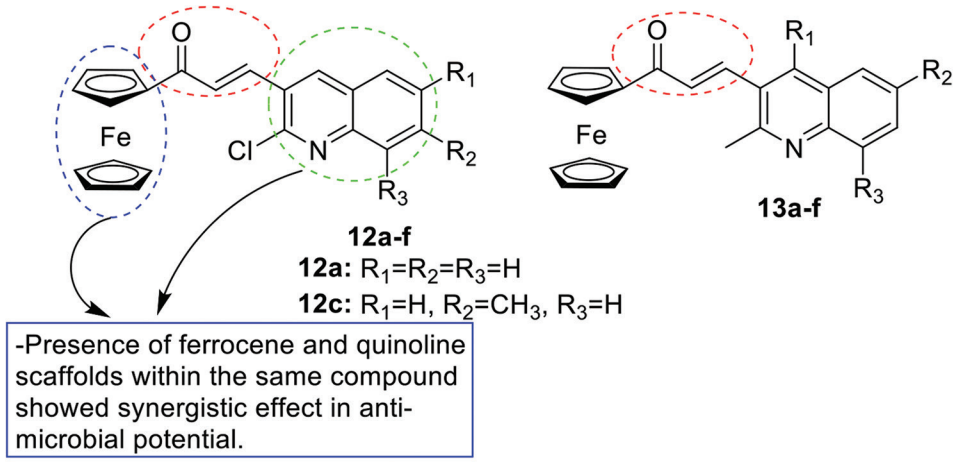

Figure 6: Quinoline clubbed ferrocenyl chalcones congeners as anti-microbial agents

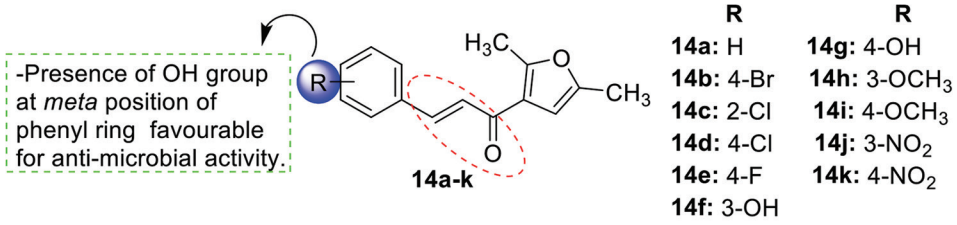

Figure 7: 2,5-Dimethyl-3-furyl chalcones derivatives as anti-microbial agents

evaluated them as antibacterial, antifungal potential using the Kirby-Bauer disk diffusion method as well as insect antifeedant activity. All the compounds were synthesized using MW assisted reaction and characterized by IR, ^{1}H NMR, and ^{13}H NMR. Among the series, compound bearing–OH group at 3-position of phenyl ring was found to be more active against all Gram-positive (*B. subtilis* and *M. luteus*), except *S. aureus*, and Gram-negative bacterial strains (*E. coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*) having IZ values ranging between 6–11 mm and 6–9 mm, respectively. Moreover, most of the compounds showed less inhibition toward fungal strains, whereas few of them were active against *A. niger*, *Micrococcus* spp., and *T. viride* fungal strains with IZ values between 5 and 8 mm.[30]

Siddiqui *et al.* synthesized pyrazolyl-substituted chalcone derivatives [Figure 8, **15a-c** and **16a-c**] and evaluated them for an anti-microbial activity through a modified disk diffusion method against Gram-positive and Gram-negative bacterial and also against fungal strains. All the synthesized chalcones derivatives possessed promising inhibition potential having IZ ranging between 15.4 mm and 27.2 mm against bacterial strains (*S. pyogenes*, *MRSA*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*) and 14.1–25.5 mm toward fungal strains (*C. albicans*, *A. fumigatus*, *Trichophyton mentagrophytes*, *Penicillium marneffei*). Among the series, compound **15b** (MIC = 12.5 mg/mL) was found to promising inhibitory candidate toward all tested bacterial strains than that of standard drugs (ciprofloxacin, griseofulvin, and fluconazole).[31]

Mohamed *et al.* described the design and synthesis of a new series of chalcones bearing pyrazole scaffold [Figure 9, **17a-b**, **18a-b**, and **19a-b**] and screened them for anti-proliferative along with anti-microbial activity. Results of *in vitro* cytotoxicity assay revealed that compound **18a, 18b,** and **19a** exhibited excellent inhibition potential toward MCF-7, HEPG-2, and HCT-116 breast cancer cells, as compared to reference drug doxorubicin having IC_{50} values (4.7, 4.4, and 3.9 µg/ml). All the compounds were evaluated against bacterial strains revealed that compound **19a** and **19b** showed inhibition toward *S. aureus*, *S. faecalis*, *B. subtilis*, *E. coli*, *Pseudomonas aeruginosa*,

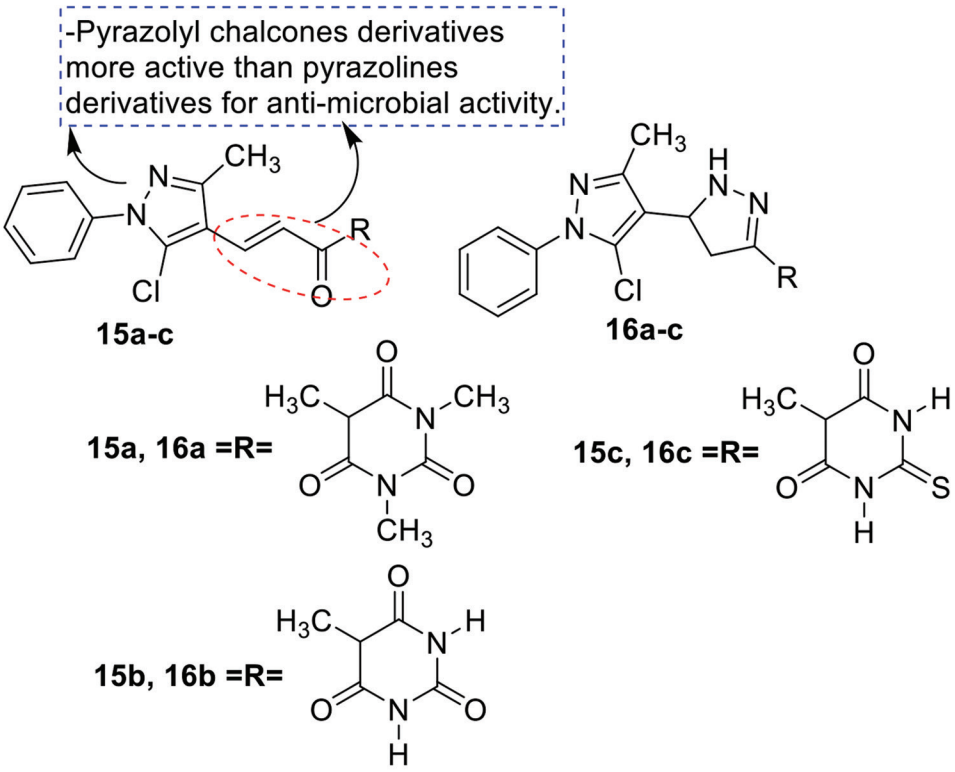

Figure 8: Pyrazolyl chalcones and pyrazolines derivatives as anti-microbial agents

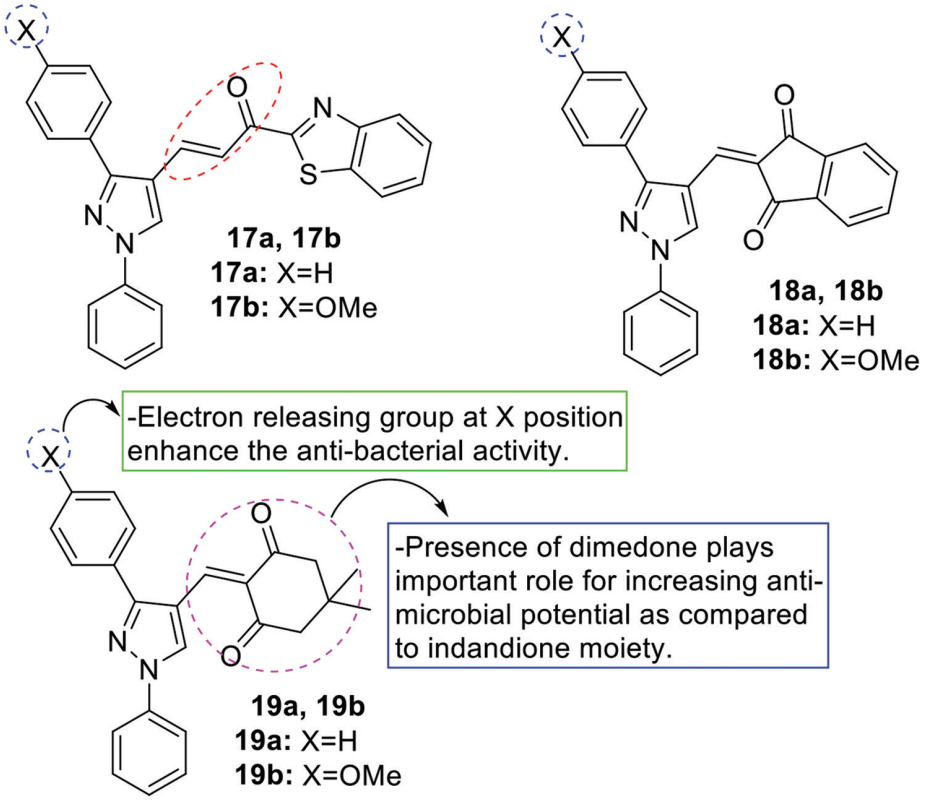

Figure 9: Chalcones bearing pyrazole scaffold as anti-microbial agents

and *Neisseria gonorrhoeae*, whereas compound **18b** showed inhibition against *N. gonorrhoeae*, *S. faecalis*, and *E. coli* at MIC 20 mg/ml.[32]

Sarveswari *et al.* synthesized the 4-Hydroxy-2(1H)-quinolone-based chalcones, pyrazoline derivatives [Figure 10, **20a-j** and **21a-j**] by

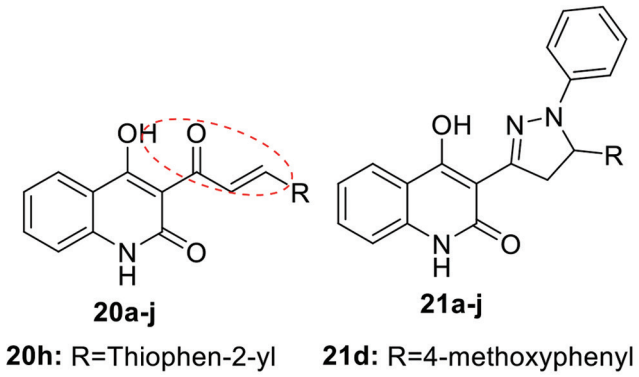

Figure 10: 4-Hydroxy-2(1H)-quinolone-based chalcones, pyrazoline derivatives as anti-microbial agents

MW assisted synthesis and evaluated them as anti-microbial along with anti-malarial agents. Among the series, compound **20h** and **21d** displayed more anti-malarial activity as compared to reference drug, whereas other compounds revealed less anti-malarial and moderate anti-microbial activity.[33]

CONCLUSION

Chalcones are versatile scaffolds for synthetic modification and showed a wide variety of biological activities. Chalcones have better bioavailability and high tolerance in the body so that chalcones are a great interest for development of new potent molecules to treat various diseases worldwide. This review updates recent developments regarding synthetic and biological activities of chalcones and their derivatives. Clinical studies have proven their excellent bioavailability and maximum tolerance in the human body. At present, various drugs are available in the market containing chalcone nucleus and also in clinical trials.

It is believed that the information compiled in this mini-review article with antimicrobial activity of chalcones can present this promising moiety for the design of novel chalcone molecules with enhanced medicinal properties.

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