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*REVIEW*

# Chalcone-based Ferrocenyl-Derivatives as an Antimicrobial Drug

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The lack of development of new antibiotics is the major concern at the present scenario. One key factor contributing to the rise of antibiotic-resistant bacteria is the widespread movement of people throughout the world. The world has seen the consequences of the migration in the case of COVID-19 very recently. To tackle or cope with the situation, development of new antibiotics is very essential, which can be inhibited multidrug-resistant bacteria. In this framework, chalcone-based ferrocenyl containing 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. Thus, there is a 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 relationship studies (SAR). This review will help to the researchers in the medical field to find out the future generation potential drug discovery and development.

**Keywords: Chalcone-based ferrocenyl-derivatives, Drug resistant bacteria, Promising antibiotics.**

## INTRODUCTION

Now a day, it is a major concern about the antibiotic resistant bacteria and human deaths caused by the antibiotic resistant bacteria all around the world. In USA every year, 2.8 million peoples are infected and 99000 people are being died due to antibiotic-resistant bacteria [1], it has increased health concerns and resulted in mortality and morbidity from treatment failures [2,3]. This is due to the researchers are unable to develop new drugs which are suitable for pathogen treatment.

Persistent failure to develop or discover new antibiotics and non-judicious use of antibiotics are the predisposing factors associated with the emergence of antibiotic resistance [4]. It is expected that vaccine could give protection from bacterial infection, but a vaccine may not cover all strains within a species, it has been thought that it can reduce the resistance burden by inducing protective immunity against the most prevailing resistant strains within the community. Antibiotic resistance bacteria are frequently spread in society by particular successful clonally related strains [5]. So, it is a continuous process to search new appropriate or potent drugs for antibiotic resistant bacteria. Many strains of Gram-positive organism are antibiotic resistant against clinically useful antibiotic groups like penicillin, glycopeptide, carbapenem, cephalosporin and floroquinolone [6,7].

Derivatives of ferrocene have now drawn much more attention in the pharmaceutical industries and researchers. Ferrocene itself is a neutral, chemically stable and non-toxic molecule [8,9] and its derivatives display interesting cytotoxic [10-13], antitumor [14-16], antimalarial [17-19], antifungal [19,20], antioxidant [21], anti-HIV [22] and antibacterial activity [22-24]. Ferrocene contain $Fe^{2+}$ ion is an essential metal in the human body which is less toxic than other non-essential metal like platinum, rhodium and other traditional transition metals. Moreover, its derivatives have small size, lipophilicity, easy of chemical modification and accessible one electron-oxidation potential [25-27]. The main fragment of the compounds discussed here is chalcone moiety or chalcone like structure. Since chalcones (1,3-diaryl-2-propen-1-ones) is a very important class of compound due to its structure and electronic environ-

ment. It can be found in natural products and pharmaceutical products as well [28,29]. Hence, chalcone-based ferrocenyl derivatives can be the promising drugs for various diseases, *e.g.* cancer, malaria, tuberculosis, HIV, dengue, chikungunya fever and many others infectious diseases. Some of the chalcone based ferrocenyl derivatives are more potent than conventional drugs available in the market. Only the recently synthesized and increasingly important chalcone-based ferrocenyl derivatives and their structure-activity relationship (SAR) studies are discussed in this review. This will be helpful for future development antibacterial agents.

## Antibacterial properties of some chalcone-based ferrocenyl derivatives

**Antibacterial activity of chalcones-based ferrocenyl and O-alkylated vanillin compounds:** Muskinja *et al.* [30] synthesized six novel ferrocenyl chalcones (**1-6**) with O-alkylated vanillins analogues (Fig. 1) 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). All the compounds were shown antibacterial activity against both the Gram-positive (*S. aureus*, *B. subtilis* and *B. cereus*) and Gram-negative bacteria (*E. coli* and *P. mirabilis*). The MIC values of all the novel compounds against all the tested bacteria were found in the ranged from 0.312 to 5.00 mg/mL. Again, all six compounds were found to more potent against Gram-positive bacteria than Gram-negative bacteria, this can be easily understood by means of average MIC values for Gram-positive bacteria is approximately 1.892 mg/mL whereas in case of Gram-negative bacteria it was 1.979 mg/mL. Compound **3** showed promising anti-bacterial activity against *B. subtilis* and *B. cereus* with the MIC values 0.312 mg/mL each. Again, compounds **2** and **4** also showed promising antibacterial activity against *E. coli* and *P. mirabilis* with the MIC values of 1.25 mg/mL each. In comparison compound **6** was less potent among all the tested compounds (**1-6**) and all the six compounds are less potent than clinically available antibiotic streptomycin [31].

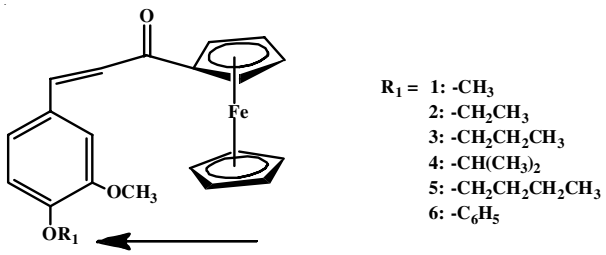
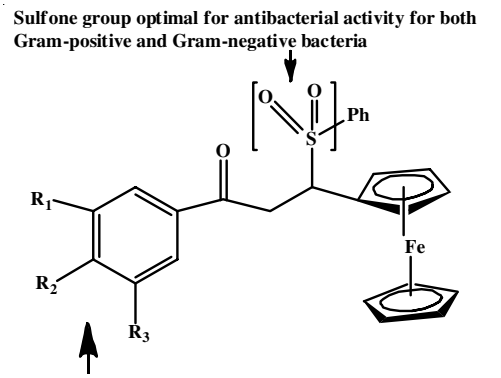



Fig. 1. Compounds **1-6**

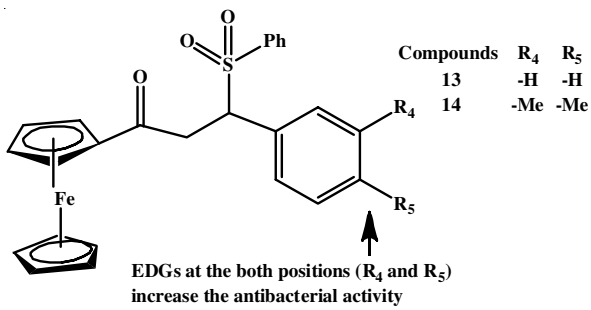
The SAR indicated that the alkoxy group (-$OR_1$) can acts both electron withdrawing group (EWG) due to inductive effect of the oxygen atom as well as electron donating group (EDG) through resonance. Both effect can be observed at the *para* position of benzene ring, but EDG effect predominate over EWG effect, that's why compounds **1-4** exhibited more potency against the antibacterial effect. Whereas compounds **5** and **6** were less active due to large size of *n*-butyl and benzene groups lost their planarity with the other part of the molecule.

**Chalcone-based ferrocenyl and sulfone compounds:** A library of 21 chalcone-based sulfones and bisulfones novel compounds were synthesized by Ahmed *et al.* [32] and only eight compounds **7-14** (Figs. 2 & 3) were screened for *in vitro* antibacterial activity. These eight novel chalcone-based ferrocenyl-sulfones compounds have shown exceptional antibacterial activity (MIC values ranged within 1.95 to 250 µg/mL) even maximum compounds are much more or equal potent with the clinically available drug ampicillin (MIC: 125-500 µg/mL) [33]. Especially compounds **10** and **14** were found as capable to inhibit both the Gram-positive bacteria (*B. subtilis*, *S. aureus* and *L. monocytogenes*) and the Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *K. pneumonia*, and *P. vulgaris*) at very low MIC.




| Compound No. | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 7 | -H | -Cl | -H |
| 8 | -H | -Me | -H |
| 9 | -H | -OMe | -H |
| 10 | -OMe | -OMe | -OMe |
| 11 | -Me | -Me | -H |
| 12 | -H | -H | -H |

Fig. 2. (Type-A) compounds **7-12**




| Compounds | $R_4$ | $R_5$ |
|---|---|---|
| 13 | -H | -H |
| 14 | -Me | -Me |

Fig. 3. (Type-B) compounds **13** and **14**

The eight novel compounds (**7-14**) were capable to inhibit tested Gram-positive bacteria with MIC values ranged within 3.90 to 250 µg/mL and found to be equally potent than antibiotic ampicillin (MIC: 250-500 µg/mL). Whereas compound **10** (MIC: 3.90 µg/mL) was more potent, while compound **14** (MIC: 7.81 µg/mL) was equally potent with the antibiotic kanamycin (MIC: 7.81 µg/mL) against *B. subtilis* Gram-positive bacteria. All eight novel drugs (MIC: 3.90-250 µg/mL) were more potent than both clinically drugs ampicillin (MIC: 500

μg/mL) and kanamycin (MIC: 500 μg/mL) against *S. aureus*. In case of another Gram-positive bacteria *L. monocytogenes* was inhibited by seven novel drugs more potentially than ampicillin (MIC:250 μg/mL), but in comparison with kanamycin (MIC: 500 μg/mL) only compound **10** (MIC: 15 μg/mL) was more potent and compounds **(7)** (MIC: 250 μg/mL) and compound **13** (MIC: 250 μg/mL) were equally potent.

All the eight novel compounds were capable to inhibit all the tested Gram-negative bacteria as well, the MIC values ranged from 250 to 1.95 μg/mL. In case of Type-B, two compounds **13** and **14** (MIC: 1.95-80.0 μg/mL) are exceptionally more potent than other tested compounds against Gram-negative bacteria in the same assay, even they are more potent than market available antibiotics ampicillin (MIC: 125-200 μg/mL) and kanamycin (MIC: 50-250 μg/mL). Compound **10** was found to be more potent against *K. pneumonia* (MIC: 1.95 μg/mL), *E. coli* (MIC: 10.0 μg/mL) and *P. vulgaris* (MIC: 25.0 μg/mL).

The SAR revealed that some compounds of Type A were found more active towards antibacterial activity due to more EDG as present in the benzene ring. Three electron donating groups –OMe are attached in compound **10** at the *ortho*, *meta* and *para* position of the benzene ring. It is expected that only two -OMe groups can be acted as EDG due to its position *ortho*- and *para*- through resonance, but *meta* position -OMe group can act as an EWG. Due to electronic environment and structure of sulfone group is responsible for optimal antibacterial activityshown by these compounds in presence of EWG or EDG.

**Chalcone-based ferrocenyl derivative: (*E*)-3-(2-methylpyrimidin-5-yl)-1-ferroceynlprop-2-en-1-one:** A novel chalcone based ferrocenenyl containing derivative (*E*)-3-(2-methylpyrimidin-5-yl)-1-ferroceynlprop-2-en-1-one (**14**) (Fig. 4) was synthesized using Claisen-Schmidt condensation reaction [34]. Compound **14** showed antibacterial activity against Gram-negative bacteria *Pseudomonas aeruginosa* and Gram-positive bacteria *Staphylococcus aureus*. The SAR studies suggested that the location of ferrocenyl and polarity of α-β-unsaturated carbonyl linkage influenced the ease of oxidation of $Fe^{2+}$ in ferrocenyl and thus enhanced the antibacterial activity. More over two hetero atoms (N) containing loan pair present in the heterocyclic moiety are likely to play the key role in the compound towards antibacterial activity.

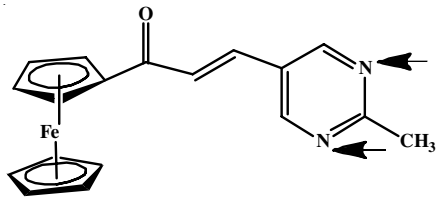
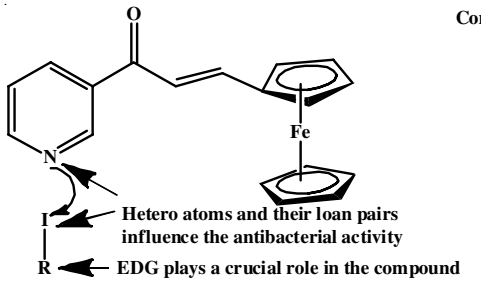



Fig. 4. Compound **14**

**Ferrocenyl chalcone derivatives with pyridine and alkyl iodide:** Novel 10 ferrocenyl chalcogen compounds **15-24** (Fig. 5) were synthesized by Crouch [35] and later on the *in vitro* antibacterial activity of these ten compounds were also evaluated [36]. Two-fold broth microdilution method as described by Andrews [37] was followed to evaluate the antibacterial activity and estimated the MIC values in 12% DMSO medium. Four




| Compound | R = |
|---|---|
| 15 | $-CH_3$ |
| 16 | $-C_2H_5$ |
| 17 | $-C_3H_7$ |
| 18 | $-C_4H_9$ |
| 19 | $-C_5H_{11}$ |
| 20 | $-C_6H_{13}$ |
| 21 | $-C_7H_5$ |
| 22 | $-C_8H_{17}$ |
| 23 | $-C_9H_{19}$ |
| 24 | $-C_{10}H_{21}$ |

Fig. 5. Compounds **15-24**

types of Gram-positive isolate (*S. aureus* NCIMB 8244, *K. kristinae*, *E. faecalis* and *S. aureus*), four types of Gram-negative isolates (*E. coli*, *K. pneumonia*e, *Salmonella* and *E. coli*) and three types of non-resistant isolates (PEN-resistant *S. aureus* (RCH), PEN-ERY- CLI-resistant *S. aureus* (RCH) and MRSA (RCH))were used as tested microorganism against the novel compounds **15-24**.

The MIC values of compounds **15-24** were found within the ranged from 0.008 to 0.125 mg/mL against all the tested pathogens. In comparison, compounds **15-19** (MIC value 0.125 mg/mL each) were less potent than compounds **20-24** (MIC values ranged from 0.008 to 0.063 mg/mL) against tested Gram-positive bacteria except for compound **20** (MIC value 0.125 mg/mL) against clinically isolate *S. aureus* fully sensitive. Sensitivity was also seen for hexyl (**20**) to decyl (**24**) against PEN-resistant *S. aureus* (RCH), PEN- ERY-CLI-resistant *S. aureus* clinical isolates (RCH) and MRSA (RCH) (MIC values ranged from 0.031 to 0.063 mg $mL^{-1}$). In the same assay, the MIC values of penicillin-G and oxytetracycline (antibiotics) were 0.125 mg/mL each. This suggested that compounds with higher alkyl chain *i.e.* compounds **20-24** were found more potent than penicillin-G and oxytetracycline, while the remaining compounds **15-19** were found to be equally potent.

In case of Gram-negative tested bacteria MIC values of the 10 compounds were 0.0125 mg/mL which mean they are equally potent to penicillin-G and oxytetracycline. However, these ten novel ferrocenyl chalcone compounds **15-24** were more found to be effective against Gram-positive bacteria than Gram-negative bacteria.

The SAR indicated that these compounds are very active against the organism due to the additional driving force come from hetero atoms and EDG *i.e.* alkyl group. The two hetero atoms nitrogen and iodine present in one part of the compound in juxtaposition. The loan pair or pairs present in the nitrogen and iodine can be used in resonance to raise the valence electron of the chalcone molecule. The another and most important contribution came from alkyl groups joined with the iodine atom. The electron donating properties of alkyl group increases from methyl to decyl. Large EDG *i.e.* alkyl group contained compounds were showed more antibacterial effect.

**Chalcone origin pyrazoline derivatives with ferrocene framework and vanillin fragment:** Novel 24 chalcone origin pyrazoline derivatives with ferrocene framework and vanillic fragment containing compounds (Figs. 6-9) were synthesized and characterized by Burmudzija *et al*. [38]. Total 24 novel the pyrazoline derivatives (**25-48**) showed the antibacterial effect

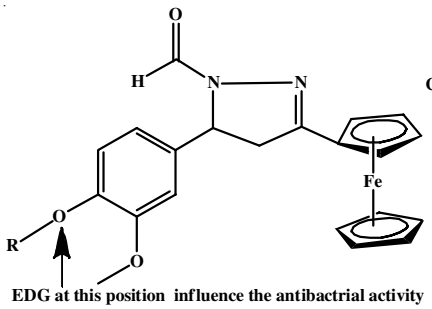



Fig. 6. (Type-A) compounds **25-30**

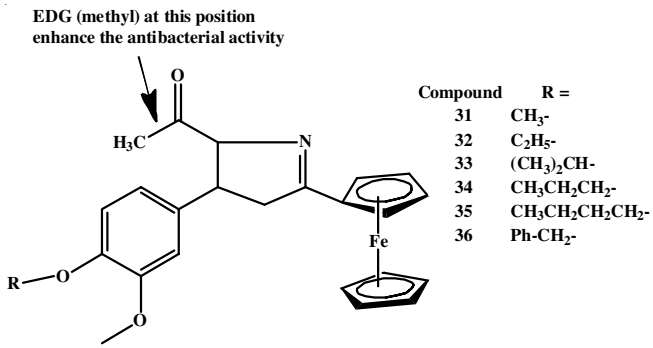



Fig. 7. (Type- B) compounds **31-36**

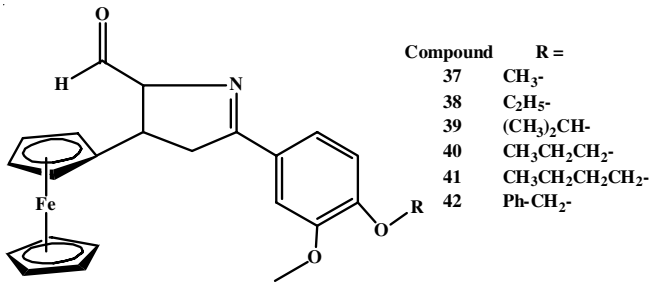



Fig. 8. (Type-C) compounds **37-42**

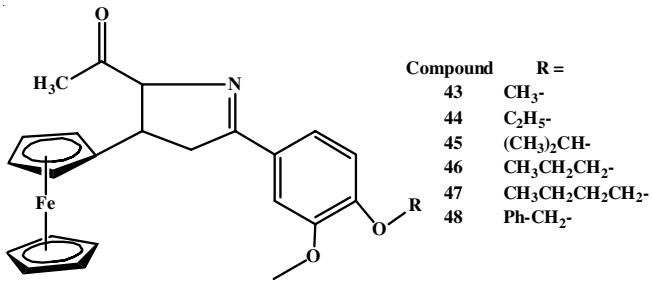



Fig. 9. (Type-D) compounds **43-48**

against five bacteria namely *S. aureus*, *B. subtilis*, *B. cereus*, *E. coli* and *P. mirabilis*. All the 24 novel compounds were capable to inhibit both Gram-positive and Gram-negative bacteria with the MIC values were ranged from 0.156 mg/mL to 15.00 mg/mL, however, compounds **31**, **35** and **36** were found to be the most potent than others tested compounds. In the same assay, the MIC values of streptomycin were ranged from 0.016 to 0.062 mg/mL against all the five tested bacteria. This result showed that the probable antibiotic compounds **24-48** are not much potent in comparison with the antibiotic streptomycin.

The SAR suggested that both the EDG and EWG groups are present in the synthesized chalcone-based ferrocenyl compound, which influences the antibacterial effect. The EDG at the R-position decreased the antibacterial activityof the types B compounds. Among the subsitute groups, methyl, *n*-butyl and benzyl groups are less EDG groups. Methyl is one carbon group so least +R effect, long chain group *n*-butyl and large size benzyl group are lost its planarity with the vanillin moiety, hence they are less EDG. Another important issue is keto group was more active towards the antibacterial activity than formaldehyde group connected to the pyrazoline moiety. Type-C and Type-D compounds were less active than Type-A and Type-B compounds towards antibacterial activity due to different structure and electronic environment.

**Chalcone-based ferrocenyl derivatives with S-benzyl dithiocarbazate:** Another 12 novel types of S-benzyl dithiocarbazates containing chalcone and ferrocenyl moieties (**49-60**) were synthesized by the condensation of various chalcones with S-benzyl dithiocarbazate in absolute ethanol using a catalytic amount of glacial acetic acid (Figs. 10 and 11) [39]. *In vitro* antimicrobial activity also evaluated of the newly synthesized compounds by using MTT assay colourimetry method against *S. aureus* ATCC 9144, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 43288.

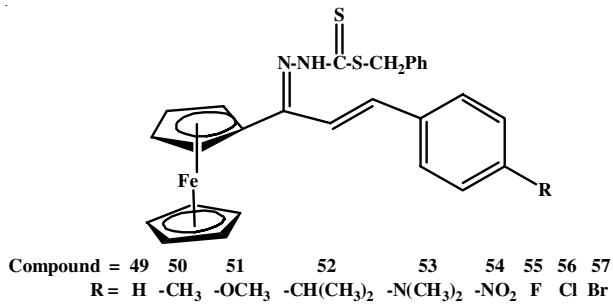



Fig. 10. (Type-A) compounds **49-57**

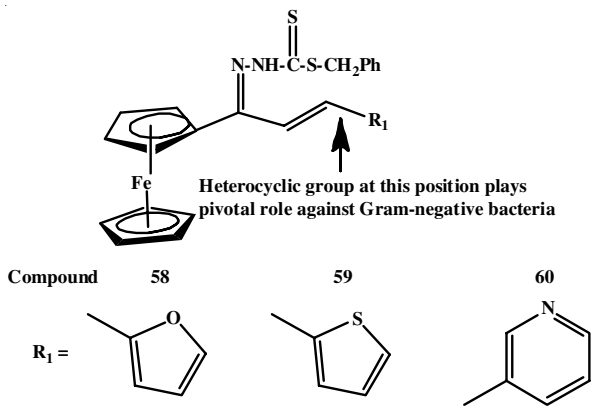



Fig. 11. (Type-B) compounds **58-60**

Compounds **55-60** were found to be capable to inhibit all the tested Gram-negative microorganisms (MIC: 1.6-40.5 µg/mL) and also, they were found to be more potent than antibiotic penicillin (MIC: > 50 µg/mL). Both compounds **51** and **53** were found to inhibit *S. aureus* (MIC Values; 19.5 µg/mL and 25 µg/mL, respectively) and *P. aeruginosa* (MIC values: 12.5 µg/mL and 3.1 µg/mL, respectively).

The SAR revealed that compounds **49** and **50-54** had a slight difference in the structure, but their antibacterial activity was very different. Compound **53** showed the highest activity against *P. aeruginosa* (3.1 l µg/mL). These might be due to the presence of an electron donating substituent dimethyl amino groups. Compounds **54** showed mild activity against Gram-positive bacterial strains while exhibited no activity against Gram-negative bacterial strains. These might be due to the presence of electron withdrawing substituent nitro groups. While other compounds, though they contain electron donating group like methyl, isopropyl, methoxy group do not exhibit significant *in vitro* antibacterial activity. Due to the high electronegativity and high electron dense atoms in compounds **55** and **56**, which are of comparable size to the carbon atom contribute significantly to their antibacterial activity against Gram-negative bacteria. It is also noticeable that all tested compounds showed all most inactive against *B. cereus* except compound **54**, whose MIC value was 12.5 mg/mL.

## Conclusion

Ferrocenyl-chalcone based compound and its derivatives have the potential to inhibit the bacterial growth even some of them are much more potential than the commercial available antibiotic drugs. The present review focuses on the recent development in the area of medicinal chemistry to explore the diverse chemical compound of potential antibacterial agent and discussed their structure activity relationships studies. About 60 novel compounds of chalcone based ferrocenyl moiety with vanillin, sulfone, pyrimidine, alkyl iodide, pyrazole and S-benzyl dithiocarbazate moiety containing different substitution groups like alkyl, methoxy, phenyl, benzyl, dimethyl ammine, nitro, fluro, chloro, bromo, *etc*. are discussed. Several classes of compounds have been found effective against various Gram positive and Gram-negative bacterial pathogens, not only that they have been found capable to inhibit antibiotic resistant pathogens. Similarly, the structure-activity relationships (SAR) investigation on the influence of the substitution pattern, involving electron-donating (alkyl, $-OCH_3$, $-N(CH_3)_2$), electron-withdrawing ($Cl^-$, $Br^-$, $F^-$ and $-NO_2$) groups as well as other heterocyclic substituents of ferrocenyl-chalcones on their antibacterial activity against human pathogenic microorganisms. Moreover, compounds containing sulfone and S-benzyl dithiocarbazate groups with electron donating or electron withdrawing groups have shown optimal activity against both Gram-positive and Gram-negative bacteria.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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