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Synthesis, Structure-Activity Relationship and Antibacterial Activity of Some Simple (*E*)-Chalcones

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In present work, 14 simple (*E*)-chalcones (**1**-**14**), synthesized *via* the Claisen-Schmidt condensation between arylmethyl ketone and aromatic aldehyde in the presence of either in NaOH or H_3BO_3, were tested for *in vitro* antibacterial activity against two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and three Gram-negative (*Escherichia coli*, *Enterobacter cloacae* and *Klebsiella pneumoniae*) bacterial strains. Among them, (*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one (**8**) was found most efficient, while (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one (**4**) and (*E*)-1-(2,4-dihydroxyphenyl)-3-(4-(dimethylamino)-phenyl)prop-2-en-1-one (**14**) were completely ineffective. The rest of the (*E*)-chalcones have displayed moderate to good antibacterial activity, particularly against Gram-positive bacteria, while *E. coli* was found resistant. From the structure-activity relationship (SAR) analysis, it is revealed that the presence of a strong electron-withdrawing group (NO_2) in ring A and the presence of electron-donating group in ring B of (*E*)-chalcones could enhance the antibacterial activity. The presence of hydroxyl and/or alkoxyl substituents in both 3 and 4 positions of ring B proved beneficial.

Keywords: (*E*)-Chalcones, Antimicrobial, Claisen-Schmidt condensation, Flavonoid, Organic synthesis.

INTRODUCTION

Chalcones possess a common 1,3-diaryl-2-propene-1-one skeletal system with diverse bioactivities (Fig. 1) [1,2]. Medicinal properties of chalcones have been reviewed by several authors [3-14]. In 2009, Batovska *et al*. [15] reported that (*E*)-chalcones with unsubstituted, 4′-chloro substituted or 3′,4′,5′-trimethoxy substituted in ring-A possess antibacterial activity against Gram-positive *S. aureus*. They have mentioned that the presence of hydroxyl group in ring-B is not enough for the anti-staphylococcal activity, but the lipophilicity in ring-A of the hydroxyl chalcones is more important. Furthermore, none of the chalcones tested could inhibit Gram-negative *E. coli*. Sugamoto *et al*. [16] found that (*E*)-chalcones bearing prenyl- or geranyl groups in ring-A inhibit Gram-positive *B. subtilis*, *Staphylococcus epidermidis* and *Micrococcus luteus* with a peak minimum inhibitory concentration (MIC). Prasad *et al*. [17] and Basic *et al*. [18] have shown antibacterial activity of (*E*)-2′-hydroxy chalcones. The former group utilized *Bacillus pumilis*, *B. subtilis*, *E. coli* and *Proteus vulgaris* as bacterial strains, which were considerably inhibited at 10 µg/well dose level. The latter group has reported that the (*E*)-2′-hydroxychalcones bearing hydroxyl group in ring-B exhibits good antibacterial activity against eight bacterial strains, namely *S. aureus*, *S. epidermidis*, *Enterococcus faecalis*, *Micrococcus flavus*, *M. luteus*, *B. subtilis*, *K. pneumoniae* and *Pseudomonas aeruginosa* with MIC values ranging from 0.052 to 2.10 mM and also performed the computational analysis for the SAR. Feng *et al.* [19] reported that (*E*)-2′,4′-dihydroxychalcones inhibit *E. faecalis* and *S. aureus*. Bicylic myrtenal moiety, 2-allyloxy and 2-alkyoxy substituents in ring-B favour antibacterial activity with a peak MIC value of 1.56 µg/mL.

Different groups have modified ring-A of chalcones with 2,5-dichlorothiophene [20], 4-piperazylphenyl [20], 2,5-dimethyl-3-furyl [21,22], 4′-hydroxyphenyl [23], 2′-hydoxynaphthalenyl [23], thiazole [24], pyrazine [25], triazolyl [26], *etc.* and reported their antibacterial activity. Ring-B of chalcone is also diversified. Antibacterial activity of chalcones bearing 2-chloro-6-methyl quinolinyl [27], indole [28], *etc.* in ring-B is also reported.

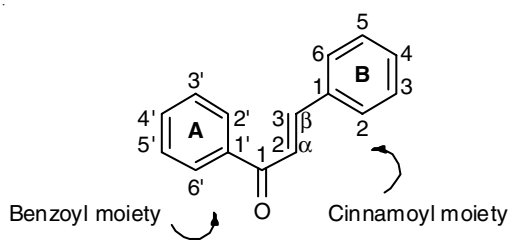


Fig. 1. Chalcone skeleton showing numbering system

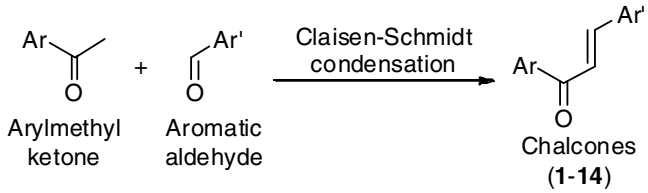
Several chalcone hybrid molecules have been synthesized and reported their antibacterial activity. Chalcone-oxazolidinone hybrid molecules showed activity against methicillin-resistant *S. aureus* (MRSA) and *E. faecalis* [29]. Chalcone-rhodanine-3-acetic acid compounds presented high potency against *S. aureus* [30]. Some (*E*)-chalcones with 4-alkylthio- or 4-alkoxy side chains in ring-B; that tethered with bromo-, piperidino-, morphlino- or piperazino group; are found effective against Gram-positive *S. aureus*, *E. faecalis* and *B. subtilis* [31]. Chalcone-thiazolidinedione-benzoic acid derivatives are found effective against Gram-positive bacteria (MICs = 0.5-4 µg/mL) [32]. Chalcone-thiazole hybrid molecules displayed potential activity against *S. aureus* [33]. Pyrazolyl-pyrazolines hybrid molecule exhibited anti-MRSA activity [34]. A few aryloxy-azolyl chalcones inhibited *Mycobacterium tuberculosis* H37Rv (MICs = 0.78-3.12 µg/mL) [35]. Although these complex chalcones are found efficient antibacterials; however, synthesis of these compounds is a tedious and time-consuming task.

Literature study shows that the 2′-OH group in ring-A of chalcones is not necessary for antibacterial activity, but 2-OH or 4-OH group at ring-B may show antibacterial activity [13,18, 19,23,29,36-38]. Furthermore, methoxylation of the hydroxyl group may eliminate the activity. On the other hand, the presence of halo group(s) as electron-withdrawing group(s) favours the activity. Replacement of carbocyclic aromatic rings (rings A and B) with heterocylic ring(s) or tethered heterocyclic ring(s) may enhance antibacterial activity. Eventually, it can be concluded that the antibacterial activity of chalcones is often the case sensitive. Therefore, the antibacterial activity of chalcones is still not well understood and warrants further studies. Previously, several structurally diverse and complex antibacterial chalcones have been synthesized, but the identification of simple and efficient antibacterial chalcone is the most desirable. In continuation of our work searching for flavonoids as potential drug candidates [36-38]; herein, we report the antibacterial activity of some simple (*E*)-chalcones and their SAR study.

EXPERIMENTAL

Analytical grade chemicals were purchased from Fischer, Qualigens, Aldrich, Merck and Loba companies. Antibiotic gentamicin (25 µg/disc) was purchased from Himedia, India. For thin layer chromatography (TLC), pre-coated TLC Silica gel 60 F_{254} (Merck) was used. Silica gel (100-200 Mesh, Fisher Scientific) was used for column chromatography. Melting point (m.p.) was determined by the open capillary method and are uncorrected. Recording of UV spectra was carried out by using Jenway 6715 and Agilent Cary 60 UV-Visible spectrophotometer. The IR spectra were recorded in KBr using a Tracer 100 FTIR (Shimadzu).

Synthesis of chalcones: Corresponding chalcones (**1**-**14**) were synthesized *via* the Claisen-Schmidt condensation between arylmethyl ketone (acetophenone, *m*-nitroacetophenone and *o*-hydroxyacetophenone) and aromatic aldehyde (anisaldehyde, vanillin, benzaldehyde, 4-(dimethylamino)benzaldehyde, 4-(benzyloxy)-3-methoxybenzaldehyde and furfuraldehyde) following reported protocols [37,39-41]. Few chalcones (**1**-**3**, **5**-**11** and **13**) were synthesized according to the reported method [37], while amino chalcones (**4**, **12** and **14**) were synthesized newly for the present study (**Scheme-I**).



Scheme-I: Synthetic route of (*E*)-chalcones (**1-14**) *via* Claisen-Schmidt condensation

Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one (4): 4-(Dimethylamino)benzaldehyde (0.149 g, 1 mmol), acetophenone (0.120 g, 1 mmol), methanol (3 mL) and NaOH pellet (~ 100 mg) were stirred at room temperature for 24 h. A yellow solid obtained was filtered and washed with cold methanol. Repeated recrystallization using EtOAc/hexane (3:7) afforded a yellow crystals of (*E*)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1one (**4**) (0.171 g, 0.68 mmol, 68%). m.p.: 57 ºC. R_f = 0.3 (silica gel, hexane/ethyl acetate, 1.7:0.3). UV (MeOH) λ nm: 265 (π→π*, cinnamoyl moiety) and 420 (n→π*, benzoyl moiety). IR (KBr, ν_{max}, cm^{-1}): 1647 (C=O), 1562 (C=C) and 1230 (C–O) [39].

Synthesis of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (12): 4-(Dimethylamino)-benzaldehyde (0.746 g, 5 mmol) was added slowly to a stirring solution of 2-hydroxyacetophenone (0.681 g, 5 mmol) and ethanol (25 mL) at room temperature followed by the addition of 40% NaOH (20 mL). After 72 h, the reaction mixture was diluted with cold water, neutralized with 10% HCl and left for overnight. The precipitate obtained was filtered and washed with the water-ethanol mix. The product was purified by recrystallization with ethanol affording bright red crystals of (*E*)-3-(4-(dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**12**) (0.695 g, 2.6 mmol, 52%). m.p.: 175 ºC. R_f = 0.35 (silica gel, hexane/ethyl acetate, 1.7:0.3). UV (MeOH) λ nm: 274 (π→π*, cinnamoyl moiety) and 435 (n→π*, benzoyl moiety). IR (KBr, ν_{max}, cm^{-1}): 3373 (OH), 2970 (C–H), 1612 (C=O), 1525 (C=C) and 1210 (C–C) [40].

Synthesis of (*E*)-1-(2,4-dihydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (14): Boric acid (0.699 g, 11.3 mmol) was added to a stirring solution of 4-(dimethylamino)-benzaldehyde (0.895 g, 6 mmol), 2,4-dihydroxyacetophenone (0.913 g, 6 mmol) and ethylene glycol (3 mL) at room temperature. After refluxing at 120 ºC for 12 h, the content was cooled, concentrated, extracted with diethyl ether (30 mL × 3), washed

with brine, dried over Na_2SO_4, filtered and finally concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc mixture) afforded (*E*)-1-(2,4-dihydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (**14**) (0.737 g, 2.6 mmol, 43%). m.p.: 180 ºC. R_f = 0.41 (silica gel, chloroform/methanol, 1.9:0.1). UV (MeOH) λ nm: 263 (π→π*, cinnamoyl moiety) and 425 (n→π*, benzoyl moiety). IR (KBr, ν_{max}, cm^{-1}): 3346 (OH), 2970 (C–H), 1670 (C=O), 1583 (C=C) and 1232 (C–O) [41].

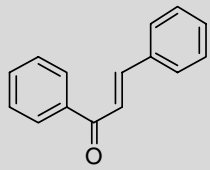
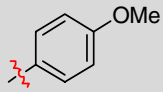
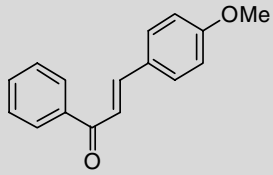
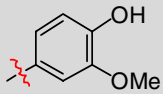
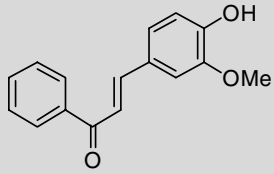
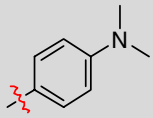
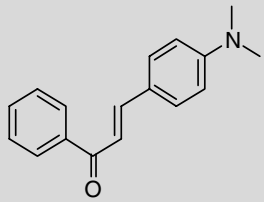
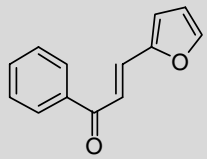
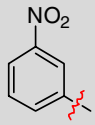
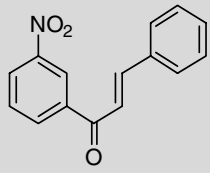
Antibacterial assay: The antibacterial activity of (*E*)-chalcones was performed against two Gram-positive *S. aureus* (ATCC 25952) and *B. subtilis* and three Gram-negative *E. coli* (ATCC 25922), *K. pheumoniae* (ATCC 13883) and *E. cloacae* (ATTCC 27853) bacterial strains using the agar well diffusion assay [42,43]. Briefly, 50 µL of each chalcone solution in DMSO (10 mg/mL concentration) was loaded in the well (6 mm), bored in an agar plate that streaked with the bacteria, in triplicate. DMSO (50 µL) and gentamicin (25 µg/disc) were used as negative and positive controls, respectively. After incubation at 37 ºC for 24 h, the zone of inhibition (ZOI) was measured.

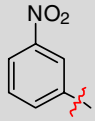
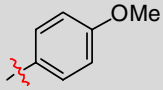
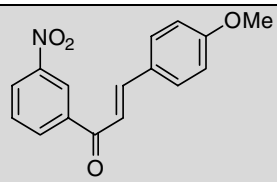
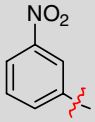
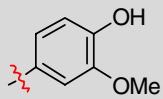
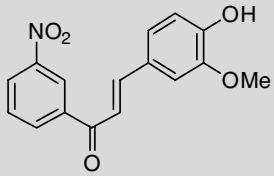
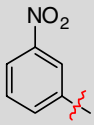
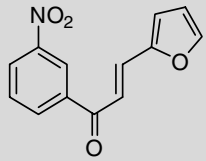
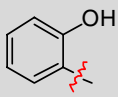
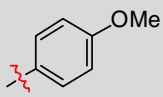
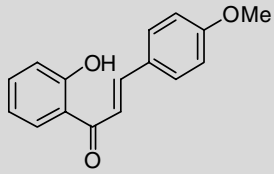
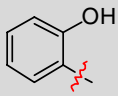
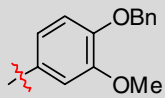
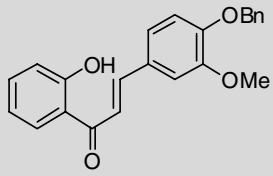
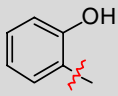
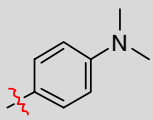
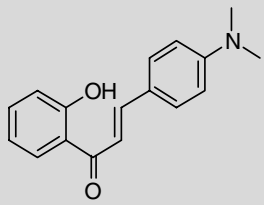
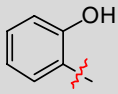
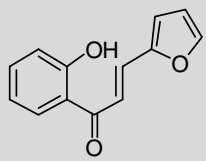
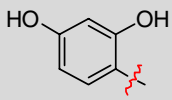
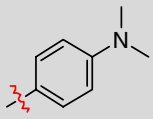
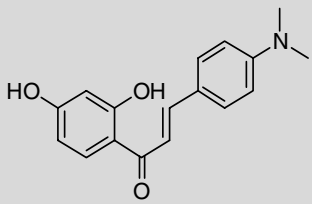
RESULTS AND DISCUSSION

Claisen-Schmidt condensation between arylmethyl ketone and aromatic aldehyde afforded the corresponding chalcones (**1**-**14**) (Table-1), which were screened for the antibacterial activity against five bacterial strains. Compared to the inhibition of Gram-negative bacteria, Gram-positive bacteria *viz*. *S. aureus* and *B. subtilis* were more efficiently inhibited with ZOI ranges of 8-12.6 mm (Table-2). In accordance with Batovska *et al.* [15], compounds **2** and **4** together with compounds **10** and **14** bearing either a methoxy or dimethylamino group at the *para* position of aromatic ring-B, had displayed anti-staphylococcal activity. Detrimental effect of replacement of hydroxyl group with methoxy or amino group in inhibiting *B. subtilis* was also realized with methoxylated chalcones **2** (ZOI = 8 ± 0.81 mm) and **7** and amino chalcones **4** and **14**.

Chalcone **8** was found most effective against all the five bacteria tested. The antibacterial activity of compound **8** was enhanced perhaps due to the presence of an electron with-

TABLE-1
STRUCTURES OF SIMPLE (*E*)-CHALCONES THAT SYNTHESIZED AND USED FOR THE ANTIBACTERIAL ASSAY

(*E*)-Chalcone	IUPAC	Ar	Ar′	Product
1	(*E*)-1,3-Diphenylprop-2-en-1-one			
2	(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one			
3	(*E*)-3-(4-Hydroxy-3-methoxy-phenyl)-1-phenylprop-2-en-1-one			
4	(*E*)-3-(4-(Dimethylamino)-phenyl)-1-phenylprop-2-en-1-one			
5	(*E*)-3-(Furan-2-yl)-1-phenylprop-2-en-1-one			
6	(*E*)-1-(3-Nitrophenyl)-3-phenylprop-2-en-1-one			

7	(*E*)-3-(4-Methoxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one			
8	(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-1-(3-nitrophenyl)prop-2-en-1-one			
9	(*E*)-3-(Furan-2-yl)-1-(3-nitrophenyl)prop-2-en-1-one			
10	(*E*)-1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one			
11	(*E*)-3-(4-(Benzyloxy)-3-methoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one			
12	(*E*)-3-(4-(Dimethylamino)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one			
13	(*E*)-3-(Furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one			
14	(*E*)-1-(2,4-Dihydroxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one			

drawing NO_2 group in ring-A and an electron-donating *para*-hydroxyl group in ring-B that accompanied with a methoxy group at adjacent position (*i.e.* at 3-position) as well. Chalcone **3** was also found to be effective against all the bacteria except *E. coli*. These results also indicated an additional beneficial effect of electron withdrawing group (NO_2) in ring-A (compare ZOI displayed by compounds **3** *versus* **8** against *E. coli*). When the antibacterial activity of chalcones **1**-**4**, **6**-**8** and **10**-**12** were compared, two electron-donating groups in ring-B remarkably enhanced the antibacterial activity. When the antibacterial activity of chalcones **1** *versus* **6**, **2** *versus* **7** and **3** *versus* **8** were compared, the presence of an electron withdrawing group (NO_2) in ring-A was found to be beneficial.

Simple (*E*)-chalcones understudy was ineffective towards Gram-negative *E. coli*. A similar observation has also been reported by Batovska *et al.* [15]. Inhibition of *E. cloacae* was observed with compounds **1**, **3**, **8**, **10**, **11** and **13**. Compound **11** showed a maximum activity with a ZOI value of 13.5 ± 0.57 mm against *E. cloacae*, nearly comparable with the standard antibiotic gentamicin (ZOI = 15 mm). The growth of *K. pneumoniae*

TABLE-2
ZONE OF INHIBITION DISPLAYED BY (*E*)-CHALCONES AGAINST SOME BACTERIA IN THE AGAR WELL DIFFUSION ASSAY[a]

Compound	ZOI ± Standard deviation (standard mean error) at 500 µg dose level against				
	Gram-positive		Gram-negative		
	S. aureus	*B. subtilis*	*E. coli*	*E. cloacae*	*K. pneumoniae*
1	10.0 ± 0 (0)	10.0 ± 0.8 (0.5)	–	11.0 ± 1.1 (0.6)	–
2	–	8.0 ± 0.8 (0.5)	–	–	–
3	10.3 ± 2.0 (1.2)	11.6 ± 1.2 (0.8)	–	12.5 ± 0.5 (0.3)	7.6 ± 0.5 (0.3)
4	–	–	–	–	–
5	9.0 ± 1.0 (0.5)	12.0 ± 0 (0)	–	–	–
6	12.6 ± 2.0 (1.2)	11.6 ± 1.2 (0.8)	–	–	–
7	9.3 ± 1.1 (0.6)	–	–	–	–
8	12.0 ± 1.0 (0.5)	12.3 ± 1.2 (0.8)	8.0 ± 0 (0)	11.0 ± 3.0 (1.7)	10.6 ± 2.0 (1.2)
9	11.3 ± 1.1 (0.6)	12.5 ± 0.4 (0.3)	–	–	–
10	–	11.6 ± 0.9 (0.6)	–	10.0 ± 0 (0)	–
11	12.3 ± 1.5 (0.8)	10.0 ± 0 (0)	–	13.5 ± 0.5 (0.3)	–
12	9.3 ± 0.5 (0.3)	9.3 ± 1.2 (0.8)	–	–	–
13	12.3 ± 2.5 (1.4)	12.0 ± 0 (0)	–	9.0 ± 1.1 (0.6)	–
14	–	–	–	–	–
Gentamicin	25	23	15	15	16

[a]Values of the ZOI (mm) include the diameter of well (6 mm) after 24 h of incubation at 37 °C. (–) Sign indicates no significant ZOI was observed.

was inhibited by chalcones **3** and **8** only. Apparently, the presence of a hydroxyl group in an (*E*)-chalcone was more potent against the Gram-negative bacteria *E. cloacae*. Amino chalcones **4** and **14** were completely ineffective against all the bacteria tested. This result indicated that unsubstituted or the presence of two hydroxyl groups in 2′- and 4′- positions is less effective compared to the presence of a single 2′-OH group at ring-A, since chalcone **12** could exhibit antibacterial activity against *S. aureus* (ZOI = 9.3 ± 0.57 mm) and *B. subtilis* (ZOI = 9.3 ± 1.24 mm).

Although a concurrent SAR for the antibacterial activity of (*E*)-chalcones could not be derived due to limited examples of the compounds screened; however, few assumptions can be drawn from this study, for example, (i) introduction of a strong electron-withdrawing group, such as NO_2, in 3′-position could increase the antibacterial activity. It has been reported that electron-withdrawing substituent (*i.e.* halogen) at ring-A displays superior activity [30]; (ii) free 2′-OH group (rather than a free 4′-OH group) is more important for the antibacterial activity of (*E*)-chalcones. Earlier, it was generalized that a free hydroxyl in the 4′-position of ring-A appeared to be very useful for the enhancement of antibacterial property of the chalcones [44]; (iii) compounds bearing electron donating groups in the 3- and 4-positions of ring-B (*i.e.* compounds **3**, **8** and **11**) showed comparably a good activity than the unsubstituted compounds indicating the presence of two electron-donating groups in ring-B enhances the activity. On the other hand, the antibacterial activity was diminished when only 4 position is occupied by the electron-donating group (compound **1** *versus* compounds **2** and **4** and compound **6** *versus* compound **7**); (iv) a heterocyclic ring, such as furyl (ring-B) (compounds **5**, **9** and **13**), may enhance the antibacterial efficacy [29]; (v) compared to the Gram-negative bacteria (*E. coli*, *E. cloacae* and *K. pneumoniae*), Gram-positive bacteria (*S. aureus* and *B. subtilis*) are more susceptible towards the synthesized (*E*)-chalcones; and (vi) apparently, the presence of a hydroxyl group in chalcone was found to be more potent against the Gram-negative bacteria *E. cloacae*. To inhibit Gram-negative *K. pneumoniae*, at least two electron-donating groups are essential in ring-B.

Through various SAR studies, it has been realized that different electron-donating and electron-withdrawing groups at certain positions of the chalcone skeleton are responsible for their antibacterial activity. Chen *et al.* [30] studied the SAR of chalcone–rhodanine-3-acetic acid and reported introducing electron-donating group(s) such as alkyl-, methoxy- or amido group in ring-A displays a lower activity than the halogen-substituted derivatives. On the other hand, a beneficial effect of the presence of electron-donating group(s) in ring-B is reported by Prasad *et al*. [23] and Subramanian *et al*. [22]. However, in these studies, the role of either halogen substituent at ring-A or heterocyclic ring-A cannot be ignored. Our study showed that the presence of electron-withdrawing group(s) in ring-A and electron-donating group(s) in ring-B provide optimal benefits in the antibacterial activity of (*E*)-chalcones.

The presence of 2′-OH group is often encountered in several natural chalcones as it stabilizes the structure through hydrogen bonding. It is also a key feature in the equilibrium of chalcone-flavanone during natural biosynthesis. At the same time, these chalcones can behave as bidentate chelating agents where the ketone moiety forms a coordinate bond and 2′-OH group forms a covalent bond with a relevant metal ion [19]. Present study showed that the presence of 2′-OH group might enhance the antibacterial activity, indicating a ray of hope for identifying an effective antibacterial chalcone from nature. The present SAR study in antibacterial activity of synthesized (*E*)-chalcones is summarized in Fig. 2.

Conclusion

Several novel chalcone-based antibacterial agents have been used in therapeutics and also difficult to synthesize, though they had a specific effect on the bacteria and at the same time, were equipped with side effects as well. In this work, 14 simple

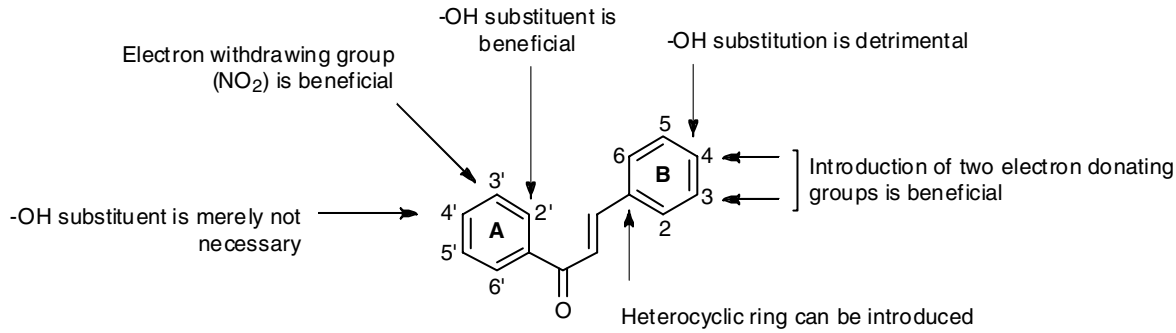


Fig. 2. Structure of antibacterial activity relationships for (*E*)-chalcones

(*E*)-chalcones were evaluated for their antibacterial activity against five bacteria (*S. aureus*, *B. subtilis*, *E. coli*, *E. cloacae* and *K. pneumoniae*) and the result was used for the SAR study. These simple (*E*)-chalcone derivatives are easy to synthesize through Claisen-Schmidt condensation using readily available substrates, which is cost-effective and can be easily modified for further studies.

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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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