

The Benefits of Chalcone and Its Derivatives as Antibacterial Agents: A Review

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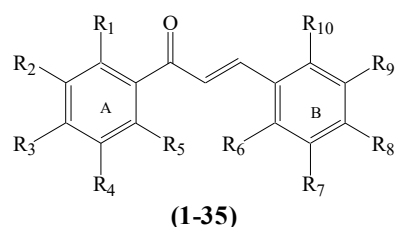
Abstract. Chalcone is a secondary metabolite compound found in plants. Chalcones contain two aryl rings, namely ring A and B which connected to the α,β unsaturated ketones. Chalcone derivatives are synthesized by various substituent groups in both rings, as well as the types of rings. These variations make chalcone and its derivatives, have interesting bioactivity, one of which is antibacterial. This review is considered the chalcone-derived compounds that have antibacterial bioactivity, including methoxy, hydroxy, prenyl, and halogen groups in ring A or B. Besides, there are two forms of these rings as well such as pyrrolyl-furanyl-chalcones and indolyl-thiophenyl-chalcone. We hope this review is useful for the development of the synthesis of organic compounds and the discovery of new drug design.

1 Introduction

Chalcone (1,3-diphenyl-2-propen-1-one) (**1**) is one of the secondary metabolites, belongs to the flavonoid class, found in plants. Structurally chalcone has two benzene rings, namely rings A and B, which both connected by α,β unsaturated ketones. In other words, chalcone derivatives can be synthesized through a condensation reaction of Claisen-Schmidt. The derivatives have many substituent groups, as well as the types of rings. Because of both differences, these derivatives have many interesting biological activities, one of which is antibacterial.

1.1 Chalcone Derivatives with Various Substituents Group in The Ring

Hasan *et al.* [1] successfully synthesized chalcone and its derivatives (**1-6**) and then tested for antibacterial. In their study, these compounds can inhibit the growth of gram-positive and negative bacteria, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as *Escherichia coli* and *Bacillus cereus*, respectively. In this case, the addition of hydroxy and fluoro groups on ring B can increase inhibitory activity against *S. aureus* and *B. cereus*. It can be seen from the chalcone inhibition zone (**2-3**) of both bacteria of 16-35 mm, while the chalcone inhibition zone (**1**) is only 9-11 mm. However, the inhibitory zone value of chalcone (**2-3**) is greater when compared to the amoxicillin inhibition a positive control (15-25 mm). Further, the inhibitory activity of compounds (**2-3**) against gram-negative bacteria (*E. coli*) also shows greater activity when compared to chalcone (**1**), but is relatively lower than the positive control.



Ocampo *et al.* [2] succeeded in synthesizing chalcone (**1**) and its derivatives (**7-13**) with variations of chloro groups in rings A and B. The compounds showed the antibacterial activity as well against *E.coli*, *P. aeruginosa*, and *S. aureus*. The substitution of the chloro group in the meta and para position of (ring A) in compound (**8-9**) tends to decrease the inhibitory activity when compared to compound (**1**). However, the substitution in the ortho position in ring A of compound (**7**) causing it to become inactive. Interestingly, the substitution of chloro groups in ring B of compounds (**10-12**) shows the opposite activity, which can increase its inhibitory activity against all three bacteria tested. In this case, the highest inhibitory activity shown by compound (**13**), approaching the sulfanilamide activity as a positive control.

Synthesis and antibacterial testing of other chalcone derivatives (**14-20**) have reported by Burmaoglu *et al.* [3]. The compound tested against *S. aureus*, *E. coli*, and *P.aeruginosa*. In their results, the compound (**14**) with methoxy group of ring A in the ortho and meta position could inhibit the activity of all bacteria tested, with the MIC values of 31.25, 31.25, and 62.5 $\mu\text{g/mL}$, respectively. The inhibitory activity of *S. aureus* is greater than the inhibitory activity of ampicillin as a positive control of the same bacteria. However, when adding one fluoro group in the ortho, meta, and para position in ring B compound (**15-17**), there was a decrease in the inhibitory activity of all three types of bacteria. Similarly, the addition of two fluoro groups in the ortho position and the ring B meta compound (**18**),

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No	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	R ₉	R ₁₀
(1)	H	H	H	H	H	H	H	H	H	H
(2)	H	H	H	H	H	H	H	OH	H	H
(3)	H	H	H	H	H	H	H	F	H	H
(4)	H	H	H	H	H	H	H	OCH ₃	H	H
(5)	H	H	H	H	H	H	H	N(CH ₃)	H	H
(6)	H	H	H	H	H	H	H	NO ₂	H	H
(7)	H	H	H	H	Cl	H	H	H	H	H
(8)	H	H	H	Cl	H	H	H	H	H	H
(9)	H	H	Cl	H	H	H	H	H	H	H
(10)	H	H	H	H	H	Cl	H	H	H	H
(11)	H	H	H	H	H	H	Cl	H	H	H
(12)	H	H	H	H	H	H	H	Cl	H	H
(13)	H	H	H	Cl	H	H	H	Cl	H	H
(14)	OCH ₃	H	OCH ₃	H	OCH ₃	H	H	H	H	H
(15)	OCH ₃	H	OCH ₃	H	OCH ₃	F	H	H	H	H
(16)	OCH ₃	H	OCH ₃	H	OCH ₃	H	F	H	H	H
(17)	OCH ₃	H	OCH ₃	H	OCH ₃	H	H	F	H	H
(18)	OCH ₃	H	OCH ₃	H	OCH ₃	F	H	H	F	H
(19)	OH	H	OH	H	OH	F	H	H	H	H
(20)	OH	H	OH	H	OH	F	H	H	F	H
(21)	OCH ₃	CH ₃	OCH ₃	CH ₃	OH	H	H	OCH ₃	H	H
(22)	OCH ₃	CH ₃	OCH ₃	CH ₃	OH	H	H	OCH ₃	OCH ₃	H
(23)	OCH ₃	CH ₃	OCH ₃	CH ₃	OH	H	H	OCH ₃	OCH ₃	OCH ₃
(24)	OH	H	OCH ₃	H	Oprenyl	H	H	H	H	H
(25)	OH	Prenyl	OCH ₃	H	Oprenyl	H	H	H	H	H
(26)	OH	Prenyl	OCH ₃	Prenyl	Oprenyl	H	H	H	H	H
(27)	H	OCH ₃	OCH ₃	OCH ₃	H	H	H	OH	OH	H
(28)	OCH ₃	H	H	OCH ₃	H	H	H	OH	OCH ₃	H
(29)	H	OCH ₃	OCH ₃	OCH ₃	H	H	H	OH	OCH ₃	H
(30)	H	H	OCH ₃	H	OCH ₃	H	H	OH	OCH ₃	H
(31)	OCH ₃	H	H	OCH ₃	H	H	H	H	H	H
(32)	H	OCH ₃	OCH ₃	H	H	H	H	OH	OCH ₃	H
(33)	H	H	H	H	H	H	H	OH	OCH ₃	H
(34)	H	H	H	H	H	H	H	OH	OH	H
(35)	H	H	OH	H	OH	H	OCH ₃	OCH ₃	OCH ₃	H

except for *S. aureus*, which can increase the inhibitory activity until 50%, with the MIC value of 15.6 µg/mL. The decreasing antibacterial activity also very significantly occurs in compounds (19-20) after the methoxy group on ring A is replaced by a hydroxy group.

The antibacterial activity of chalcone (21-23) to *Mycobacterium tuberculosis* (H₃₇Rv) have studied by Anandam *et al.* [4]. In their study, the compounds (21) and (22) show the antibacterial activity with MIC₉₀ of 1.6 µg/mL. This value is stronger than the positive control of pyrazinamide (3.125 µg/mL only). The presence of two methoxy groups on ring B (compound 21) does not affect as an antibacterial activity when compared to compound (22), which has only one methoxy group. However, the presence of three methoxy groups in ring B compound (23) can reduce the MIC₉₀ value to 6.25 µg/mL.

The synthesis of prenylated chalcones on ring A was successfully carried out by Marliyana *et al.* [5], there are differences in the number of prenyl groups in compounds (24-26). All compounds of this study were

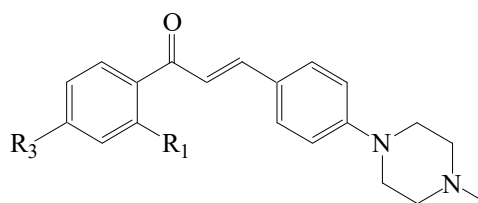
tested to *B. subtilis*, *S. aureus*, *E. coli*, and *P. aeruginosa*. Antibacterial test results showed that the compound (24-26) produced the same inhibitory activity against the four types of bacteria, with MIC values of 50, 25, 25, and 25 µg/mL, respectively. The MIC value is relatively much lower when compared to chloramphenicol as a positive control, which ranges between 1.17-12.5 µg/mL. However, the antibacterial activity of the compound (24-26) is still greater than the compound without the prenyl group, for example, compound (14) from the study of Burmaoglu *et al.* [3]. The MIC values of compounds (14) against *S. aureus*, *E. coli*, and *P. aeruginosa* were 31.25, 31.25, and 62.5 µg/mL.

Vasquez-Martinez *et al.* [6] succeeded in synthesizing nine polyoxygenated chalcones (27-35), which had a variety of hydroxy and methoxy groups in rings A and B. The compounds were tested for their antibacterial activity against *E.coli* and *S. aureus*. However, the MIC value of the nine types of chalcone compounds (27-35) against *E.coli* is only > 100 µg / mL,

which means it is less active in inhibiting the activity of these bacteria. The same thing happened to *S.aureus* bacteria, except for compound **(34)** with a MIC value of 50 µg / mL. The compound **(34)** is substituted by only two hydroxy groups in ring B, with no other substituents in ring A.

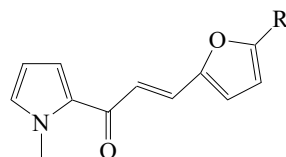
Chalcone derivatives with the addition of piperazinyl groups in the position of para (ring B) have been successfully synthesized and tested for their activity against *E.coli*, *S. typhi*, and *S. aureus*. In this study, the variation of functional groups in ring A, namely the fluoro, chloro, methyl, and nitro groups in the para position. The results showed that the presence of chloro groups in compound **(36)** generated a greater inhibition to all bacteria tested than nitro **(37)**, fluoro **(38)**, and methyl **(39)** compound groups. Even the presence of two chloro groups in compound **(40)** in the ortho and para position produces an inhibitory zone which is almost close to the positive control of

penicillin [7].



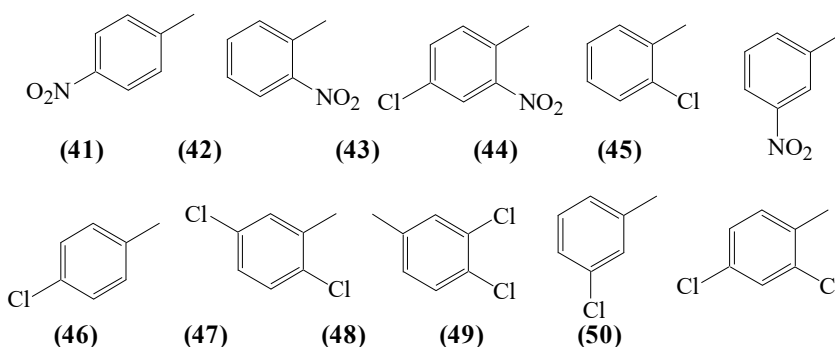
(36-40)

	R ₁	R ₃
36	H	F
37	H	Cl
38	H	CH ₃
39	H	NO ₂
40	Cl	Cl



(41-50)

R =



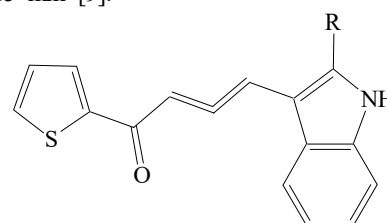
1.2 Chalcone derivatives with various ring types

One of the chalcone derivatives with variations in ring type is the pyrolyl-furanyl-chalcones **(41-50)**. The compound consists of pyrolyl (ring A) and furan (ring B), with substituents variations in ring B.

The compounds **(41-50)** above were tested for antibacterial properties against *S. aureus*, *E. faecalis*, *E.coli*, and *Klebsiella pneumoniae*. Test results showed that the ten compounds were not active as antibacterial, their MIC values ranged from 100-400 µg/mL [8].

The indolyl-thiophenyl-chalcone **(51-58)** have successfully synthesized and show antibacterial properties against *S. aureus*, *P. aeruginosa*, and *E. coli*. The compound consists of thiophene (ring A) and indole (ring B). The variations in the nitro, sulfite, methyl, ethyl, halogen, and acyl halide groups were found in ring B. The antibacterial assay showed that almost all variations of the groups, mainly compounds **(51-56)**, generated the inhibitory zones (21-28 mm) close to the positive control of ciprofloxacin. Except for the methyl and ethyl groups in compounds **(57-58)**, their presence can reduce the antibacterial activity, with the inhibition

zone of 12-15 mm [9].



(51-58)

(51)	R=NO ₂
(52)	R=SO ₃ H
(53)	R=Cl
(54)	R=Br
(55)	R=I
(56)	R=CH ₂ Cl
(57)	R=CH ₃
(58)	R=C ₂ H ₅

4 Conclusion

In this review, we discussed the antibacterial properties of some chalcone derivatives. This review is considered the chalcone-derived compounds that have antibacterial bioactivity, including methoxy, hydroxy, prenyl, and halogen groups in ring A or B. Besides, there are two forms of these rings as well such as pyrrolyl-furanyl-chalcones and indolyl-thiophenyl-chalcone. The results of the review indicate that some chalcone derivatives have potential as an antibacterial agent.

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