CHALCONES: A MINI REVIEW

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ABSTRACT
Chalcones are natural products which belong to falvonoid family. Chalcones can be synthesized by using conventional organic synthetic protocols. Substituted chalcones are of particular interest for various studies because of their diverse range of biological activities as well as precursor in the synthesis of varied bioactive heterocyclic compounds. This review describes methods of synthesis, spectroscopic characterization and special emphasis given to the compounds that have shown promising antimicrobial and anti-inflammatory properties.

Keywords: Chalcone, Antimicrobial activity, Anti-inflammatory activity.

INTRODUCTION
Chalcone (1) is a generic term given to compounds bearing the 1,3-diphenyl-2-propen-1-one framework and belong to the flavonoid family.³³. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. Chalcones are abundantly present in nature starting from ferns to higher plants and a number of them are polyhydroxylated in the aryl rings. In plants, chalcones are converted to the corresponding (2S)-flavanones in a stereospecific reaction catalyzed by the enzyme chalcone isomerase. This close structural and biogenetic relationship between chalcones and flavanones explains why they often co-occur as natural products.
All the chalcones give pink coloration with concentrated sulphuric acid (positive Wilson test) \(^5\) and when a phenolic hydroxyl group is present, they give violet coloration with alcoholic ferric chloride solution.

Chalcones on heating with traces of iodine in dimethylsulphoxide (DMSO) for two hours give the corresponding flavones. Chalcones were converted into the corresponding flavonols by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution and these flavonols showed a characteristic greenish yellow fluorescence in ethanolic solution as well as with concentrated sulphuric acid.

**GENERAL METHODS OF SYNTHESIS OF CHALCONES**

Chalcones can be obtained by the acid or base catalyzed aldol condensation of acetophenones with aromatic aldehydes \(^6-8\).

1. 2'-hydroxyacetophenone react with benzaldehyde in the presence of 0.1 M NaOH to give the chalcone \(^9\) (Scheme 3.1).

2. Liquid phase Claisen–Schmidt condensation between 2'-hydroxyacetophenone and benzaldehyde was carried out over a zinc oxide supported metal oxide catalyst under solvent free conditions to form 2'-hydroxychalcone \(^10\) (Scheme 3.2).
3. 2,4,5-trimethoxyacetophenone, when condensed with equimolar proportions of aromatic aldehydes in the presence of 30% alcoholic alkali at room temperature yield chalcones \[^{[11]}\] (Scheme 3.3).

$$\text{H}_3\text{CO} - \text{OC}_6\text{H}_4\text{O}_3\text{H}_3 + \text{OHC} \rightarrow \text{H}_3\text{CO} - \text{OC}_6\text{H}_4\text{O}_3\text{H}_3$$

**Scheme 3.3**

4. Claisen-Schmidt condensation between benzaldehyde and acetophenone by sonochemical and thermally activated reactions over zeolite as catalyst under solvent free conditions give chalcone \[^{[12]}\] (Scheme 3.4).

$$\text{C}_6\text{H}_5\text{COCH}_3 + \text{OHC} \rightarrow \text{C}_6\text{H}_5\text{COCH}_3$$

**Scheme 3.4**

5. 4-Acetyl-3-aryl-syndones when subjected to grinding with various arylaldehydes in the presence of a base catalyst under solvent free conditions yield syndonechalcones \[^{[13]}\] (Scheme 3.5).

$$\text{C}_6\text{H}_5\text{N} + \text{OHC} \rightarrow \text{C}_6\text{H}_5\text{N}$$

**Scheme 3.5**

6. Condensation of 2-naphthylmethylketones with substituted arylaldehydes in the presence of NaOH under methanol as solvent gave the corresponding chalcones \[^{[14]}\] (Scheme 3.6).

$$\text{MeO} + \text{OHC} \rightarrow \text{MeO}$$

**Scheme 3.6**
SPECTRAL FEATURES OF CHALCONES

UV SPECTRA OF CHALCONES
The major absorption band in chalcones (Band I) usually occurs in the range 340-390 nm, although chalcones lacking B-ring oxygenation may have their Band I absorption at considerably shorter wavelengths and Band II is usually a minor peak in the 220-270 nm region [15]. In the spectra of chalcones containing a free 4''-hydroxyl group, the addition of NaOMe causes a 60-100 nm bathochromic shift of Band I with an increase in peak intensity. Chalcones without a 4''-hydroxyl group but with either a free 2'' or 4'-hydroxyl group also give, in the presence of NaOMe, a 60-100 nm bathochromic shift of Band I but without an increase in peak intensity [16,17]. UV spectroscopy proved useful to distinguish between substituted chalcones and flavanones, which is not possible by EI mass spectrometry due to thermal isomerization of 2'-hydroxychalcones in the ion source [18,19].

IR SPECTRA OF CHALCONES
The α, β-unsaturated carbonyl group, characteristic of a chalcone usually appear as a prominent band in between 1625-1650 cm⁻¹ in its IR spectrum [20,21]. The region at which other absorption bands appear depends on the type of aromatic/ heteroaromatic rings as well as the substituents present on these rings.

NMR SPECTRA OF CHALCONES
The H-α and H-β protons of chalcones occur as two doublets (J= 17 Hz) in the ranges 6.7 - 7.4 ppm (H-α) and 7.3 -7.7 ppm (H-β) in the ¹H NMR spectra [22]. The other aromatic protons usually appear in between δ 6.9-8.0, depending on the type of aromatic / heteroaromatic ring and also based on the electronic effects of the substituents present on these rings. The large J value (17 Hz) clearly reveals the trans geometry at the double bond. The carbonyl carbon of the chalcones usually appears between δ 188.6 and 194.6 in its ¹³C NMR spectrum [23]. The α and β- carbon atoms with respect to the carbonyl group give rise to characteristic signals in between δ 116.1-128.1 and δ 136.9-145.4 respectively, which can also be readily identified by their characteristic appearance as a six line multiplet in the half resonance decoupled spectrum [24]. The presence of 2'-hydroxy group shifts the carbonyl carbon shift downfield by 3 ppm relative to corresponding acetoxy and methoxy compounds, presumably owing to hydrogen bonding. The β-hydroxychalcones are a relatively small group of chalcones that occur naturally sometimes as the enol-tautomers of dibenzoylemthane derivatives. The extent of keto-enol tautomerism is largely solvent dependent, and nuclear
magnetic resonance spectroscopy (NMR) provides one of the best methods to determine the ratio of the tautomers present. In the $^1$H NMR spectra recorded in CDCl$_3$, the exchangeable proton of the β-OH of the enol tautomer appears as a 1H singlet at δ 16.0, whereas the α-CH$_2$ protons of the keto tautomer appear as a 2H singlet at δ 4.50. Another diagnostic resonance is the 1H methine singlet of the enol tautomer (α-CH), which is found at δ 6.5, with its corresponding C-α resonance at δ 90 to 92 in the $^{13}$C NMR spectra$^{[25,26]}$.

**MASS SPECTRA OF CHALCONES**

Cleavage of the heterocyclic C-ring via a Retro Diels-Alder (RDA) mechanism represents an important fragmentation pathway in chalcones. RDA fission leads to two characteristic fragments, which provides useful information as to the number of hydroxyl, methoxyl and other substituents on each ring$^{[27]}$ (Scheme 3.7). The same information was also obtained by a HPLC-tandem mass spectrometer system equipped with a heated nebulizer- atmospheric pressure chemical ionization (APCI) interface$^{[28]}$.

The EIMS of chalcones also give rise to the unusual fragment ion [M-H]$^+$ involving a type of intramolecular aromatic substitution reaction by the elimination of an *ortho* substituent from an aromatic ring with further cyclization. This results in the formation of a highly stabilized benzopyrylium cation$^{[29]}$ (Scheme 3.8) and this type of fragmentation is sometimes known as proximity effect. The cation so formed undergoes structural rearrangements, which permits fragmentation pathways that may eventually lead to loss of CO$^{[30-32]}$.

Protonated chalcones generated by electrospray ionization during MS/MS experiments were found to form three important fragment ions due to loss of H$_2$O, CO and benzene$^{[33]}$ (Scheme 3.9).
Scheme 3.7. A typical fragmentation pattern of a 2'-Hydroxychalcone.

Scheme 3.8. Mechanism of formation of [M-H]^+ and loss of CO from [M-H]^+ ion of chalcone
THERAPEUTIC POTENTIAL OF CHALCONES

Chalcone is a unique template that is associated with several biological activities and is well known intermediates for synthesizing various heterocyclic compounds \(^{[34]}\). They are secondary metabolites of terrestrial plants, precursors for the biosynthesis of flavonoids. The introduction of a halogen into the benzenoid part of these \(\alpha,\beta\)-unsaturated ketones enhances their biological activity \(^{[35]}\).

The compounds with chalcone as backbone have been reported to possess varied biological and pharmacological activities \(^{[36]}\), including antimicrobial, anti-inflammatory, analgesic, cytotoxic, antitumor, antimalarial, antitubercular, antiviral, anti-HIV, antiulcerative, antileishmanial, antioxidant, antiprotozoal, antihistaminic, antifedent, immunomodulatory, anticonvulsant, antihyperglycemic, antihyperlipidemic and antiplatelet activities. Thus chalcones continue to attract considerable scientific attention because of their association with a variety of biological activities. Given below is a brief account of various modifications reported on chalcones, which resulted in a variety of biological and pharmacological activities.
ANTIMICROBIAL ACTIVITY

The antimicrobial activity of chalcones is being increasingly documented. Many research groups either isolated or synthesized chalcones that possess antimicrobial activity. The presence of a reactive α,β-unsaturated keto function in chalcones was found to undergo conjugate addition with a nucleophilic group like a thiol group in an essential protein, thus partly contributing for their antimicrobial activity, which may be altered depending on the type and position of the substituents on the aromatic rings.

Bandgar et al.\textsuperscript{[37]} synthesized some β-chlorovinylchalcones (2) by Claisen-Schmidt condensation reaction and the compounds were screened for their antimicrobial activity. It was observed that the compounds having bromo, chloro, methoxy and fluoro substituents enhanced the antimicrobial activity with MIC values ranging from 50-100 µg/mL against selected pathogenic bacteria and fungi.

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle,fill=white] (a) at (0,0) {$R^1$= H, -OCH\textsubscript{3}; $R^2$= -OCH\textsubscript{3}; $R^3$= H, -OCH\textsubscript{3}; $R^4$= H, Cl; $R^5$= H, -OCH\textsubscript{3}, F, Cl, Br; $R^6$= H.}
\end{tikzpicture}
\end{center}

(2)Bandgar et al.\textsuperscript{[38]} also reported in another study that the chalcones (3) having 2-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl and 2,4-dichlorophenyl moieties showed maximum antibacterial activity against \textit{Bacillus subtilis}, \textit{Escherichia coli}, \textit{Staphylococcus aureus}, \textit{Klebsiella pneumoniae} and \textit{Pseudomonas vulgaris}. It was also found that the compounds having 4-bromophenyl, 4-fluorophenyl and 2,4-dichlorophenyl moieties contributed favourably to the antifungal activity against \textit{Aspergillus fumigatus}, \textit{Aspergillus niger}, \textit{Trichoderma viride}, \textit{Candida albicans} and \textit{Penicillium chrysogenum}.

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle,fill=white] (a) at (0,0) {$R^2$= H, -Cl, -OCH\textsubscript{3}; $R^3$= H, -Cl, -OCH\textsubscript{3}; $R^4$= H, -F, -Cl, -Br, -CH\textsubscript{3}, -OCH\textsubscript{3}; $R^5$= H,-OCH\textsubscript{3}.}
\end{tikzpicture}
\end{center}

(3)
Chen et al.\(^{[39]}\) synthesized some new chalcones having a rhodanine-3-acetic acid moiety (4). The results of antibacterial activity studies on these compounds revealed the potential antibacterial activity against Gram-positive bacteria, particularly against multidrug-resistant strains of clinical isolates. Of all the compounds, the chalcone with 2,4-dichlorophenyl moiety was found to have the most potent inhibitory capacity against \textit{S.aureus}, \textit{Staphylococcus mutans} and \textit{E.coli} with a MIC value of 2 \(\mu\)g/mL. The study also revealed that the hybrid compounds possessing chalcone and rhodanine-3-acetic acid moieties contributed favourably to the antibacterial activity. This might also be due to the fact that the rhodanines alone were earlier reported to possess antibacterial and insecticidal activities, which now has been further enhanced when present as an additional structural feature of chalcone structure.

\[
\begin{align*}
\text{R} &= \text{4-CH}_3, \text{2,4-(CH}_3)_2, \text{3-OCH}_3, \text{4-OCH}_3, \text{H, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 2,4-(Cl)}_2, \text{2-Br, 3-Br, 4-Br, 3-F, 4-NO}_2, \text{3-OCH}_2\text{OCH}_3, \text{4-OCH}_2\text{OCH}_3, \text{4-NHCOCH}_3
\end{align*}
\]

(4)

Vibhute et al.\(^{[40]}\) reported the synthesis of some new chalcones containing substituted naphthalene nucleus (5). These compounds when screened for antibacterial activity revealed that the compounds with chloro substituents possessed remarkable inhibition against \textit{E.coli}.

\[
\begin{align*}
\text{R}^1 &= \text{2-OH; 5-Br; 3,5-Cl; 5-Cl; 3-I, 5-CH}_3; \text{3-1,5-Cl; 3-I, 4-CH}_3, \text{5-Cl; 3-Br,5-CH}_3; \text{R}^2 = \text{4-Br; 2-OCH}_3
\end{align*}
\]

(5)

Vibhute et al.\(^{[41]}\) also synthesized some new chalcones having a 2-chloro-8-methoxyquinolinyl moiety (6) and evaluated their antibacterial activity against \textit{Xanthomonas citri}, \textit{Ervinia carotovara}, \textit{E.coli} and \textit{B.subtilis}. The compounds having 2'-hydroxy-3'-ido-5'-
chlorophenyl and 2'-hydroxy-3'-chloro-5'-iodophenyl moieties showed significant activity which is more than that of the ampicillin used as the standard.

\[
\text{R}= -\text{I}, -\text{Cl}, -\text{Br}; \ R^1= \text{H}, -\text{OH}; \ R^2= -\text{I}, -\text{Cl}, -\text{Br}, -\text{CH}_3
\]

(6)

Rathod et al.\cite{42} prepared some novel chalcones of phthalimidoester (7) and the compounds having halogen substituents exhibited good antimicrobial activity.

\[
\text{R}= 4-\text{Cl}, 4-\text{F}, 4-\text{Br}, 4-\text{OCH}_3, 2-\text{OH}, 3-\text{NO}_2, 3,4,5-\text{OCH}_3, 6-\text{methoxynaphthalene}
\]

(7)

Gautam et al.\cite{43} reported the synthesis of some new cinnoline based chalcones (8) which were evaluated for antimicrobial activity. The cinnoline system was found to contribute favourably to antibacterial activity against *E.coli*.

\[
\text{R}= 3-\text{NO}_2; 2-\text{Cl}; 3-\text{Cl}; 4-\text{Cl}; 3-\text{Br}; 2-\text{NO}_2; 4-\text{OCH}_3; 4-\text{NO}_2; 2-\text{OH}; 4-\text{OH}; 3-\text{OCH}_3; 4-\text{N}-(\text{CH}_3)_2.
\]

(8)
Paramesh et al.\cite{44} reported the synthesis and antimicrobial activity of some new chlorine containing chalcones (9). It was found that the compounds having furan ring enhanced the activity.

\[
\begin{align*}
\text{Cl} & \quad \text{C} \quad \text{CH} = \text{CH} - \text{R} \\
& \quad \text{O}
\end{align*}
\]

\(R = -\text{C}_6\text{H}_5, 2-\text{OHC}_6\text{H}_4, 4-\text{OHC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{OCH}_3\text{C}_6\text{H}_4, 3,4,5-(\text{OCH}_3)_3\text{C}_6\text{H}_2, 4-\text{N(CH}_3)_2\text{C}_6\text{H}_4, -\text{C}_4\text{H}_3\text{O}.
\] (9)

Guptha et al.\cite{45} reported an improved synthesis of chalcones (10) under ultrasonic irradiation and screened them for antimicrobial activity. Some of these compounds showed promising activity against \textit{E. coli}, \textit{S. aureus, C. albicans} and \textit{A. niger}.

\[
\begin{align*}
\text{COCH}_3 & \quad + \quad \text{CHO} & \quad \xrightarrow{\text{ultrasonic irradiation}} & \quad \text{O} \\
\text{X} & \quad \text{Cl} & \quad \xrightarrow{2\ N\ NaOH} & \quad \text{X} \quad \text{Cl}
\end{align*}
\]

\(X = 4-\text{H}, 4-\text{Br}, 4-\text{Cl}, 4-\text{F}, 4-\text{CH}_3
\] (10)

Batovska et al.\cite{46} reported the synthesis of a large series of new chalcones (11) and studied their antibacterial activity against \textit{S. aureus} and \textit{E. coli}. Most of these synthesized chalcones were either unsubstituted in ring A or possessed 4'-chloro or 3',4',5'-trimethoxy groups while ring B was variously substituted. It was found that the antistaphylococcal activity of chalcones was related to the energy difference between the two highest occupied molecular orbitals HOMO and HOMO-1. The presence of hydroxyl group in ring B was not a determinant factor for antistaphylococcal activity, but the lipophilicity of ring A of the hydroxylchalcones was of importance.
Baviskar et al.\textsuperscript{47} synthesized some new benzimidazolylchalcones (12) and were screened for their \textit{in vitro} antibacterial and antifungal activities. Marked bacterial inhibition was observed in the compounds bearing phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 3-fluorophenyl and 3-bromophenyl moieties. The compounds having 2-nitrophenyl, N,N-dimethylaminophenyl and 4-methoxyphenyl moieties exhibited marked antifungal activity.

\begin{center}
\text{\begin{tikzpicture}
\node[draw, circle] (A) {N};
\node[draw, circle, above right=1cm and 2cm of A] (B) {O};
\node[draw, circle, below right=1cm and 2cm of A] (C) {O};
\node[draw, circle, below right=1cm and 2cm of B] (D) {H};
\node[draw, circle, below right=1cm and 2cm of C] (E) {R};
\node[draw, circle, below right=1cm and 2cm of D] (F) {N};
\node[draw, circle, below right=1cm and 2cm of E] (G) {O};
\node[draw, circle, below right=1cm and 2cm of F] (H) {C};
\node[draw, circle, below right=1cm and 2cm of G] (I) {H};
\node[draw, circle, below right=1cm and 2cm of H] (J) {C};
\node[draw, circle, below right=1cm and 2cm of I] (K) {C};
\node[draw, circle, below right=1cm and 2cm of J] (L) {H};
\node[draw, circle, below right=1cm and 2cm of K] (M) {C};
\node[draw, circle, below right=1cm and 2cm of L] (N) {H};
\node[draw, circle, below right=1cm and 2cm of M] (O) {C};
\node[draw, circle, below right=1cm and 2cm of N] (P) {H};
\node[draw, circle, below right=1cm and 2cm of O] (Q) {C};
\node[draw, circle, below right=1cm and 2cm of P] (R) {H};
\node[draw, circle, below right=1cm and 2cm of Q] (S) {C};
\node[draw, circle, below right=1cm and 2cm of R] (T) {H};
\node[draw, circle, below right=1cm and 2cm of S] (U) {C};
\node[draw, circle, below right=1cm and 2cm of T] (V) {H};
\node[draw, circle, below right=1cm and 2cm of U] (W) {C};
\node[draw, circle, below right=1cm and 2cm of V] (X) {H};
\node[draw, circle, below right=1cm and 2cm of W] (Y) {C};
\node[draw, circle, below right=1cm and 2cm of X] (Z) {H};
\node[draw, circle, below right=1cm and 2cm of Y] {R};
\end{tikzpicture}}
\end{center}

R= \text{-C}_6\text{H}_5, \text{2-NO}_2\text{C}_6\text{H}_4, \text{4-N(CH}_3)_2\text{C}_6\text{H}_4, \text{4-OCH}_3\text{C}_6\text{H}_4, \text{3,4,5-(OCH}_3)_3\text{C}_6\text{H}_2, \text{4-OHC}_6\text{H}_4, \text{3-BrC}_6\text{H}_4, \text{3-FC}_6\text{H}_4.

\begin{center}
\text{(12)}
\end{center}

Baviskar et al.\textsuperscript{48} also synthesized some new thiazolylchalcones (13) and evaluated them for their antimicrobial activity. The compounds having phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, 3-fluorophenyl and 3-bromophenyl moieties showed maximum activity.

\begin{center}
\text{\begin{tikzpicture}
\node[draw, circle] (A) {N};
\node[draw, circle, above right=1cm and 2cm of A] (B) {O};
\node[draw, circle, below right=1cm and 2cm of A] (C) {O};
\node[draw, circle, below right=1cm and 2cm of B] (D) {H};
\node[draw, circle, below right=1cm and 2cm of C] (E) {R};
\node[draw, circle, below right=1cm and 2cm of D] (F) {N};
\node[draw, circle, below right=1cm and 2cm of E] (G) {O};
\node[draw, circle, below right=1cm and 2cm of F] (H) {C};
\node[draw, circle, below right=1cm and 2cm of G] (I) {H};
\node[draw, circle, below right=1cm and 2cm of H] (J) {C};
\node[draw, circle, below right=1cm and 2cm of I] (K) {C};
\node[draw, circle, below right=1cm and 2cm of J] (L) {H};
\node[draw, circle, below right=1cm and 2cm of K] (M) {C};
\node[draw, circle, below right=1cm and 2cm of L] (N) {C};
\node[draw, circle, below right=1cm and 2cm of M] (O) {C};
\node[draw, circle, below right=1cm and 2cm of N] (P) {C};
\node[draw, circle, below right=1cm and 2cm of O] (Q) {C};
\node[draw, circle, below right=1cm and 2cm of P] (R) {C};
\node[draw, circle, below right=1cm and 2cm of Q] (S) {C};
\node[draw, circle, below right=1cm and 2cm of R] (T) {C};
\node[draw, circle, below right=1cm and 2cm of S] (U) {C};
\node[draw, circle, below right=1cm and 2cm of T] (V) {C};
\node[draw, circle, below right=1cm and 2cm of U] (W) {C};
\node[draw, circle, below right=1cm and 2cm of V] (X) {C};
\node[draw, circle, below right=1cm and 2cm of W] (Y) {C};
\node[draw, circle, below right=1cm and 2cm of X] {R};
\end{tikzpicture}}
\end{center}

R= \text{-C}_6\text{H}_5, \text{3-NO}_2\text{C}_6\text{H}_4, \text{4-N(CH}_3)_2\text{C}_6\text{H}_4, \text{4-OCH}_3\text{C}_6\text{H}_4, \text{3,4,5-(OCH}_3)_3\text{C}_6\text{H}_2, \text{4-OHC}_6\text{H}_4, \text{3-BrC}_6\text{H}_4, \text{3-FC}_6\text{H}_4.

\begin{center}
\text{(13)}
\end{center}
Reddy et al.\textsuperscript{[49]} synthesized some novel bis-chalcones (14) and evaluated for their antimicrobial activity. The results proved that the presence of methoxy/chloro groups on the phenyl ring was essential for antibacterial activity. The activity was found to be maximum when the methoxy group present at 4\textsuperscript{th} position. These compounds were also highly active against \textit{C.albicans}.

![Chemical structure of bis-chalcones (14)](image)

Lahtchev et al.\textsuperscript{[50]} reported the synthesis and antifungal activity of some new chalcones (15). The MIC values were determined by the agar dilution method and the most active chalcones possessed phenyl, 3-hydroxyphenyl, 3-hydroxy-4-methoxyphenyl and 4-hydroxyphenyl moieties in their structures. It was revealed that the yeast’s intracellular glutathione and cysteine molecules play a significant role as defense barrier against the chalcone action. It was also shown that the chalcones may react with some proteins involved in cell separation.

![Chemical structure of chalcones (15)](image)

Prasad et al.\textsuperscript{[51]} carried out QSAR analysis on a set of synthesized chalcone derivatives (16, 17 and 18) tested for growth inhibitory activity against \textit{Bacillus pumilus} by using multiple regression procedure. The activity contributions of these compounds were determined from regression equation. The generated model from a 25 molecule training set and 7 molecule validation set using 47 independent variables revealed that an increase in ADME weight, Kappa 2 index and a decrease in HOMO energy as favourable descriptors for \textit{Bacillus pumilus} inhibition.
Nowakowska et al.\textsuperscript{[52]} synthesized a series of substituted chalcones (19) and tested for their antibacterial and antifungal activities. The physico-chemical properties of these novel chalcones which contributed favorably to the observed activities were also determined.

\begin{equation}
Y=(CH_2)nN\bigg\uparrow \\
Y=S, O; \ n=4,5,6; \ X=CH-CH_2, O, NH
\end{equation}

(19)

Tomar et al.\textsuperscript{[53]} synthesized some new chalcones containing piperazine or 2,4-dichlorothiophene moiety in their structure (20). All the synthesized compounds have been evaluated for antimicrobial activity. Some of these compounds were potentially active against \textit{S.aureus} and \textit{E.coli}. The most potent compound that showed antifungal activity in this series possessed a simple phenyl moiety with a MIC value of 2.22 µg/mL against \textit{C.albicans}. The study also revealed the importance of electron withdrawing groups in enhancing the antibacterial activity.
Prasad et al.\textsuperscript{[54]} synthesized 3-[1-oxo-3-(2,4,5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-ones (21) that showed significant antimicrobial activity against \textit{B.subtilis}, \textit{B.pumilis} and \textit{E.coli} when tested at a concentration of 1000 µg/ml. The study revealed the importance of electron releasing groups such as hydroxyl and methoxyl groups in enhancing the activity. Chalcones with halogen substituents like bromine and chlorine contributed favorably to the antifungal activity.

Karthikeyan et al.\textsuperscript{[55]} synthesized 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones (22) showing antimicrobial activity, again consistent with the observations that the halogens possess favorable lipophilic character required for antimicrobial activity.

Prasad et al.\textsuperscript{[56]} synthesized a chalcone (23) having a naphthalene moiety on one side and an aryl moiety having substituents on the other side, which showed significant antifungal
activity against *A. niger* and *Rhizopus oryzae*. This compound can also be considered to provide optimal hydrophilic and hydrophobic properties as evidenced by hydroxyl groups and the halogens.

![Chemical structure of compound 23](image)

Machodo *et al.*[^57] isolated isoliquiritigenine (24) which showed antibacterial activity.

![Chemical structure of compound 24](image)

Boeck *et al.*[^58] synthesized novel xanthoxylin-derived chalcones (25) showing antifungal activity.

![Chemical structure of compound 25](image)

Nielsen *et al.*[^59] synthesized some new chalcones by the bioisosteric replacement of the 4'- hydroxy group (26). This resulted in the synthesis of bioisosters of varied degrees of acidity with potent antibacterial activity. The increased antibacterial activity was related to the increased aqueous solubility. The more acidic 4\(^1\)-hydroxy analogs gave almost inactive analogs whereas exchanging the hydroxyl group with a carboxy group resulted in a potent compound with a high aqueous solubility. Further optimization and SAR analysis resulted in more soluble and potent carboxychalcones.
\[ R^1 = 2\text{-F}-4\text{-OH}; 3\text{-F}-4\text{-OH}; 3,5\text{-}(\text{F})_2\text{-4-OH}; 4\text{-COOH}; 4\text{-Tetrazolyl} \\
R^2 = 2,4\text{-}(\text{Cl})_2 \]

(26)

Rao et al.\(^{[60]}\) synthesized chalcones having chlorine and fluorine substitution (27), which showed antimicrobial activity.

\[ \text{Rao et al.}^{[60]} \text{synthesized chalcones having chlorine and fluorine substitution (27), which showed antimicrobial activity.} \]

(27)

Stevaz et al.\(^{[61]}\) isolated a 2',4'-dihydroxy-3'-methoxychalcone (28) from the methanolic extract of Zuccagnia punctata which exhibited antifungal activity.

(28)

Tsukiyama et al.\(^{[62]}\) isolated a retrochalcone, licochalcone-C (29) from Glycyrrhiza infanta which showed potent antibacterial activity.

(29)
Sohly et al.\textsuperscript{[63]} isolated prenylated chalcones (30) from the leaves of \textit{Malclura tinctoria} possessing antifungal activity.

\begin{center}
\begin{align*}
\text{(30)}
\end{align*}
\end{center}

Desai et al.\textsuperscript{[64]} reported the synthesis of some new chalcones having substituted pyrazoline moiety (31) and screened them for antibacterial activity. The results revealed that some of the compounds possessed moderate antibacterial activity.

\begin{center}
\begin{align*}
\text{(31)}
\end{align*}
\end{center}

Okunade et al.\textsuperscript{[65]} synthesized a dihydrochalcone (32) having antibacterial activity.

\begin{center}
\begin{align*}
\text{(32)}
\end{align*}
\end{center}

Tsuchiya et al.\textsuperscript{[66]} synthesized a hydroxychalcone (33) which exhibited antifungal activity.

\begin{center}
\begin{align*}
\text{(33)}
\end{align*}
\end{center}

Swami et al.\textsuperscript{[67]} synthesized some new chalcones having benzofuran moiety (34) and evaluated for their antimicrobial activity. Some of these compounds were found to possess significant activity.
Some novel S-triazine based chalcones and their derivatives were prepared \cite{68} by the reaction of 2,4-bis-(phenylamino)-6-(4'-acetylphenylamino)-s-triazine with different aldehydes to form chalcones \eqref{35}. These chalcones were screened for their antibacterial activity by using the disc diffusion method, TLC-bioautographic and microdilution methods against a panel of Gram-positive and Gram-negative, using streptomycin and ampicillin as standards. It was observed from the results that the most sensitive bacteria among Gram-positive is \textit{Micrococcus flavus} and the chalcone found to be active is the one having 2-furanyl ring in the structure. It showed lower activity than streptomycin but higher than ampicillin. Compounds with 4-nitrophenyl and 2-furanyl moieties inhibited \textit{E.coli} better than ampicillin. The results of antibacterial activity obtained by micro dilution method indicated that \textit{Bacillus cerius} was the most sensitive with very low MIC and MBC, while, \textit{L-monocytogenes} is the most resistant one with high MIC and MBC. Among the chalcones, the compound with 2-methylphenyl substitution exhibited the best antibacterial activity (MIC of 13.4-26.8 \(\mu\text{mol/mL} \times 10^{-2}\) and MBC of 26.8-53.6 \(\mu\text{mol/mL} \times 10^{-2}\)).

\begin{equation}
\text{R}= 4\text{-nitrophenyl, 4-chlorophenyl, 2-furanyl, 2-thienyl, 2-methoxyphenyl}
\end{equation}

\textbf{ANTI-INFLAMMATORY ACTIVITY}

Kotra \textit{et al.} \cite{69} synthesized a new series of quinolinyl chalcones \eqref{36} and evaluated for them for their anti-inflammatory activity. The anti-inflammatory activity was performed by
carrageenan-induced acute paw edema method in rats. The compounds with 2-furyl and 2-thienyl moieties have been found to exhibit significant reduction in rat paw oedema.

\[
\begin{align*}
R &= H, Cl \\
Ar &= -C_6H_4NO_2, p-C_6H_4Cl, p-C_6H_4OH, p-C_6H_4OCH_3, p-C_6H_4CH_3, p-C_6H_4N(CH_3)_2, \\
p-C_6H_4N(C_2H_5)_2, -furyl, -thiophene. \\
\end{align*}
\]

Reddy et al.\(^{[70]}\) synthesized some novel mono and di-O-prenylated chalcone derivatives (37 and 38). It was found that the compound with 3,4,5-trimethoxy phenyl moiety as substituent exhibited maximum activity.

\[
\begin{align*}
37 \text{ (a-e)} \\
37_a, 38_a & \quad R^1=R^2=R^4=H; R^3=OMe \\
37_b, 38_b & \quad R^1=R^2=OMe; R^3=R^4=H \\
37_c, 38_c & \quad R^1=R^2=R^3=OMe; R^4=H \\
37_d, 38_d & \quad R^1=R^4=H; R^2=R^3=OMe \\
37_e, 38_e & \quad R^1=H; R^2=R^3=R^4=OMe \\
\end{align*}
\]

Bandgar et al.\(^{[71]}\) synthesized some methoxychalcones (39) by Claisen-Schmidt condensation reaction and the compounds were screened for their anti-inflammatory activity. Anti-inflammatory activity of all the synthesized compounds was evaluated in terms of TNF-\(\alpha\) and IL-6 inhibitory activity. It was observed that the compounds having trimethoxy substituents
enhanced the anti-inflammatory activity against TNF-α and IL-6 with 90-100% inhibition at 10 µm concentration.

![Chemical Structure](image)

Bandgar et al.\textsuperscript{[72]} synthesized some novel nitrogen containing chalcones (40) by Mannich reaction and were screened for anti-inflammatory activities such as inhibition of cyclooxygenase-2 (COX-2), trypsin and β-glucuronidase. The chalcones with N-methylpiperazine moiety and piperidinemethyl substitution seems to be important for inhibition of β-glucuronidase, whereas the chalcones with piperidine methyl substitution were observed as effective inhibitors of COX-2.

![Chemical Structure](image)

R = 3-Cl, 3-Br, 3-F, 2-F, 2-Cl, 2-Br

More et al.\textsuperscript{[73]} synthesized a new series of five 1-(2',4'-difluorophenyl)-3-(substituted phenyl)-1,3-propanediones (41) from 2',4'-difluorinated chalcones. All the five compounds synthesized have shown good anti-inflammatory activity in the carrageenan-induced paw edema method. Of all the compounds, the m-bromo substituted compound exhibited highest inhibition i.e.; 93.00%. Conversion of the difluorinated chalcones to difluorinated propanediones seems to provide better protection against inflammation.

![Chemical Structure](image)

R\textsuperscript{1} = H or -NO\textsubscript{2} or -Br; R\textsuperscript{2} = H or -F or -Cl or -OCH\textsubscript{3}
Gaikwad et al.\(^7\) \(^4\) synthesized some novel chalcones of phthalimidoester (42) possessing good anti-inflammatory activity. These compounds have been subjected to preliminary anti-inflammatory screening using the carrageenan-induced rat paw edema model. Compounds with electron releasing groups such as methoxy and hydroxyl showed good anti-inflammatory activity than those which do not have such groups. Compounds having the halogen substituents such as chloro, fluoro and bromo groups also exhibited significant anti-inflammatory activity. These results suggest that the synthesized novel chalcones of phthalimidoester have excellent scope for further development as commercial anti-inflammatory agents.

R= 4-Cl, 4-F, 4-Br, 4-OCH\(_3\), 2-OH, 3-NO\(_2\), 3,4,5-(OCH\(_3\))\(_3\) and 6-Methoxynaphthalene

Heidari et al.\(^7\) \(^5\) synthesized a novel rigid benzofuran-3,4-dihyrophychalcone (43) and its anti-inflammatory effects were evaluated by carrageenan-induced paw edema method. The results showed that the compound induced significant anti-inflammatory effect (p<0.01). Administration of 25 mg/kg of the compound inhibited the inflammation induced by carrageenan, 32.8\% and 41.7\%, 1 and 3 hr after carrageenan injection, respectively. The compound has potential for discovery of a compound with potent anti-inflammatory activity and its scaffold could be used for further structural modifications.

Maria et al.\(^7\) \(^6\) synthesized a series of chalcones (44) prepared by Claisen-Schmidt condensation of appropriate acetophenones with appropriate aldehydes. The compounds were
tested in vivo for anti-inflammatory activity. Almost all the tested compounds possessed high inhibitory activity on lipid peroxidation.

\[
\text{Ar}_1 = \begin{array}{c}
\text{Ar}_2 = \begin{array}{c}
\text{Ar}_1 = \\
\text{Ar}_2 = \\
\end{array}
\end{array}
\]

Ito et al.\cite{77} isolated a reduced chalcone (45) having cyclooxygenase-2 inhibitory activity.

Okunrobo et al.\cite{78} synthesized some chalcones (46) which were evaluated for anti-inflammatory activity at doses of 20, 40 and 80 mg/kg. Anti-inflammatory activity was measured using carrageenan-induced rat paw edema assay. From the results of anti-inflammatory activity, it was observed that the methoxy groups are needed for a faster onset of activity. The activities at 80 mg/kg showed that the bromine atom at position 3 of ring B seems to be necessary for more inhibition of inflammation. From the results obtained, it is evident that the synthesized compounds have increasing activity from third hour to fourth hour.
Shen et al.\textsuperscript{[79]} synthesized a 2'-hydroxy-3,4-dichlorochalcone (47) possessing anti-inflammatory and cancer chemopreventive activity.

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image1.png}
\caption{(47)}
\end{figure}}
\]

Rani et al.\textsuperscript{[80]} synthesized chalcones of indole (48) and were evaluated for their anti-inflammatory activity against carrageenan-induced edema in albino rats at a dose of 50 mg/kg oral. All the compounds of this series showed promising anti-inflammatory activity.

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image2.png}
\caption{(48)}
\end{figure}}
\]

Viana et al.\textsuperscript{[81]} carried out anti-inflammatory activity from a fraction containing three dimeric chalcones (49, 50 and 51) (Chalcone Enriched Fraction-CEF), isolated from the stem-bark ethyl acetate of \textit{Myracrodruon urundeuva}. In the carrageenan-induced paw edema test in
mice, the CEF (20 and 40 mg/kg body wt.) decrease paw volume significantly, after i.p. administration 2-4 hrs after carrageenan injection.

Zhao et al.\textsuperscript{[82]} isolated dihydroxanthohumol (52) from fruits of \textit{Mallotus philippinensis} which showed anti-inflammatory activity.
Herencia et al.\textsuperscript{[83]} synthesized some chalcones and evaluated for their anti-inflammatory activity. A series of 2-chloroquinolinyl chalcones \textbf{(53)} were prepared by condensing aromatic aldehydes and methyl ketones to form the expected compounds, using solid sodium hydroxide as a catalyst in methanol at room temperature. Compounds with 4-methylphenyl, 4-fluorophenyl, 3,5-dimethylfuryl, 4-bromophenyl and 2,4-dichlorophenyl moiety as substituents inhibited degranulation and 5-lipoxygenase in human neutrophils, whereas compound having 3,4-dimethoxyphenyl moiety as substituent behaved as scavenger of superoxide.

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