eISSN 2583-6986
IDEALISTIC JOURNAL OF ADVANCED RESEARCH IN PROGRESSIVE SPECTRUMS (IJARPS)
A MONTHLY, OPEN ACCESS, PEER REVIEWED (REFEREED) INTERNATIONAL JOURNAL
Volume 04, Issue 04, April 2025

Biological Properties, Environmental Applications, Synthesis and Mechanisms of Chalcone Derivatives and Their Heavy Metal Complexes

Dr. Brajesh Singh[1]
[1]Assistant Professor, Chemistry Department Rajkiya P.G. College Musafirkhana, Amethi, U.P.

Received: 15 April 2025 Accepted & Reviewed: 25 April 2025, Published: 30 April 2025

Abstract

Chalcone derivatives have garnered significant attention due to their structural versatility and wide range of biological applications. This research explores the synthesis of chalcone derivatives and their transition metal complexes, focusing on their antimicrobial, antioxidant, anticancer, and environmental properties. Through Claisen–Schmidt condensation and complexation with metals like Cu(II), Ni(II), and Zn(II), novel bioactive compounds were developed. Mechanistic studies reveal interactions with cellular biomolecules and potential applications in medicinal and green chemistry. This work emphasizes the importance of chalcone-based metal complexes in future drug development and sustainable technologies.

Key words: Antimicrobial, Chalcone, Derivatives, Biological activity, Bioavailability

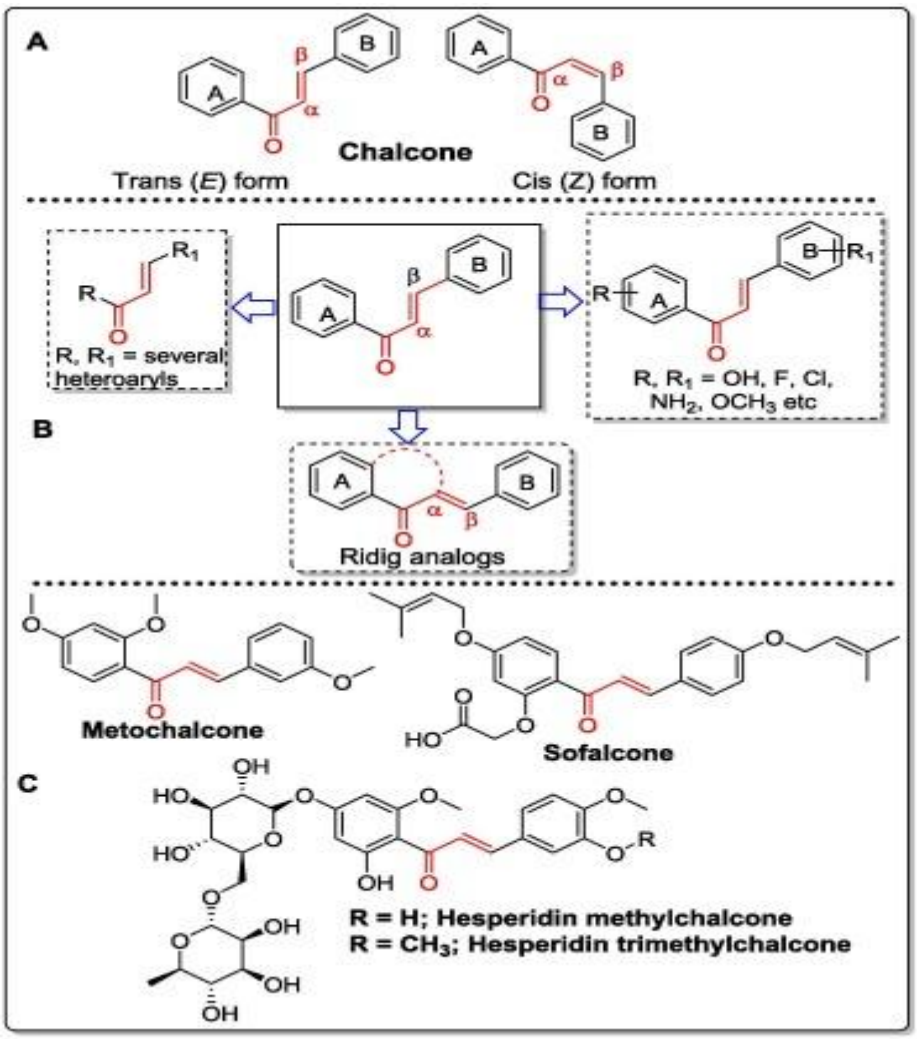
Introduction

Chalcones, chemically recognized as 1,3-diaryl-2-propen-1-ones, are open-chain flavonoids bearing two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system. These compounds are essential intermediates in the biosynthesis of flavonoids and isoflavonoids and have been extensively studied for their diverse pharmacological activities. Due to their conjugated double bonds and reactive enone moiety, chalcones exhibit remarkable biological activities, including antimicrobial, anti-inflammatory, antioxidant, anticancer, and antimalarial effects. Their structural flexibility enables further derivatization and metal coordination, which often enhances their pharmacological profile and stability. The synthesis of chalcone derivatives typically involves the Claisen–Schmidt condensation between an aryl ketone and an aromatic aldehyde under basic or acidic conditions. This reaction yields a variety of substituted chalcones with tailored functional properties. Additionally, the complexation of these chalcone ligands with transition metals like copper, nickel, cobalt, and zinc has been reported to improve biological efficacy, solubility, and bioavailability. These metal complexes may also play critical roles in interacting with biomolecular targets, such as DNA and enzymes, leading to enhanced pharmacological effects.

Moreover, in recent years, the environmental relevance of these compounds has emerged, particularly in catalysis and sensing applications. The coordination chemistry of chalcones opens up possibilities in both medicinal and environmental sectors, establishing their importance in modern chemical research. This study focuses on the synthesis and structural characterization of chalcone derivatives and their metal complexes, as well as an evaluation of their biological properties and underlying mechanisms of action. The paper aims to highlight the potential of these hybrid systems in developing new therapeutic agents and environmentally friendly solutions

Structure of Chalcone

eISSN 2583-6986
IDEALISTIC JOURNAL OF ADVANCED RESEARCH IN PROGRESSIVE SPECTRUMS (IJARPS)
A MONTHLY, OPEN ACCESS, PEER REVIEWED (REFEREED) INTERNATIONAL JOURNAL
Volume 04, Issue 04, April 2025



Simple chalcone derivatives

New derivatives containing chalcone as a central core. Here both phenyl rings were substituted with functional group and showed different inhibitory results. Compound showed the highest potency (drug efflux inhibition: IC_{50} value 0.17 μM) and less toxicity than any other compound in this series. The docking study exhibited a preferable interaction position of chalcone moiety with the amino acid. Amino acid residue formed π-π interaction with phenyl ring of chalcone moiety.

Indole based chalcone

Replacing one phenyl ring of chalcone with an indole ring yielded the new derivatives Indolylphenylpropenone. Substitution of the phenyl ring of indolylphenylpropenone moiety with methoxy group resulted in different inhibitory activity. Surprisingly, the N-methyl-1-indolyl reduced the interactions that suggested the hydrophobic interactions likely to be essential for the binding. having methoxy substitution at the 2nd and 6th positions showed the highest activity than any other compound in this series with an IC_{50} value of 0.27 μM [44].

Bis chalcones

Bis chalcones contain two chalcone groups which are fused with each other. Compound **10** (IC_{50} value 0.20 μM) exhibited better potency. Surprisingly, the proximity of carbonyl group with phenyl ring showed better activity.

eISSN 2583-6986
IDEALISTIC JOURNAL OF ADVANCED RESEARCH IN PROGRESSIVE SPECTRUMS (IJARPS)
A MONTHLY, OPEN ACCESS, PEER REVIEWED (REFEREED) INTERNATIONAL JOURNAL
Volume 04, Issue 04, April 2025

Tariquidar related chalcone

Tariquidar was reported as one of the potent compounds for inhibiting so far but it had less selectivity. Hybridization of tariquidar with chalcone yielded a new compound that showed inhibition in ABCG2 overexpressing MCF-7 cell line, investigated by Scholler . The compound (IC_{50} value 0.88 μM) revealed higher potency . Notably, the insertion of ethylene and triethylene glycol chains at the tetrahydroisoquinoline moiety showed no effect on the IC_{50}

2.Synthesis of Chalcone Derivatives

Chalcone derivatives are generally synthesized using the Claisen–Schmidt condensation reaction, a base- or acid-catalyzed aldol condensation between aromatic aldehydes and ketones. Typically, an equimolar mixture of a substituted acetophenone and a substituted benzaldehyde is stirred in ethanol with sodium hydroxide or potassium hydroxide as the catalyst. This method yields α,β-unsaturated carbonyl compounds as yellow crystalline solids.

For example:

1. 4-methoxyacetophenone + 4-nitrobenzaldehyde → (E)-1-(4-methoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one
2. 2-hydroxyacetophenone + benzaldehyde → (E)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one

Microwave-assisted and ultrasonic methods have also been explored to enhance yield and reduce reaction time. Purification is usually done by recrystallization or column chromatography. These methods provide access to a broad variety of chalcone frameworks with different functional groups, enabling bioactivity tuning.

3. **Synthesis of Heavy Metal Complexes of Chalcones –** Chalcones containing donor atoms like hydroxyl, carbonyl, and amino groups act as excellent ligands, coordinating with transition metal ions to form stable metal complexes. Typically, the synthesized chalcone is dissolved in ethanol and reacted with metal salts (e.g., $CuCl_2$, $Ni(NO_3)_2$, $ZnSO_4$) under reflux.

Example:

$CuCl_2$ + chalcone ligand → $[Cu(chalcone)_2Cl_2]$

The coordination may occur through the carbonyl oxygen and hydroxyl oxygen, forming chelated structures. Characterization of these complexes is done using FTIR, UV-Vis, ^1H NMR, and elemental analysis. These complexes often display enhanced stability and biological activities compared to free chalcones. Metal complexes of chalcones are synthesized by reacting a chalcone ligand with a metal salt in a suitable solvent, often under reflux conditions, and sometimes with the addition of a base to facilitate the reaction. The resulting metal complex is then isolated, purified, and characterized.

4. **Mechanistic Insights into Biological Activities-**

The biological activity of chalcones and their metal complexes stems primarily from their ability to interact with biomolecules such as enzymes, DNA, and proteins. The α,β-unsaturated carbonyl group acts as a Michael acceptor, forming covalent bonds with nucleophilic residues of enzymes.

Metal complexes enhance lipophilicity, facilitating easier passage through cell membranes. Complexes can intercalate into DNA, disrupting replication and transcription. Some metal ions such as Cu(II) also catalyze the generation of reactive oxygen species (ROS), inducing apoptosis in cancer cells. The mechanism varies depending on the metal ion and substitution on the chalcone backbone.

eISSN 2583-6986
IDEALISTIC JOURNAL OF ADVANCED RESEARCH IN PROGRESSIVE SPECTRUMS (IJARPS)
A MONTHLY, OPEN ACCESS, PEER REVIEWED (REFEREED) INTERNATIONAL JOURNAL
Volume 04, Issue 04, April 2025

5. **Biological Activities**

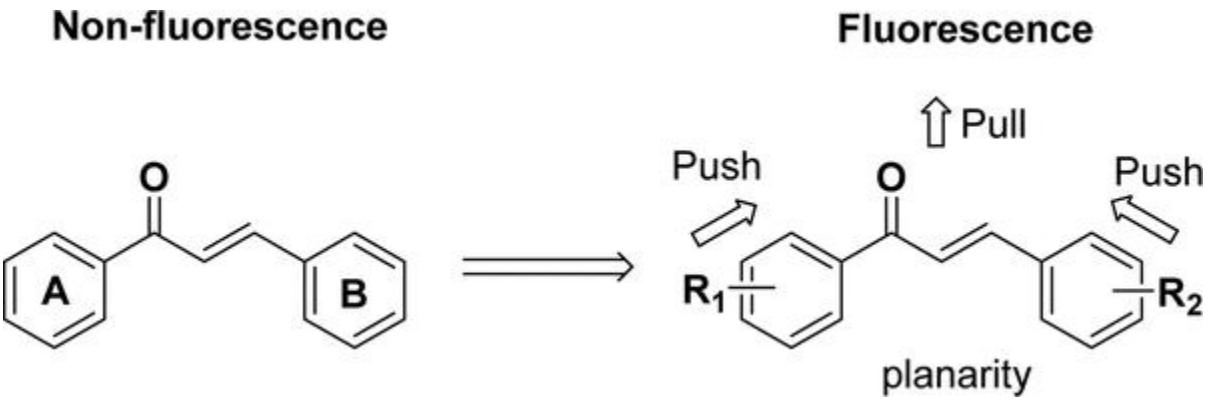
Chalcones and their metal complexes exhibit a broad spectrum of biological activities:
• Antioxidant activity: Due to phenolic groups and conjugated systems scavenging free radicals.
• Antimicrobial activity: Active against Gram-positive and Gram-negative bacteria and fungi. Metal complexes show enhanced activity.
• Anticancer activity: Metal complexes induce apoptosis and inhibit proliferation in cancer cells.
• Anti-inflammatory activity: Inhibition of cyclooxygenase (COX) enzymes and nitric oxide production.
In vitro and in vivo models have confirmed the therapeutic potential of these compounds, especially those coordinated with transition metals like Cu(II), Zn(II), and Ni(II).

6. **Environmental Relevance and Applications**

Apart from medicinal chemistry, chalcone-metal complexes have applications in environmental chemistry:
• Catalysis: Used as catalysts in oxidation and polymerization reactions.
• Sensors: Some complexes act as fluorescent or colorimetric sensors for detecting metal ions or pollutants.
• Antifouling agents: Inhibit the growth of marine organisms on surfaces.
Their tunable redox properties and eco-friendly synthesis routes make them valuable in green chemistry applications.

7. **Fluorescent Properties Of Chalcones**

Because of its conjugated system, chalcones with proper electron-pulling and electron-pushing functional groups on the benzene ring(s) can be fluorescent making them potential chemical probes for mechanistic investigations and imaging/diagnosis.



Electron push–pull pairs for fluorescent chalcones.

As a fluorescent compound, the photophysical parameters, which include the absorption (Abs λ_m) and emission (Emi λ_m) wavelengths, extinction coefficient (ε), and quantum yield (ϕ), are critical for biological applications. The dynamic range of detection is determined by the Abs λ_m and Emi λ_m values. The fluorescence brightness, which is the product of ε and ϕ at the maximum absorption wavelength, is associated with the detection sensitivity. Some nonstructural factors are also critical to the fluorescent intensity, such as the solvents and the biological components/additives.

The dimethylamino group is a widely used substituent in fluorescent probes and has also been introduced into fluorescent chalcone compounds . 4-Dimethylaminochalcone was first reported by Jiang et al. as a fluorescent probe for detecting micelle formation. Very recently, the authors have synthesized a small library of fluorescent chalcones to systematically characterize the structural effects on their intrinsic fluorescence and

eISSN 2583-6986
IDEALISTIC JOURNAL OF ADVANCED RESEARCH IN PROGRESSIVE SPECTRUMS (IJARPS)
A MONTHLY, OPEN ACCESS, PEER REVIEWED (REFEREED) INTERNATIONAL JOURNAL
Volume 04, Issue 04, April 2025

evaluate the influence of several biologically relevant environmental factors. The 4-dimethylaminochalcone compounds exhibited similar-absorptions, with an Abs λ_m between 390 and 460 nm and an Emi λ_m between 450 and 620 nm. The ε and ϕ values were between 28 000 and 38 000 and 0 and 0.40, respectively. Several compounds showed good fluorescence brightness, with values exceeding 6000 M^{-1} cm^{-1}, which is comparable to that of commercial fluorophores (e.g., Cy 3.18–6000 M^{-1} cm^{-1}). A structure–fluorescence relationship (SFR) study demonstrated the following: for the chalcone moiety, the molecular planarity played a critical role in the fluorescence, e.g., introducing a methyl group to the α-position of the unsaturated ketone resulted in the loss of fluorescence; for the A ring, weak electron-donating groups (e.g., a methoxyl group) were favorable to the quantum yield, while electron-withdrawing (e.g., a nitro group) or strong electron-donating (e.g., a dimethylamino group) substituents significantly decreased it; for the B ring, disubstituted amino groups were essential for fluorescence, such as piperidine, piperazine, dimethylamino, and diethylamino groups; and for the α,β-unsaturated ketone system, the extension of the double bond decreased the fluorescence and caused a red shift of the maximum emission wavelength. The fluorescence–environment relationship (FER) showed that the fluorescent intensity of chalcone-based compounds depends highly on the solvent polarity, the pH, and the interactions with proteins or detergents. In aprotic solvents, chalcone's fluorescence decreases as the solvent polarity decreases, although the fluorescence is completely lost in protic solvents, such as water or EtOH, at neutral pH. However, it could be partially recovered by the addition of BSA, Triton-X100, or Tween-20. A similar result was obtained by another study, in which 4′-N,N-dimethylamino-4-methylacryloylamino chalcone (2) containing both electron-withdrawing and electron-donating groups was synthesized as a fluorescent sensor for determining the water content in organic solvents.The fluorescent intensity of compound 2 decreased with an increase in the water concentration in acetone, ethanol, and acetonitrile solutions. Such a sensor was useful for water determination with a low detection limit (<0.01%). The loss of fluorescence in a protonic solvent is potentially due to the formation of hydrogen bonds between the solvent and the nitrogen of chalcone's dialkylamino group, keeping the nitrogen lone pair electrons out of the conjugate system and leading to the nonfluorescent property.

Conclusion

An overview of design, development and structure-activity relationships of various types of chalcones as potential antiplasmodial and antimalarial agents to highlight the approach for the progress of novel anti-malarial agents. Advantaged chalcone derivatives have been generally utilized as an effective strategy in the area of medicinal chemistry for drug innovation. As chalcone derivatives represent a very simple scaffold, it is an easy to explain the structure, whereas new structures are not an easy to recognize. This mini-review covers the progresses of chalcone derivatives counting chloroquinoline-chalcone, triazole linked chalcone, coumarin-chalcone, ferrocenyl-chalcone, diaryl chalcones and various other types of chalcone derivatives as antimalarial agents and potential antiplasmodial. Addition of various functional groups to chalcones may enhance solubility, lipophilicity and oral bioavailability properties inactive analogs. These noteworthy points categorize the huge potential of different chalcone cores in pharmaceutical applications signifying a huge scope for these capable moieties due to their varied molecular targets.

References

[1] M.N. Gomes, E.N. Muratov, M. Pereira, J.C. Peixoto, L.P. Rosseto, P.V.L. Cravo, C.H. Andrade, B.J. Neves, *Molecules*, 2017, *22*, 1210. [CrossRef], [Google Scholar], [Publisher]

[2] P.K.P. Gaitry Chopra, *Int. J. Res. Eng. Appl. Sci.,* 2016, *6*, 173–185. [CrossRef], [Google Scholar]

[3] S.N.A. Bukhari, M. Jasamai, I. Jantan, W. Ahmad, *Mini-Rev. Org. Chem.*, 2013, *10*, 73–83. [Google Scholar], [Publisher]

[4] C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing, Z. Miao, *Chem. Rev*., 2017, *117*, 7762–7810. [CrossRef], [Google Scholar], [Publisher]

[5] S. Syam, S.I. Abdelwahab, M.A. Al-Mamary, S. Mohan, *Molecules*., 2012, *17*, 6179–6195. [CrossRef], [Google Scholar], [Publisher]

[6] S. Sumathi, P. Tharmaraj, C.D. Sheela, R. Ebenezer, *J. Coord. Chem.,* 2011, *64*, 1707–1717. [CrossRef], [Google Scholar], [Publisher]

[7] A.K.A. Hussien, B.A. Kateb, P.A. Kulkarni, *Res. J. Recent Sci*., 2017, *6*, 11–21. [Google Scholar], [Publisher]

[8] S. Tabti, A. Djedouani, D. Aggoun, I. Warad, S. Rahmouni, S. Romdhane, H. Fouzi, *J. Mol. Struct*., 2018, 1155, 11–20. [CrossRef], [Google Scholar], [Publisher]

[9] U.M. Kocyigit, Y. Budak, M.B. Gürdere, F. Ertürk, B. Yencilek, P. Taslimi, M. Ceylan, *Arch. Physiol. Biochem*., 2018, *124*, 61–68. [CrossRef], [Google Scholar], [Publisher]

[10] A.T. Bale, K.M. Khan, U. Salar, S. Chigurupati, T. Fasina, F. Ali, S. Perveen, *Bioorg. Chem*., 2018, *79*, 179–189. [CrossRef], [Google Scholar], [Publisher]

[11] S. Khatua, S. Ghosh, K. Acharya, *Asian J. Pharm.*, 2017, *11*, S327–S335. [CrossRef], [Google Scholar], [Publisher]

[12] H.L. Hergert, E.F. Kurth, *J. Am. Chem. Soc*., 1953, *75*, 1622–1625. [CrossRef], [Google Scholar], [Publisher]

[13] D.N. Dhar, V.P. Gupta, *Indian J. Chem.*, 1971, *9*, 818. [Google Scholar]

[14] T.J. Mabry, K.R. Markham, M.B. Thomas, *The Ultraviolet Spectra of Flavones and Flavonols*, Springer, New York. 1970, 267, pp. 41–164. [CrossRef], [Google Scholar], [Publisher]

[15] K. Nakamoto, *Infrared and Raman spectra of inorganic and coordination compounds, part B: applications in coordination, organometallic, and bioinorganic chemistry*, John Wiley & Sons: *New York,* 2009. [Google Scholar]

[16] C.M. Sharaby, *Spectrochim. Acta A. Mol. Biomol. Spectrosc*., 2007, *66*, 1271–1278. [CrossRef], [Google Scholar], [Publisher]

[17] A. Kulkarni, P.G. Avaji, G.B. Bagihalli, S.A. Patil, P.S. Badami, *J. Coord. Chem*., 2009, *62*, 481–492. [CrossRef], [Google Scholar], [Publisher]

[18] T.S.R. Rao, K.L. Reddy, P. Lingaiah, *J. Chem. Sci*., 1988, *100*, 363–373. [CrossRef], [Google Scholar], [Publisher]

[19] P.B. Chakrawarthi, *J. Indian Chem. Soc*., 2001, *78*, 273. [Google Scholar]

[20] C.D. Sheela, C. Anitha, P. Tharmaraj, D. Kodimunthri, *J. Coord. Chem*., 2010, *63*, 884–893. [CrossRef], [Google Scholar], [Publisher]

[21] N. Raman, A. Kulandaisamy, C. Thangaraja, P. Manisankar, S. Viswanathan, C. Vedhi, *Transit. Met. Chem*., 2004, *29*, 129–135. [CrossRef], [Google Scholar], [Publisher]