

REVIEW ARTICLE

A Review on Chalcones as Versatile Scaffolds in Drug Discovery and Development



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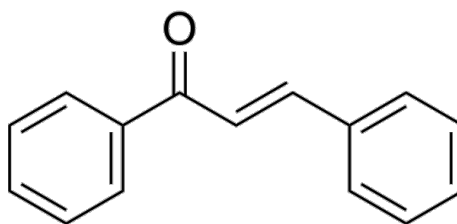
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Abstract: Chalcones are a unique class of organic compounds characterized by their 1,3-diphenyl-2-propen-1-one structure, which serves as a crucial pharmacophore in medicinal chemistry. The inherent flexibility of the chalcone structure enables diverse biological activities, making them valuable leads in drug development. Recent advances in chalcone-based therapeutic agents demonstrate their potential in treating various pathological conditions, including cancer, inflammation, microbial infections, and neurodegenerative disorders. The α,β -unsaturated carbonyl system of chalcones facilitates multiple interaction patterns with biological targets, contributing to their broad spectrum of pharmacological effects. Molecular modification strategies applied to the basic chalcone scaffold have yielded numerous derivatives with enhanced potency and improved therapeutic profiles. The incorporation of heterocyclic moieties and various substituents on both aromatic rings has led to the development of novel drug candidates with optimized pharmacokinetic properties. Modern synthetic approaches, structure-activity relationships, and molecular mechanisms underlying the therapeutic effects of chalcones continue to expand their applications in pharmaceutical research. The advent of hybrid molecules incorporating chalcone pharmacophores presents promising directions for developing more effective therapeutic agents.

Keywords: Chalcones; Drug discovery; Molecular modifications; Pharmacological activities; Structure-activity relationship

1. Introduction

Chalcones, belonging to the flavonoid family, represent an essential class of naturally occurring compounds with a fundamental C6-C3-C6 skeleton [1]. The basic structural framework consists of two aromatic rings (A and B) connected by an α,β -unsaturated carbonyl system, forming a unique three-carbon α,β -unsaturated carbonyl system [2]. The presence of this distinctive structural feature contributes significantly to their chemical reactivity and biological properties [3]. Historical records indicate that chalcones were first isolated from natural sources, particularly from various plant species, where they serve as precursors in flavonoid biosynthesis [4]. Their presence in traditional medicine systems across different cultures highlighted their therapeutic potential, leading to increased scientific interest in their pharmaceutical applications [5]. The chalcone structure comprises two aromatic rings designated as A and B, linked by a three-carbon α,β -unsaturated carbonyl system [6]. This structural arrangement allows for extensive conjugation, resulting in unique electronic properties and reactivity patterns [7].



Structure 1. Chalcone

Chalcones exhibit distinctive physicochemical properties that influence their biological activities. The presence of the α,β -unsaturated carbonyl group provides sites for nucleophilic addition reactions, while the aromatic rings offer opportunities for various substitution patterns [8]. Most chalcones display poor water solubility but demonstrate good lipophilicity, affecting their absorption and distribution properties [9].

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Table 1. Natural Chalcones and Their Sources

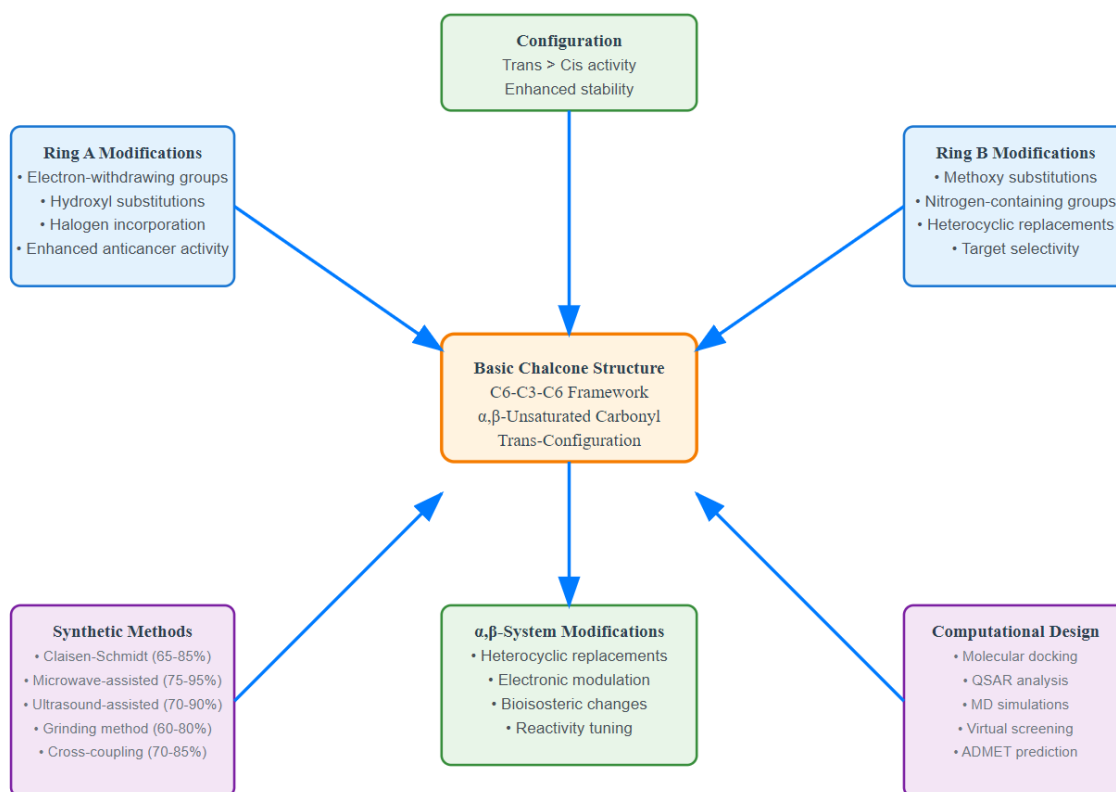
Compound Name	Plant Source	Family	Major Biological Activities
Xanthohumol	<i>Humulus lupulus</i>	Cannabaceae	Anticancer, Anti-inflammatory
Butein	<i>Butea monosperma</i>	Fabaceae	Antioxidant, Anti-inflammatory
Licochalcone A	<i>Glycyrrhiza inflata</i>	Fabaceae	Antimicrobial, Anticancer
Phloretin	<i>Malus domestica</i>	Rosaceae	Antidiabetic, Antioxidant
Isoliquiritigenin	<i>Glycyrrhiza glabra</i>	Fabaceae	Cardioprotective, Anti-inflammatory
Cardamonin	<i>Alpinia katsumadai</i>	Zingiberaceae	Antiplatelet, Anti-inflammatory

2. Structural Activity Relationship

2.1. Role of Substituents

The nature and position of substituents on both aromatic rings significantly influence the biological activities of chalcones [10]. The strategic placement of various functional groups fundamentally alters the molecular properties, including lipophilicity, hydrogen bonding capacity, and overall molecular geometry, which directly correlates with their pharmacological efficacy. Electron-donating groups such as hydroxyl, methoxy, and amino substituents enhance electron density on the aromatic rings, facilitating stronger interactions with nucleophilic sites on biological targets. These groups particularly improve antioxidant activities by stabilizing phenoxyl radicals formed during oxidative processes. Conversely, electron-withdrawing substituents including nitro, halogen, and carbonyl groups decrease electron density, often enhancing electrophilic character and improving antimicrobial properties through increased membrane penetration capabilities.

Electron-donating and electron-withdrawing groups modify the electronic distribution, affecting their interaction with biological targets [11]. The positioning of hydroxyl groups on ring A, particularly at the 2' and 4' positions, creates optimal geometric arrangements for chelation with metal ions and hydrogen bonding with amino acid residues in protein active sites. Multiple hydroxyl substitutions can lead to catechol or pyrogallol moieties, which significantly enhance radical scavenging activities but may also increase susceptibility to metabolic degradation. Methoxy groups provide a balance between hydrophilic and lipophilic properties, often improving bioavailability while maintaining favorable interaction profiles with biological membranes.

**Figure 1. Structure-Activity Relationship and Synthetic Techniques for Chalcone Derivatives**

The introduction of halogen substituents, particularly fluorine and chlorine, enhances lipophilicity and metabolic stability while potentially improving binding affinity through halogen bonding interactions. Fluorine substitution offers unique advantages due to its high electronegativity and small van der Waals radius, often leading to improved pharmacokinetic properties without significantly altering molecular geometry. Ring B modifications frequently involve the incorporation of nitrogen-containing heterocycles, which can act as hydrogen bond acceptors and provide additional sites for specific receptor interactions. The presence of amino groups enables the formation of ionic interactions with negatively charged residues, while also serving as sites for further chemical modifications to optimize therapeutic profiles.

2.2. Importance of Configuration

The trans-configuration of the double bond in chalcones plays a crucial role in their biological activities, with studies indicating superior activity compared to their cis-counterparts [12]. This geometric preference stems from several fundamental molecular factors that influence both the stability and bioactivity of chalcone compounds. The trans-configuration provides optimal spatial arrangement of the aromatic rings, allowing for extended conjugation across the α,β -unsaturated carbonyl system. This extended conjugation stabilizes the molecule through delocalization of π -electrons and creates a more planar structure that facilitates better binding interactions with biological targets.

The planar geometry of trans-chalcones enables effective π - π stacking interactions with aromatic amino acids in protein binding sites, particularly with phenylalanine, tryptophan, and tyrosine residues. This planar arrangement also optimizes the distance between the two aromatic rings, typically ranging from 12-14 Å, which corresponds well with the binding pocket dimensions of many enzymatic targets. The trans-configuration positions the carbonyl oxygen and the β -carbon in favorable orientations for nucleophilic attack by cellular nucleophiles, including cysteine thiols and lysine amino groups, which is essential for the covalent modification of target proteins.

Moreover, the trans-isomers demonstrate superior photostability compared to their cis-counterparts, which is crucial for pharmaceutical applications requiring long-term storage and consistent bioactivity. The energy barrier for cis-trans isomerization is sufficiently high under physiological conditions, ensuring that the active trans-configuration is maintained during biological interactions. Molecular dynamics studies have revealed that trans-chalcones exhibit more favorable binding conformations and lower binding free energies when interacting with various biological targets, including enzymes involved in inflammatory cascades and cancer cell proliferation pathways. The geometric constraints imposed by the trans-configuration also influence the accessibility of the α,β -unsaturated system to enzymatic metabolism, often resulting in improved metabolic stability and prolonged biological half-lives.

Table 2. Structure-Activity Relationships of Chalcone Derivatives

Structural Modification	Position	Effect on Activity	Target Activity
Hydroxyl group	Ring A (2')	Enhanced	Antioxidant
Methoxy group	Ring B (4)	Improved	Anticancer
Halogen	Ring A (3',4')	Increased	Antimicrobial
Amino group	Ring B (4)	Enhanced	Anti-inflammatory
Nitro group	Ring A (4')	Improved	Antitumor
Heterocyclic substitution	Ring B	Enhanced	Multiple activities

3. Pharmacological Activities

3.1. Anticancer Properties

Chalcones demonstrate significant anticancer potential through multiple mechanisms [13]. The multifaceted approach of chalcones in cancer therapy involves intricate molecular interactions that target fundamental cellular processes essential for malignant transformation and tumor progression. The α,β -unsaturated carbonyl system serves as a critical pharmacophore that enables Michael addition reactions with nucleophilic residues in key regulatory proteins, effectively disrupting oncogenic signaling cascades. This electrophilic nature allows chalcones to form covalent bonds with cysteine residues in proteins such as tubulin, topoisomerases, and various kinases involved in cell cycle regulation.

Their cytotoxic effects against various cancer cell lines manifest through several interconnected pathways. The selectivity of chalcones toward cancer cells often results from the altered metabolic environment in malignant tissues, including elevated reactive oxygen species levels, modified pH conditions, and upregulated specific enzyme systems. Studies have revealed that chalcones effectively induce apoptosis through mitochondrial pathway activation, leading to programmed cell death in cancer cells. This intrinsic apoptotic pathway involves the release of cytochrome c from mitochondria, subsequent activation of caspase-9 and caspase-3, and ultimately DNA fragmentation. The mitochondrial membrane depolarization triggered by chalcones also disrupts ATP synthesis, compromising the energy-dependent survival mechanisms of rapidly proliferating cancer cells.

The compounds exhibit remarkable ability to inhibit cell cycle progression, particularly at G2/M phase, preventing uncontrolled cellular proliferation. This cell cycle arrest occurs through the inhibition of cyclin-dependent kinases, particularly CDK1/cyclin B complex, which is essential for mitotic entry. Chalcones also interfere with DNA repair mechanisms, causing accumulation of DNA damage that triggers checkpoint responses and prevents cells from progressing through critical cell cycle transitions. The disruption of microtubule dynamics by chalcones further contributes to mitotic arrest, as proper spindle formation becomes compromised, leading to chromosomal instability and eventual cell death.

Moreover, chalcones actively modulate various signal transduction pathways crucial for cancer cell survival and proliferation. The PI3K/Akt pathway, frequently hyperactivated in cancer, is significantly inhibited by various chalcone derivatives, leading to reduced cell survival signals and enhanced sensitivity to apoptotic stimuli. The MAPK signaling cascades, including ERK, JNK, and p38 pathways, are also modulated by chalcones, affecting cell proliferation, differentiation, and stress responses. Additionally, chalcones influence the p53 tumor suppressor pathway, enhancing its transcriptional activity and promoting the expression of pro-apoptotic genes while simultaneously inhibiting anti-apoptotic factors such as Bcl-2 and survivin.

Their anti-angiogenic properties have been well-documented, showing significant inhibition of new blood vessel formation, thereby limiting tumor growth and metastasis [14, 15]. The anti-angiogenic effects involve multiple mechanisms, including the inhibition of vascular endothelial growth factor (VEGF) expression and signaling, disruption of endothelial cell migration and tube formation, and interference with matrix metalloproteinase activities essential for vascular remodeling. Chalcones also suppress hypoxia-inducible factor-1 α (HIF-1 α) expression, a key transcription factor that promotes angiogenesis under hypoxic conditions commonly found in solid tumors. The inhibition of angiogenesis not only limits primary tumor growth but also significantly reduces the potential for metastatic spread by restricting the vascular supply necessary for tumor cell dissemination.

3.2. Anti-inflammatory Activity

The anti-inflammatory effects of chalcones operate through multiple cellular and molecular mechanisms [16]. The comprehensive anti-inflammatory profile of chalcones encompasses both acute and chronic inflammatory responses, involving modulation of various inflammatory mediators, cellular signaling pathways, and immune cell functions. The molecular basis of their anti-inflammatory activity lies in their ability to interact with multiple targets simultaneously, creating a synergistic effect that addresses inflammation at various levels of the inflammatory cascade.

Research has established their potent ability to inhibit pro-inflammatory mediators, including cyclooxygenase-2 and lipoxygenase enzymes. The selective inhibition of COX-2 over COX-1 by certain chalcone derivatives provides anti-inflammatory benefits while minimizing gastrointestinal side effects associated with non-selective COX inhibition. The mechanism involves competitive binding to the enzyme's active site, where the chalcone structure mimics natural substrates while forming stable complexes that prevent arachidonic acid conversion to prostaglandins. Similarly, lipoxygenase inhibition reduces the production of leukotrienes, potent inflammatory mediators involved in asthma, allergic reactions, and various inflammatory conditions.

Chalcones effectively suppress the NF- κ B signaling pathway, a major regulator of inflammatory responses. This suppression occurs through multiple mechanisms, including the inhibition of I κ B kinase (IKK) complex activation, prevention of I κ B α degradation, and direct interference with NF- κ B DNA binding activity. The chalcone-mediated inhibition of NF- κ B translocation to the nucleus effectively blocks the transcription of numerous pro-inflammatory genes, including those encoding cytokines, chemokines, adhesion molecules, and inflammatory enzymes. This upstream intervention in the inflammatory cascade provides broad-spectrum anti-inflammatory effects with potential applications in treating chronic inflammatory diseases.

Additionally, these compounds demonstrate significant capacity to reduce the production of various inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, thereby attenuating inflammatory responses in multiple tissue types [17]. The cytokine modulation by chalcones involves both transcriptional and post-transcriptional mechanisms, including the stabilization of anti-inflammatory microRNAs and the destabilization of pro-inflammatory mRNA transcripts. Chalcones also influence the balance between pro-inflammatory M1 and anti-inflammatory M2 macrophage phenotypes, promoting the latter through modulation of specific transcription factors and metabolic pathways. The reduction in inflammatory cytokine production leads to decreased recruitment and activation of inflammatory cells, reduced tissue damage, and enhanced resolution of inflammatory responses.

3.3. Antimicrobial Activity

Chalcones exhibit broad-spectrum antimicrobial activities against numerous pathogenic organisms [18]. The antimicrobial efficacy of chalcones stems from their unique structural features that enable multiple modes of action against diverse microbial targets. The lipophilic nature of most chalcone derivatives facilitates their penetration through microbial cell membranes, while the reactive α,β -unsaturated carbonyl system provides sites for covalent interactions with essential microbial proteins and enzymes. This dual capability of membrane penetration and protein modification contributes to their effectiveness against both rapidly dividing and dormant microbial populations.

Their effectiveness extends to both Gram-positive and Gram-negative bacterial strains, with particular potency against resistant strains. The broad-spectrum activity against Gram-positive bacteria involves disruption of peptidoglycan synthesis and interference with essential metabolic pathways, while activity against Gram-negative bacteria requires additional mechanisms to overcome the outer membrane barrier. Chalcones have demonstrated remarkable efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), and extended-spectrum β -lactamase (ESBL) producing bacteria, suggesting their potential as alternatives to conventional antibiotics in treating multidrug-resistant infections.

Significant antifungal properties have been observed against various pathogenic fungi, including *Candida* species. The antifungal mechanism involves disruption of ergosterol biosynthesis, a critical component of fungal cell membranes, through inhibition of key enzymes in the sterol synthesis pathway. Chalcones also interfere with fungal cell wall chitin and glucan synthesis, compromising structural integrity and leading to osmotic instability. The activity against biofilm-forming *Candida* species is particularly noteworthy, as these structures represent significant challenges in clinical treatment due to their enhanced resistance to conventional antifungal agents.

Studies have also shown antimycobacterial activity, particularly against *Mycobacterium tuberculosis* strains. This activity is especially significant given the emergence of multidrug-resistant and extensively drug-resistant tuberculosis strains worldwide. The antimycobacterial effects involve inhibition of mycolic acid synthesis, disruption of the unique mycobacterial cell wall structure, and interference with essential metabolic pathways specific to mycobacteria. Some chalcone derivatives have shown activity against dormant mycobacterial populations, which are typically resistant to conventional anti-tuberculosis drugs and represent a major challenge in achieving complete bacterial eradication.

The primary mechanism of antimicrobial action involves disruption of cell membrane integrity and interference with essential microbial enzymatic systems, leading to cell death. The membrane disruption occurs through interaction with phospholipid bilayers, leading to increased permeability, ion leakage, and eventual cell lysis. Enzymatic interference includes inhibition of DNA gyrase, RNA polymerase, and various metabolic enzymes essential for microbial survival and replication. These compounds also show synergistic effects when combined with conventional antibiotics, enhancing their therapeutic potential [19]. The synergistic interactions often involve complementary mechanisms of action, such as chalcone-mediated enhancement of antibiotic penetration through compromised cell membranes or simultaneous targeting of different cellular processes, leading to improved therapeutic outcomes and reduced likelihood of resistance development.

Table 3. Pharmacological Activities of Chalcones Against Various Cancer Cell Lines

Cell Line	Cancer Type	IC50 Range (μ M)	Mechanism of Action
MCF-7	Breast	0.5-25	Apoptosis induction
HeLa	Cervical	1-30	Cell cycle arrest
A549	Lung	2-40	MAPK pathway inhibition
PC-3	Prostate	1-35	Antiproliferative
HepG2	Liver	3-45	ROS generation

4. Structure-Based Drug Design

4.1. Computational Approaches

Modern computational methods have revolutionized chalcone-based drug design [20]. Molecular docking studies reveal crucial binding interactions between chalcones and their molecular targets, enabling rational design of more potent derivatives. Quantitative structure-activity relationship (QSAR) analyses provide valuable insights into structural features essential for biological activity, guiding synthetic strategies for optimized compounds [21]. Advanced molecular dynamics simulations further elucidate the dynamic interactions between chalcones and their biological targets, offering detailed mechanistic understanding at the atomic level [22].

4.2. Chemical Modifications

4.2.1. Ring A Modifications

Modifications on ring A significantly influence the biological profile of chalcones [23]. Introduction of electron-withdrawing groups, particularly at positions 2' and 4', often enhances anticancer activity. Hydroxyl substitutions at specific positions improve antioxidant properties, while halogen incorporation frequently leads to enhanced antimicrobial effects [24].

4.2.2. Ring B Modifications

Ring B modifications play a crucial role in determining target selectivity [25]. Methoxy substitutions often improve bioavailability and membrane permeability. The presence of nitrogen-containing substituents frequently enhances binding to specific cellular targets, while strategic placement of hydroxyl groups can optimize hydrogen bonding interactions [26].

Table 4. Synthetic Methods for Chalcone Production

Method	Reaction Conditions	Yield (%)	Advantages	Limitations
Claisen-Schmidt condensation	Base catalysis, RT	65-85	Simple, cost-effective	Side reactions
Microwave-assisted	300-800W, 2-10 min	75-95	Rapid, efficient	Scale limitations
Ultrasound-assisted	25-35 kHz, 30-60 min	70-90	High purity	Equipment cost
Grinding method	Solvent-free, RT	60-80	Environmentally friendly	Limited scope
Cross-coupling	Pd catalyst, 60-80°C	70-85	Selective	Expensive catalyst

4.2.3. α,β -Unsaturated Carbonyl System Modifications

Alterations to the α,β -unsaturated carbonyl system profoundly affect biological activity [27]. Introduction of heterocyclic rings in place of traditional phenyl groups often leads to improved pharmacological profiles. Modifications of the electronic nature of the enone system through various substitution patterns can modulate reactivity and biological activities [28]

Table 5. Novel Drug Delivery Systems for Chalcone-Based Compounds

Delivery System	Advantages	Features	Application
Polymeric nanoparticles	Enhanced bioavailability	Controlled release	Cancer therapy
Liposomes	Improved stability	Targeted delivery	Anti-inflammatory
Cyclodextrin complexes	Better solubility	Enhanced absorption	Multiple uses
Solid lipid nanoparticles	Reduced toxicity	Sustained release	Antimicrobial
PLGA microspheres	Extended half-life	Biodegradable	Cancer therapy

5. Conclusion

Chalcones remain at the forefront of drug discovery efforts, offering universal scaffold core for developing therapeutic agents. Their diverse biological activities, coupled with the potential for structural modifications, position them as valuable leads in pharmaceutical research. Continued advances in synthetic methodologies, understanding of structure-activity relationships, and development of innovative delivery systems enhance their therapeutic potential. The emergence of hybrid molecules and novel formulation strategies opens new avenues for chalcone-based drug development. Despite challenges, ongoing research continues to unveil new applications and improved derivatives, affirming their significance in medicinal chemistry and drug development.

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