A Review of Chalcones: Synthesis, Reactions, And Biological Importance

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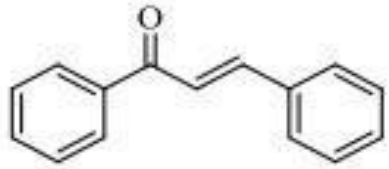
***Abstract*—Chalcones are an important class of open-chain flavonoids characterized by an α, β-unsaturated carbonyl system linking two aromatic rings. Due to their simple structure, synthetic accessibility, and remarkable biological profile, chalcones have attracted considerable attention in medicinal and synthetic organic chemistry. This review highlights classical and modern synthetic approaches for chalcone preparation, including Claisen–Schmidt condensation, coupling reactions, green methodologies, microwave-assisted synthesis, and solid-acid catalysis. Additionally, various chemical transformations of chalcones leading to five-, six-, and seven-membered heterocyclic systems are discussed. Furthermore, their diverse biological activities such as antimicrobial, anticancer, anti-inflammatory, antioxidant, ant diabetic, antihypertensive, antimalarial, and other pharmacological properties are summarized with representative examples.**

***Index Terms*—Chalcones; Claisen–Schmidt condensation; Heterocyclic synthesis; α, β-Unsaturated ketones; Biological activity**

I. INTRODUCTION

Chalcone is a naturally occurring aromatic ketone belonging to the flavonoid family and represents one of the most fundamental building blocks in natural product chemistry. Structurally, chalcones are characterized by the presence of two aromatic rings, commonly designated as ring A and ring B, which are linked through a three-carbon α, β-unsaturated carbonyl system. This enone linkage (–CO–CH=CH–) is responsible for the distinctive chemical reactivity and biological profile of chalcones. The IUPAC name of the parent chalcone is (E)-1,3-diphenylprop-2-en-1-one, where the "E" configuration denotes the trans arrangement of the aryl groups across the double bond, contributing to greater thermodynamic stability and planarity.

Chalcones are widely distributed in nature and are biosynthesized through the polyketide pathway in plants. They occur abundantly in edible fruits, vegetables, spices, tea, soy products, and various medicinal herbs. Many naturally occurring chalcones exhibit pigmentation properties and contribute to plant defense mechanisms against pathogens, ultraviolet radiation, and herbivores. In biological systems, chalcones serve as key biosynthetic precursors for several important flavonoid subclasses, including flavones, flavanones, isoflavones, and aurones. Through enzymatic cyclization and oxidative transformations, the open-chain chalcone framework can be converted into these heterocyclic flavonoid structures, highlighting its central role in plant secondary metabolism.



The IUPAC name of the parent chalcone is:
(E)-1,3-diphenylprop-2-en-1-one

Chalcones occur widely in edible plants, spices, tea, and medicinal herbs. They serve as precursors for flavones, flavanones, aurones, and other heterocyclic compounds.

Structural Features:

- Conjugated double bond (–CH=CH–)
- Carbonyl group (–CO–)
- Planar molecular framework
- High electrophilicity at β-carbon

From a structural perspective, several features account for the versatility of chalcones in chemistry and pharmacology. The conjugated double bond (–CH=CH–) in combination with the carbonyl group (–

CO–) forms a highly conjugated π-electron system. This extended conjugation stabilizes the molecule and enables efficient electron delocalization across the entire framework, often resulting in strong UV-visible absorption properties. The planar molecular geometry arising from conjugation enhances π–π stacking interactions with biological macromolecules such as DNA and proteins, which is particularly relevant in drug–target binding.

A defining characteristic of chalcones is the high electrophilicity of the β-carbon in the α,βunsaturated carbonyl system. This electrophilic center readily undergoes Michael addition reactions with nucleophiles such as thiols, amines, and enolates. In biological contexts, this property allows chalcones to interact with nucleophilic residues in enzymes and regulatory proteins, modulating signaling pathways and enzymatic activity. While this reactivity underlies many of their therapeutic effects, it also requires careful structural optimization to balance potency and selectivity.

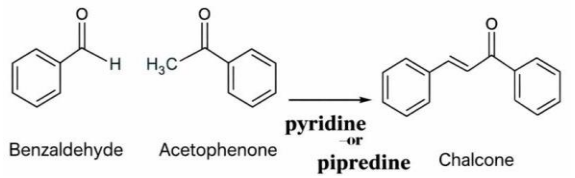
The presence of two aromatic rings provides extensive opportunities for structural modification. Substituents such as hydroxyl, methoxy, halogen, nitro, and amino groups can be introduced at various positions on rings A and B, significantly influencing electronic distribution, lipophilicity, hydrogen-bonding capacity, and metabolic stability. These substitutions directly affect biological activity, making chalcones highly adaptable scaffolds in structure–activity relationship (SAR) studies.

Due to their simple synthetic accessibility, chemical flexibility, and broad spectrum of pharmacological activities including antimicrobial, anticancer, anti-inflammatory, antioxidant, antidiabetic, and antihypertensive effects chalcones are considered valuable pharmacophores in medicinal chemistry. Their open-chain structure also makes them versatile intermediates in organic synthesis, enabling the preparation of diverse heterocyclic systems such as pyrazolines, isoxazoles, pyrimidines, and benzodiazepines. Consequently, chalcones continue to attract significant interest as both synthetic intermediates and promising lead compounds in modern drug discovery research.

II. SYNTHESIS OF CHALCONES

2.1 Claisen–Schmidt Condensation

The Claisen–Schmidt condensation is the most widely employed and classical method for the synthesis of chalcones. It is a crossed aldol condensation between an aromatic aldehyde (lacking α-hydrogen) and an aromatic ketone (containing α-hydrogen) in the presence of a base. This reaction efficiently generates α,β-unsaturated carbonyl compounds, particularly chalcones, through carbon–carbon bond formation followed by dehydration.



The reaction proceeds via three fundamental steps

- Enolate Formation:

The base abstracts the acidic α-hydrogen from the ketone to generate a resonance-stabilized enolate ion.

- Nucleophilic Addition (Aldol Step):

The enolate attacks the carbonyl carbon of the aromatic aldehyde, forming a β-hydroxy ketone (aldol product).

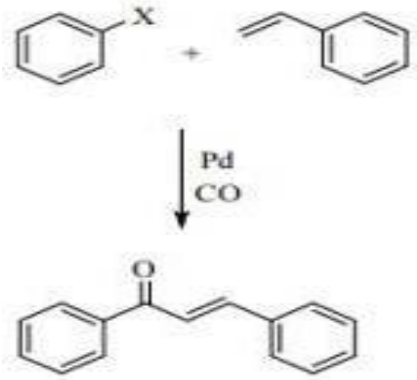
- Dehydration:

Under basic conditions, elimination of water occurs, yielding the conjugated α,β-unsaturated ketone (chalcone). The trans (E) isomer is predominantly formed due to its higher thermodynamic stability.

2.2 Coupling Reactions

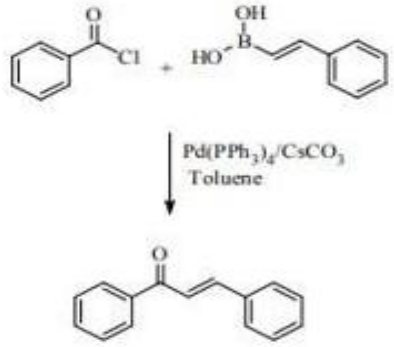
2.2.1 Carbonylative Heck Reaction

The carbonylative Heck reaction represents an advanced palladium-catalyzed methodology for the synthesis of chalcone derivatives through a carbonyl insertion strategy. Unlike the classical Heck reaction, which involves direct coupling between an aryl halide and an alkene, the carbonylative variant introduces carbon monoxide (CO) into the catalytic cycle, enabling the formation of α,βunsaturated ketones such as chalcones in a single synthetic operation.



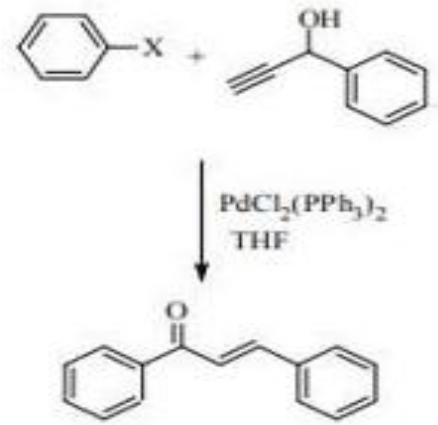
2.2.2 Suzuki–Miyaura Coupling

The Suzuki–Miyaura coupling is a powerful palladium-catalyzed cross-coupling reaction widely used for constructing carbon–carbon bonds between aryl or vinyl boronic acids and aryl or vinyl halides. In chalcone synthesis, this methodology provides an alternative and highly versatile approach, especially when traditional condensation reactions are unsuitable due to substrate sensitivity.



2.3 Sonogashira Isomerization

The Sonogashira isomerization strategy represents a modern and versatile approach for the synthesis of substituted chalcones through a two-step sequence involving carbon–carbon bond formation and subsequent double-bond rearrangement. This methodology is particularly valuable for preparing structurally complex or highly substituted chalcones that may be difficult to access via classical aldol condensation.



Step 1: Sonogashira Coupling: An aryl halide (Ar–X) reacts with a terminal alkyne (such as phenylacetylene or substituted acetylenes) in the presence of a palladium catalyst ($Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$), a copper(I) co-catalyst (CuI), and an amine base (e.g., triethylamine). This step generates an aryl-substituted alkyne.

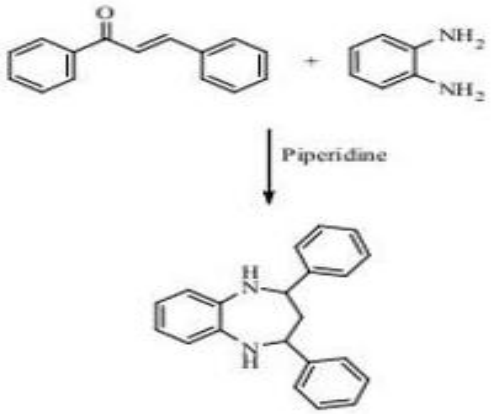
Step 2: Carbonyl Introduction and Isomerization: The coupled alkyne is converted into an alkynone intermediate (Ar–CO–C≡C–Ar′), which upon base- or metal-catalyzed isomerization rearranges into the corresponding α,β-unsaturated ketone (chalcone).

III. REACTIONS OF CHALCONES

Chalcones are highly reactive due to the electrophilic β-carbon.

3.1 Synthesis of Seven-Membered Heterocycles

The transformation of chalcones into seven-membered heterocycles represents an important synthetic application of the α,β-unsaturated carbonyl system. Among these, the synthesis of benzodiazepines through the reaction of chalcones with o-phenylenediamine is one of the most significant and widely studied conversions. This reaction provides access to 1,4-benzodiazepine frameworks, which are pharmacologically important scaffolds in medicinal chemistry.



- Michael Addition:

One of the amino groups of *o*-phenylenediamine attacks the electrophilic β-carbon of the chalcone via a Michael addition, forming a β-amino ketone intermediate.

- Intramolecular Condensation:

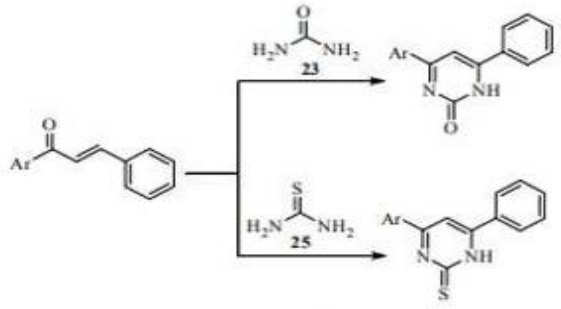
The second amino group reacts with the carbonyl carbon, leading to intramolecular cyclization and formation of a seven-membered ring.

- Dehydration and Rearrangement:

Elimination of water and stabilization of the conjugated system produce the final benzodiazepine derivative.

3.2 Synthesis of Six-Membered Heterocycles

Chalcones serve as versatile precursors for the synthesis of six-membered nitrogen-containing heterocycles, particularly pyrimidine derivatives. The reaction of chalcones with urea or thiourea is a well-established cyclocondensation method that leads to the formation of substituted pyrimidine or pyrimidinethione systems. This transformation highlights the synthetic importance
of the α,β-unsaturated carbonyl functionality present in chalcones.



The transformation proceeds through a multi-step sequence involving nucleophilic addition and intramolecular cyclization:

1. Michael Addition:

The nucleophilic nitrogen of urea or thiourea attacks the electrophilic β-carbon of the chalcone via a Michael addition, forming a β-amino carbonyl intermediate.

2. Cyclization:

The second nucleophilic site (another –NH group) attacks the carbonyl carbon, resulting in ring closure to generate a six-membered dihydropyrimidine intermediate.

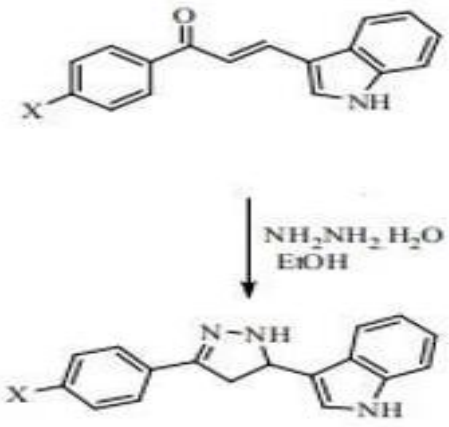
3. Tautomerization and Oxidation:

Subsequent proton transfer and elimination of water lead to aromatization or stabilization of the pyrimidine ring system.

When thiourea is used, the oxygen atom at position 2 of the pyrimidine ring is replaced by sulfur, yielding pyrimidinethione derivatives.

3.3 Synthesis of Five-Membered Heterocycles

Chalcones are excellent precursors for the synthesis of five-membered nitrogen-containing heterocycles due to the presence of a highly reactive α, β-unsaturated carbonyl system. One of the most important and widely studied transformations is the reaction of chalcones with hydrazine or substituted hydrazines to produce pyrazoline derivatives. This cyclization reaction is extensively utilized in heterocyclic chemistry and medicinal chemistry because pyrazolines exhibit diverse pharmacological activities.



The reaction proceeds via a two-step nucleophilic addition–cyclization mechanism:

- Nucleophilic Addition (Michael Addition):

The nucleophilic –NH2 group of hydrazine attacks the electrophilic β-carbon of the chalcone, forming a β-hydrazino ketone intermediate.

- Intramolecular Cyclization:

The second nitrogen atom of hydrazine attacks the carbonyl carbon, leading to ring closure and formation of a five-membered dihydropyrazole (pyrazoline) ring.

- Proton Transfer and Stabilization:

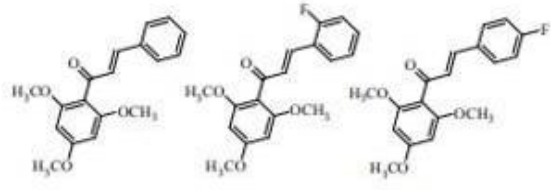
Subsequent proton shifts stabilize the newly formed heterocyclic system.

In some cases, further oxidation of pyrazolines can produce aromatic pyrazoles.

IV. BIOLOGICAL APPLICATIONS OF CHALCONES

4.1 Antimicrobial Activity

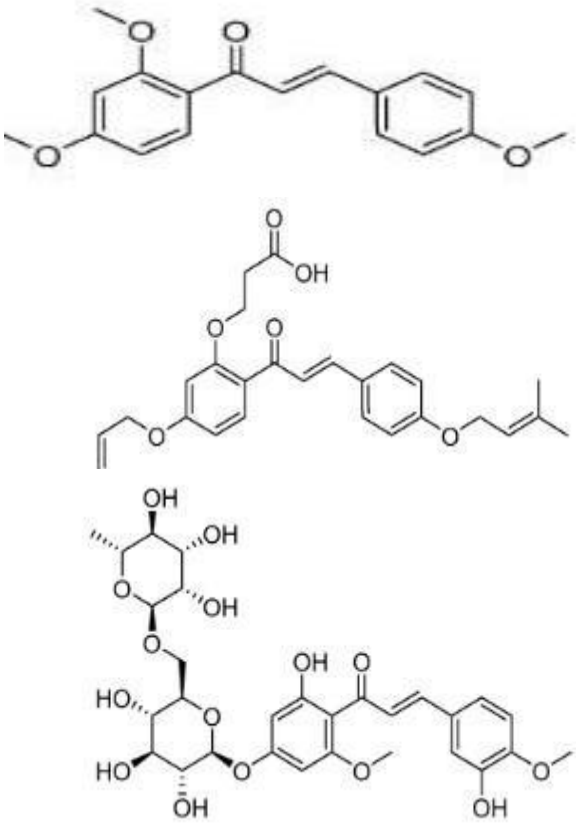
Chalcones have demonstrated strong inhibitory activity against Gram-positive bacteria such as Staphylococcus aureus, Bacillus subtilis, and Streptococcus species. Gram-positive bacteria possess a thick peptidoglycan layer but lack an outer membrane, which makes them relatively more susceptible to lipophilic compounds like chalcones.



Hydroxyl- and methoxy-substituted chalcones often show enhanced activity due to improved hydrogen-bonding interactions with bacterial enzymes. Halogen substitution (Cl, Br, F) increases lipophilicity and membrane permeability, further improving antibacterial efficacy.

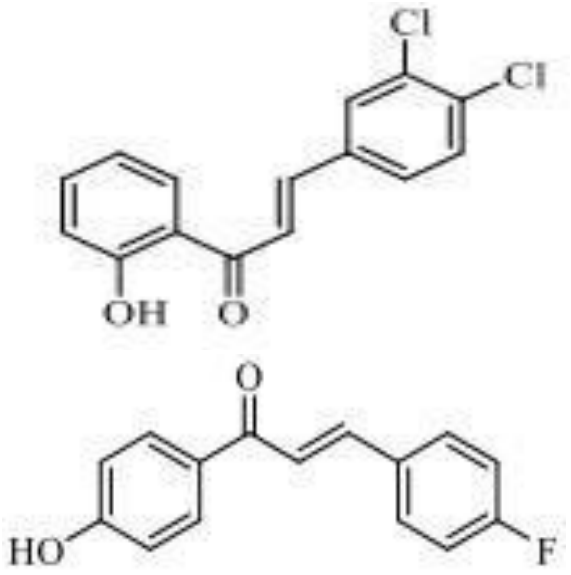
4.2 Anticancer Activity

Chalcone derivatives have emerged as promising anticancer agents due to their ability to interfere with multiple cellular pathways involved in tumor growth and progression. The α,β-unsaturated carbonyl system present in chalcones acts as a reactive pharmacophore, enabling interaction with nucleophilic amino acid residues in proteins that regulate cell proliferation and survival. Numerous studies have demonstrated that substituted chalcones exhibit cytotoxic activity against a wide range of cancer cell lines, including breast, lung, colon, prostate, and leukemia cells.



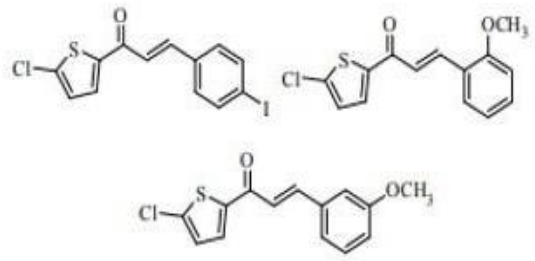
4.3 Anti-inflammatory Activity

Chalcone derivatives have demonstrated significant anti-inflammatory activity through modulation of key mediators involved in the inflammatory response. Inflammation is a complex biological process mediated by enzymes, cytokines, and reactive species. Excessive or chronic inflammation contributes to various pathological conditions, including arthritis, cardiovascular diseases, neurodegenerative disorders, and cancer. Chalcones, owing to their electrophilic α,βunsaturated carbonyl system and modifiable aromatic rings, can effectively interfere with multiple inflammatory pathways. Fluorinated chalcone 61 possesses a powerful antiinflammatory property.



4.4 Antioxidant Activity

Chalcone derivatives, particularly phenolic chalcones, exhibit significant antioxidant activity due to their ability to donate hydrogen atoms or electrons and stabilize free radicals. Oxidative stress, caused by excessive production of reactive oxygen species (ROS), is implicated in numerous pathological conditions such as cancer, diabetes, cardiovascular disorders, neurodegeneration, and aging. The conjugated π-electron system and phenolic hydroxyl groups present in chalcones contribute substantially to their free radical scavenging potential.



Hydroxyl groups enhance radical scavenging activity.

4.5 Antidiabetic Activity

Chalcone derivatives have gained considerable interest as potential antidiabetic agents due to their ability to regulate carbohydrate metabolism and improve glycemic control. Diabetes mellitus, particularly type 2 diabetes, is characterized by chronic hyperglycemia resulting from insulin resistance and impaired glucose metabolism. One effective therapeutic strategy for managing postprandial hyperglycemia involves inhibiting carbohydrate-digesting enzymes in the gastrointestinal tract. Chalcones have demonstrated promising inhibitory activity against key digestive enzymes such as α-amylase and α-glucosidase.

4.6 Antihypertensive Activity

Certain chalcone derivatives exhibit vasorelaxant properties by:

- Calcium channel modulation
- Nitric oxide pathway activation

4.7 Antimalarial Activity

Chalcone hybrids show activity against *Plasmodium falciparum*.

Morpholine and piperidine substitutions increase potency.

V. CONCLUSION

Chalcones represent a versatile and pharmacologically important class of α,β-unsaturated ketones. Their ease of synthesis, structural diversity, and wide range of biological activities make them attractive scaffolds in medicinal chemistry. Continued exploration of green synthetic strategies, hybrid molecule design, and SAR-guided optimization will likely lead to the development of novel chalcone-based therapeutic agents.

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