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# A REVIEW FOR SYNTHETIC ROUTE: PROMISING DRUG INTERMEDIATE CHALCONES

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## ABSTRACT

The scientific world has paid close attention to the versatile compounds known as chalcones because of their extensive range of medicinal characteristics and possible use in the expansion of innovative drugs. Chalcones are widely present equally in nature and pharmaceuticals. This paper offers a thorough summary of recent developments in chalcone synthesis techniques, emphasizing different strategies, certain green synthesis techniques and catalysts used to produce effective and sustainable products.

**Keywords: Chalcone, Flavonoids, Heteroaromatic, Claisen-schmidt Condensation, Green synthesis**

## INTRDUCTION

Chalcones are a fascinating category of organic combinations that have garnered noteworthy courtesy in the fields of chemistry, pharmacology, and natural product research **[1]**. The term "chalcone" arises after the Greek term "chalcos," which sense "bronze," and refers to the hue of most ordinary chalcones **[2]**. Chalcones which are originators of flavonoids **[3]** and isoflavonoids are a significant class of natural compounds that have global dispersion in fruits, tea, spices, vegetables and fruits based on soy **[2-4]**. Chemically, Chalcones contain an unsaturated ketone

group, which consists of a reactive keto-ethylenic (CO-CH=CH-) group **(Figure 1) [5-8]**. They occur as trans (E, 1) or cis (Z, 2) isomers, having two aromatic rings linked by a three-carbon α,β-unsaturated carbonyl. The E isomer is the most common structure among chalcones because it is more thermodynamically stable. The Z isomer's conformation is unstable due to a significant steric interaction between the carbonyl group and the A-ring **[9]**. Phenyl styryl ketone, or 1,3-diphenyl-2-propen-1-one, is the typical IUPAC accepted consistent nomenclature for chalcone. The significant distinction in the numbering of locations of the chalcone nucleus reversed to that of flavonoid structure. Chalcone has the aryl rings known as rings A and B. primed numbers are assigned to ring A and non-primed numbers are assigned to ring B **[10]**. Their biological activity mainly depends on the structural specificity **[11]** and the strength of interaction between a drug and receptors present in the biological system **[12]**. Most chalcones have biological activities, such as analgesic, **[13-15]** arthritis, **[16-18]** anti-inflammatory, **[19-21]** antipyretic, **[22]** anti-bacterial, **[23-25]** anti-viral, **[26-28]** anti-cancer, **[29-31]** antiulcer, **[10, 32, 33]** antifungal, **[34, 35]** anti-HIV, **[36]** anti-diabetes, **[37-39]** anti-hypertensive properties **[40]** and antioxidant effects **[41]**. Chalcone synthesis is a fundamental and widely studied chemical reaction in the field of organic chemistry and medicinal chemistry. Chalcones are used to create heterocyclic compounds and are engaged in an extensive assortment of chemical activities. Various chalcone end product can be generated by reacting aromatic aldehydes with aryl ketones in the existence of the applicable amount of condensing mediators **[11]**. Chalcones are important intermediate in the synthesis of various bioactive compounds and drugs. In this review, provide an overview of chalcone synthesis, its significance and some key methods used for their preparation.

Chalcones are organic molecules using a molecular structure of binary aromatic rings connected via an α,β-unsaturated carbonyl scheme, forming a three-carbon bond. These compounds can vary in the exchange patterns on the aromatic rings and in the kind of substituents linked to the carbonyl group. Here are some common types of chalcones based on their structural variations are given below their examples are given in **Table 1**.

**Simple Chalcones:** Simple chalcones have two aromatic rings, one of which contains an aldehyde or ketone group. The carbonyl group is usually at the β-position relative to the linkage between the rings.

**Flavonoids:** Chalcones serve as precursors to flavonoids, a larger class of compounds that play essential roles in plants and have diverse biological activities. Flavonoids

often have additional hydroxyl groups and other substituents on their aromatic rings and they are derived from chalcones through various enzymatic reactions **[42]**.

**Prenylated Chalcones:** Some chalcones have prenyl (3-methyl-2-butenyl) groups attached to one or both of the aromatic rings. These prenylated chalcones are commonly found in plants and can have unique biological activities **[43]**.

**Dimethoxy Chalcones:** Chalcones with two methoxy ($CH_3O$-) groups on one or both of the aromatic rings are known as dimethoxy chalcones. These compounds can have antioxidant and anti-inflammatory properties.

**Diflavanoid Chalcones:** In some cases, chalcones can undergo intramolecular cyclization reactions to form diflavanoids, which consist of two flavonoid units connected by a chalcone bridge. These compounds are often found in nature and can exhibit various biological activities.

**Bis-Chalcones:** Bis-chalcones are chalcone derivatives containing two chalcone moieties connected by a linker. These compounds can have enhanced biological activities compared to simple chalcones **[44]**.

**Phenylpyrazolyl Chalcones:** Chalcones can also be modified with pyrazole rings, leading to the formation of phenylpyrazolyl chalcones. These substances are of interest in medical chemistry due to their potential pharmacological properties.

**Fused Ring Chalcones:** Chalcones can be fused with other aromatic or heterocyclic rings to create complex structures with unique properties.

**Synthesis of Chalcones:**

Chalcone synthesis is a chemical reaction used to produce chalcones. Chalcones are essential structural chunks for the production of several bioactive substances, such as flavonoids, which have a broad spectrum of biological and pharmacological properties. There are multiple ways to create chalcones using synthesis. Chalcones potential therapeutic uses, such as their anti-inflammatory, antioxidant, anticancer and antimicrobial qualities, have drawn attention in medicinal chemistry. In order to create novel medications and study their biological properties, scientists are still experimenting with the synthesis and modification of chalcone products.

**Traditional Claisen-Schmidt Reaction:**

The Claisen-schmidt **[45]** reaction is supreme renowned technique for the production of chalcone. In this method, shortening of an aromatic aldehyde through an aromatic ketone in an existence of alkali (most commonly sodium hydroxide and potassium hydroxide) is involved. Numerous cyclic and heterocyclic derivatives of chalcone like pyrroline, **[46]** 2H-chromenes, thioethers, 2H-quinoline,

**[47]** cyclopropane, **[48]** pyrylium salts, **[49]** pyridyl-based phosphinines, **[50]** 3-aroylimidazo[1,2-a]pyridine, **[51]** pyridines, **[52]** thiazoles, **[53]** imidazoles, **[54]** phthalazines, **[55]** pyrimidines **[56]** and chalcone epoxide **[57]** were prepared via Claisen-Schmidt compression. This reaction has been widely used for decades and provides a straightforward way to synthesize chalcones [Scheme 1].

Alka N Choudhary **[58]** and Vijay Juyal are synthesized chalcones by base catalyst Claisen-schmidt condensation. In this reaction they used combination of benzaldehyde imitative (0.01 mol), derivatives of acetophenone (0.01 mol), Rectified spirit (as a solvent) and sodium hydroxide (as a base catalyst). Jufrizal Syahri **[59]** and co-workers are synthesize a chalcone by the Claisen–Schmidt compression reaction of vanillin and 4-chloroacetophenone in an existence of NaOH and ethanol as a solvent (%Yield=60%). Ruaa Wassim Adam **[60]** and co-workers are synthesize chalcone derivatives from acetophenone and derivative of benzaldehyde in an existence of NaOH and ethanol as catalytic agent and solvent respectively. Afzal Shaik **[61]** and co-workers are synthesized isoxazylchalcones. This compounds synthesized via the Claisen-Schmidt compression reaction in an existence of a basic catalyst aqueous KOH. In this reaction 1-(isoxazole-5-yl)ethanone react by replaced benzaldehyde. Hüseyin Karaca **[62]** and Sözcan Kazancı synthesize three different type of chalcone with claisen-schmidt condensation. In this reaction 4-hydroxybenzaldehyde condensed with different aromatic ketone (acetophenone, acetofuran and thio acetofuran) using potassium hydroxide as an alkaline catalyst and ethanol as a solvent. M. J. Joshi **[63]** and co-workers are prepared chalcone with A-ring heterocyclic. In the existence of 40% potassium hydroxide as a catalyst followed by ethanol as a solvent, 2-(4-Chlorophenyl)imidazo[1,2-a]pyridine-3-carbaldehyde and various aryl acetophenone reacted to yield (2E) heterosubstituted chalcones (pyridin-3-yl-3-(2-(4-chlorophenyl)imidazo[1,2-a])1-arylpropane-2-en-ones). Asma'u N. Hamza **[64]** and co-workers are prepared quinolinyl chalcone with Claisen-schmit condensation reaction. This compound was achieved by base catalyst condensation of corresponding replaced acetophenone and replaced benzaldehyde using sodium hydroxide as a promoter and ethanol use a solvent. Asmita V. Hirapara **[65]** and Shipra H. Baluja are synthesized a pyrazolo chalcone compounds by Claisen-schmidt reaction. They first synthesize pyrazolo aldehyde and 1-(1H-benzo[d]imidazole-2-yl] ethan-1-one. Then pyrazolo aldehyde and earlier intermediate undergoes Claisen-schmidt compression in

an existence of KOH as base promoter and methanol as a solvent.

**Modified Claisen-Schmidt Reaction:**

Matteo Tiecco **[66]** and colleagues are conducted the Claisen-Schmidt reaction in SB3-Cy / CSA DES among mono as well as bi-substituted benzaldehydes and acetophenones without the need for an additional acid catalyst [Scheme 2]. M.J. Climent **[67]** and co-workers synthesize chalcone by activated hydrotalcites as catalysts. Initial conditions for the Claisen-Schmidt compression amongst acetophenone and benzaldehyde were 423 K, no solvent, and 10 weight percent of also a calcined hydrotalcite (HTc(0.25)) or the matching rehydrated sample (HTc-R(0.25)) for a 24-hour period. Trans-chalcone is the product of the reaction with this final catalyst. These researchers have also looked at the process of rehydration, the impact of water content and the chemical construction of the rehydrated Al-Mg mixed oxides. M. R. Jayapal **[68]** and co-workers are synthesized a chalcone using $SOCl_2$/EtOH. They utilised a $SOCl_2$/EtOH as a catalyst. Aldol condensation between 2,5-dihydroxyacetophenone and substituted benzaldehyde(2-chlorobenzaldehydes, 4-chlorobenzaldehydes, 3-nitrobenzaldehydes) in the presence of $SOCl_2$/EtOH.

**Recent advances in chalcone synthesis:**

In recent years, researchers have developed new and more efficient methods for chalcone synthesis. Some notable approaches include:

**Green Chemistry Approaches:**

Green chemistry resulted in the discovery of ecologically acceptable technologies for chalcone production. Like use of catalyst, solvent and reaction condition that minimise waste and energy consumption.

Retno Aliyatul Fikroh **[69]** and co-workers are prepared chalcone by green chemistry methods. They use a grinding methods for synthesis of chalcone. The chalcone derived was prepared by grinding 6-bromoveratraldehyde and 2-hydroxyacetophenone. This approach is solvent-free, uses just mortar and pestle, and provides a quick synthesis [Scheme 3]. Keyur D. Bhatt **[70]** and co-workers are prepared chalcone by ultrasound-assisted reaction as a green method. This reaction is carried out in 100 ml flask which contained a reaction mass (2,4-dihydroxy acetophenone and furfural aldehyde in suitable amount of ethanol). This reaction mass is exposed to ultrasound irradiation. Through this route 40% sodium hydroxide is added [Scheme 4]. Ahmed Hassen Shntaif **[71]** prepared a chalcone by microwave irradiation as green chemistry approach. Microvave irradiation is not only minimise time but also increase the yield of reaction. They tried many methods for microwave

irradiation [Scheme 5]. A conical flask containing an equimolar combination of aryl aldehydes, methyl aromatic ketone, and minimal amounts of R-spirit and 40% NaOH. This flask was taken, covered with a funnel, and microwaved at home. This mixture was exposed to microvave radiation of 160–320 watts for 60–120 seconds. In 5 ml of ethanol, the substituted acetophenone and benzaldehyde were dissolved. Calcium oxide was added to this solution and stirred. Utilize the rotator evaporator's lowered pressure to eliminate the solvent. The resulting enthusiastic powder was put in a 25 ml beaker and microwaved for 15 minutes at 400 W. Anhydrous $K_2CO_3$, substituted acetophenone and substituted benzaldehyde were systematically combined to create a thick paste. The same was allowed to air dry before the remaining mass was microwave-irradiated for three to five minutes. This procedure was completed in a home microwave (600 W, 2450 NHz). Once the reaction was concluded. The reaction mass was melted in ethanol, and the inorganic substance was removed using a filter. Filtrate was obtained by leaving a concentration in a vacuum overnight. $ZnCl_2$, substituted acetophenone and substituted benzaldehyde were combined in an ACE tube before being flushed with argon and firmly sealed. The mixture was heated in a domestic oven using a microwave for three to five minutes before being allowed to cool to room temperature. Aqueous ethanol (20 ml) was included in the mixture of reactions, and the divided solid was sieved, cleaned with n-hexane and dehydrated. The concrete underwent recrystallization. Inorganic catalyst (5-7 g) was supplemental to a solution of substituted acetophenone and substituted benzaldehyde in ethanol that had been heated in a borosil flask. The reaction combination was blended, and the adsorbed substance was desiccated in the air and microwave-irradiated. In an open Corning glass test tube with a large mouth, the acetophenone, substituted aryl aldehyde, magnificently crushed base like NaOH/KOH/$Ba(OH)_2$ and a few drops of dried methanol were thoroughly mixed. Monoacidic bases, such as NaOH and KOH, were used in 0.002 moles while diacidic base S-200 $Ba(OH)_2$ was used in 0.001 moles. In a home microwave oven, this mixture was exposed to MW radiation for 25 seconds. With the aid of a mortar and pestle, the aryl ketone, aryl aldehyde, neutral alumina, and ammonium chloride were thoroughly mixed before being transferred to a pyrex beaker. The solid mixture was microwaved for three minutes at 480 W. A 50 ml beaker containing a mixture of sulphated titania, substituted aryl aldehyde, and substituted acetophenone was sealed with a lid. This mixture was exposed to a microwave radiation of 650 W for two to four minutes. Dichloromethane was added

once the reaction was finished, and it was then filtered out. Clay catalyst, aryl ketone and aryle aldehyde were heated to 150 ºC in a sealed tube under microwave radiation for a duration of one hour. Before being exposed to radiation, the solid starting components were crushed to a fine powder in a mortar. After diluting the reaction mixture with 20 millilitres of hot ethanol, the catalyst was removed through filtering, the solvent was evaporated, and the residue solidified. As all above reactions were carried out by microwave irradiation methods using different catalyst.

**Cross-Coupling Reaction:**

Using standard methods to synthesize a new class of chalcones with diverse substituents can result in unwanted products in addition to acceptable compounds, making chromatographic separation difficult. As a result, novel techniques such as cross-couplings are now being developed. For the synthesis of potent medicinal compounds such as chalcones, transition metal catalysts like Julia-Kocienski olefnation, Witting and Friedel-Crafts acylation have been utilized **[10]** [Scheme 6].

**Synthesis of Bis-Chalcone:**

Abdullah M. Asiri **[72]** and co-workers are synthesized a bis-chalcone by Utilizing 3-acetyl-2,5-dimethylthiophene and microwave irritation, bis-chalcone was created utilizing the aldol condensation process [Scheme 7]. Serdar Burmaoglu **[73]** and co-workers are synthesized bis-chalcone. Tri methoxy benzene (1) and acetyl chloride were combined to create compound 2 in the presence of $AlCl_3$. Compound 2 and the relevant benzaldehydes (3a-h) were used to create bis-chalcones in the existence of a 50% KOH solution in MeOH. The material that resulted from the conventional work-up (adding $NH_4Cl$ solution and extracting with ethyl acetate) was cleansed using column chromatography to produce the preferred products. Hatem A. Abdel-Aziz **[74]** and co-workers are prepared a bis-chalcone by the microwave irradiation. They first of all, By reacting pentan-2,4-dione by the suitable 2-oxo-N-arylpropanehydrazonoyl chloride 1ab at room temperature in ethanolic NaOH, pyrazoles 2a,b were created. There have been no investigations on the pyrazoles 2's reactivity, even with the fact that they have been recognized for more than three decades, with the exception of the reaction they have through hydrazine hydrate to produce pyrazolo[3,4-d]pyridazine products. The new bis-chalcones 3a-h have been made quickly and effectively using microwave irradiation. In order to produce the bis-chalcones 3a–h in worthy yields (70–93%), pyrazoles 2a,b were joined by a sequence of aldehydes in 10% aqueous NaOH underneath microwave irradiation (100W, 60°C) for 4 min (Scheme I). In contrast, bis-chalcones 3a–h were made the

traditional way, at room temperature, for 12 hours. The conventional approach and the outcomes of the microwave irradiation synthesis were compared. M. Chitra **[75]** and co-workers are synthesized a bis-chalcone with utilizing a acid-catalysed reaction. 2 moles Terephthaldehyde was used to treat 4-hydroxyacetophenone whereas HCl was present to treat bis-chalcone.

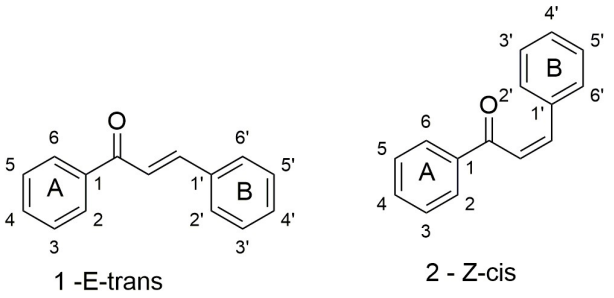
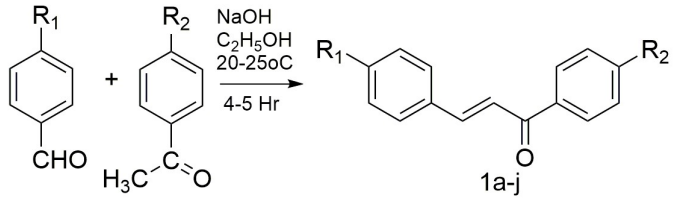
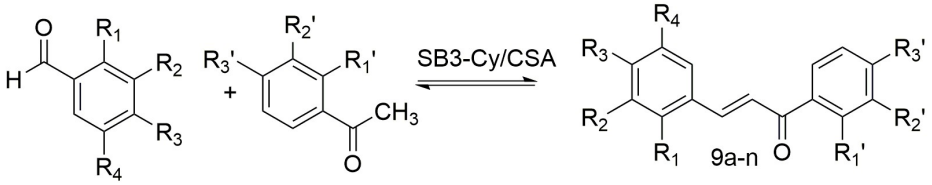



**Figure 1: Molecular structure of Chalcone**

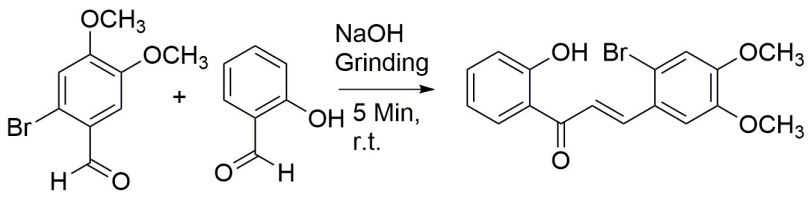
**Scheme 1 − General method for the Synthesis of Chalcone**



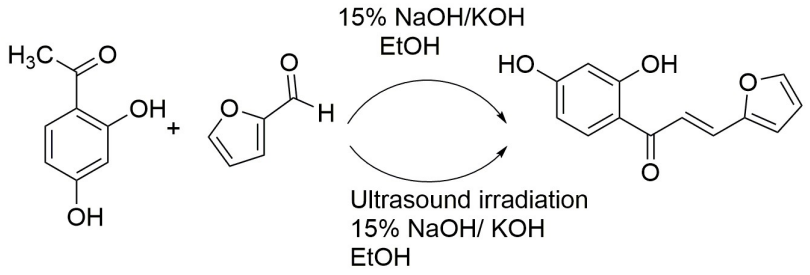

**Scheme 2 − Claisen-Schmidt reaction of mono and bi-substituted benzaldehydes and acetophenones performed in SB3-Cy/ CSA Deep Eutectic Solvent**



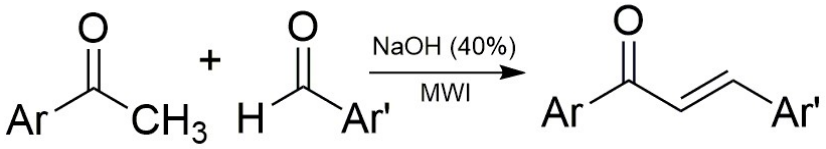

**Scheme 3 − Synthesis of Chalcone by grinding method**



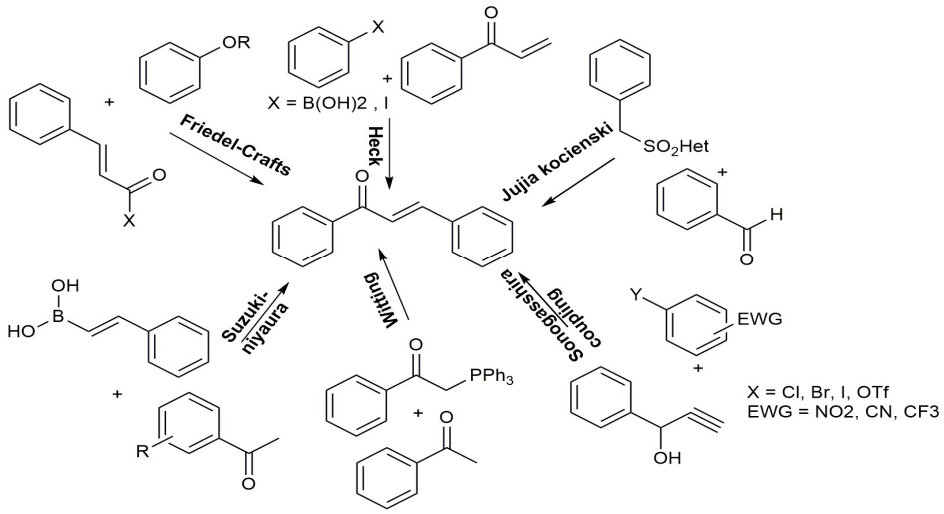
**Scheme 4 − Synthesis of Chalcone by ultrasound irradiation**




**Scheme 5 − Synthesis of Chalcone derivative by Microwave Irradiation**




**Scheme 6 − Various Cross-coupling reactions used for the synthesis of Chalcone**




**Scheme 7 − Synthesis of bis-chalcone**

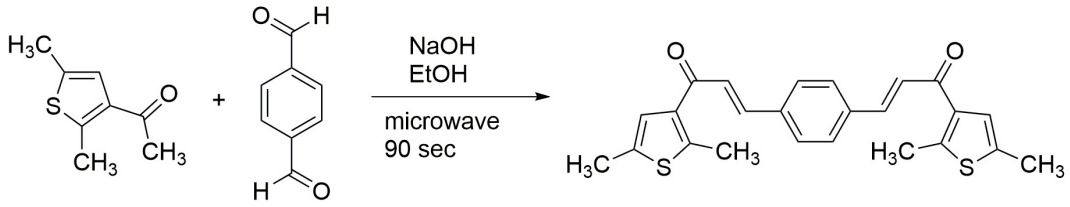
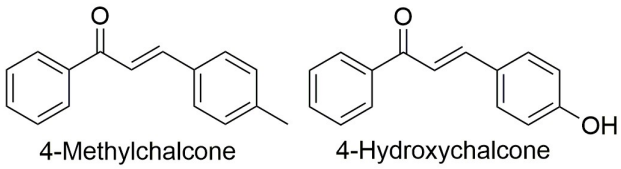
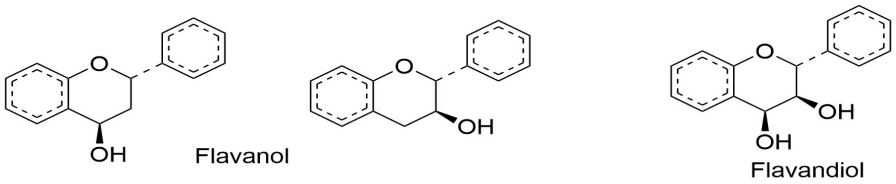
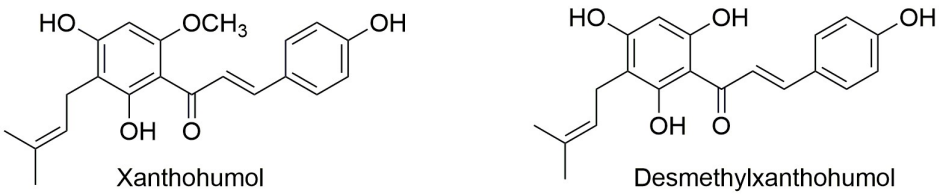
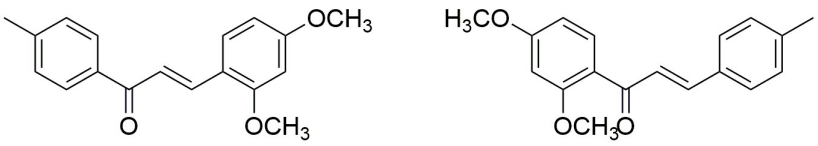
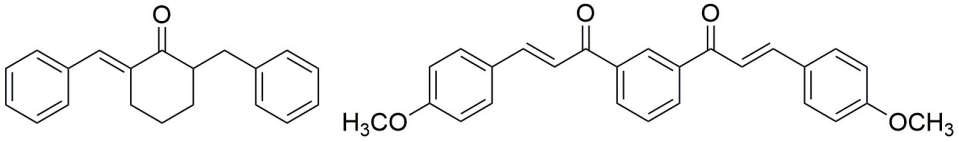


**Table 1: Common types of chalcones based on their structural variations and examples**

| Sr. No. | Type of Chalcone | Examples |
|---|---|---|
| 1 | Simple Chalcones |  4-Methylchalcone 4-Hydroxychalcone |
| 2 | Precursor of Flavonoids |  Flavanol Flavandiol |
| 3 | Prenylated Chalcones |  Xanthohumol Desmethylxanthohumol |
| 4 | Dimethoxy Chalcones |  |
| 5 | Diflavanoid Chalcones | **Found in nature** |
| 6 | Bis-Chalcones |  |
| 7 | Phenylpyrazolyl Chalcones | **Pharmacologically active compounds** |

## CONCLUSION

In conclusion, the synthesis of chalcones has emerged as a versatile and dynamic field within the area of organic chemistry. This study emphasized the numerous synthetic processes and tactics used for the effective synthesis of chalcone products. These diverse approaches include Claisen-Schmidt condensation, green chemistry methods, and transition metal-catalyzed reactions, among others.

The most notable aspects of chalcone synthesis is its relevance in medicinal chemistry. Chalcone products have showed a variety of biological accomplishments, counting anti-inflammatory, anticancer, antioxidant and antibacterial characteristics. This makes them promising candidates for

drug discovery and evolution, as they offer potential solutions to some of the most pressing healthcare challenges.

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