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Recent Updates on Synthetic Strategies of Chalcone Scaffold and their Heterocyclic Derivatives

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Abstract

Chalcones, α,β-unsaturated ketone linking two aromatic moieties gained noticeable attention in the medicinal chemistry area. Chalcone-scaffold construction has proceeded *via* verified chemical synthetic strategies, including condensation, coupling, olefination, acylation, reductive annulation, one-pot, and Fries' rearrangement methods. Specific approaches have assisted chalcone combinations using microwave radiation and ultrasound waves to enhance synthetic conditions and amplify yields. Recently, chalcones have been investigated extensively as core structures in potent bioactive hybrids such as anticancer, antimicrobial, and others. In addition, chalcones serve as parent structures for synthesizing several bioactive heterocyclic derivatives comprising five-membered and six-membered rings. This review will discuss recent applications of chalcones' synthetic strategies, physical and chemical characters, biological activities, and chemical derivatization.

Keywords
Chalcone; Biological activity; Anti-inflammatory; Anti-bacterial; Anti-fungal; Anti-cancer; EGFR kinase.

Introduction

Chalcones existed indeed flavonoid-type organic compounds, also known as 'open-chain flavonoids,' that are biosynthesized through the shikimic acid pathway [1]. Chalcones are thought to be flavonoids' metabolic constituents. Chalcones are coupled as α, ß-unsaturated ketones composed of bi-aromatic groups (rings A and B) connected by a tri-carbon alkenone group. Furthermore, Chalcones may contain saturated derivatives, called dihydrochalcones, in which a three-carbon alkanone unit replaces the three-carbon alkenone unit. Among many naturally produced chalcones, the presence of one or more phenolic hydroxyl functionalities is a commonly found substitution on the phenyl ring as prenyl and geranyl replacements. In other words, chalcones chemically are compounds including 1,3-diaryl-2-propen-1-one core structure. They are obtained in binary isomeric forms; The *trans* isomers are the predominant stable form, while the *cis* isomers are the minor form [2]. **Figure 1A** Several thousand naturally existing chalcones have been described throughout the literature[3]. Several derivatives of these natural chalcones have been shown interactions with different biological targets, including cellular protection and modulation properties, making them suitable effective options for medical approaches in a wide range of human diseases. Several applications of chalcones and their related products have been published for their biological effects [4]. The flavonoid chalcones, which serve as intermediaries and bio-precursor in the production of flavonoids, have a wide variety of pharmacological targeting and structural diversity. The chalcones family has gained a lot of interest due to their wide bioactivity range, which includes anticancer[5], antibacterial[6-7], antifungal[8], antihyperglycemic[9], and antioxidant [10] activities. Various chalcone compounds were approved as drugs for distinct diseases, for example, the gastric protective derivative Sofalcone **1 [**11], the choleretic compound metochalcone **2** [2], the vascular protecting agent, hesperidin methylchalcone **3[**12], and phase I anticancer agent Xanthohumol **4 [**13]. **Figure 1B** On the other hand, several reviews have been reported in the last decade for studying chalcones' mode of action as potential anticancer agents.[3, 14-20] The current review highlights the most recent studies, especially those have been published within the last five years. It intends to emphasize recent developments in employing chalcone as a fascinating and preferred skeleton in medicinal chemistry. Various chalcone insights are discussed, such as traditional and unconventional chalcone synthetic methods and bioactivity. In addition, recent implementations of chalcone-related, physical, and chemical properties have been discussed.

2. Synthetic strategies of Chalcones

Chalcones are traditionally synthesized *via* condensation procedures catalyzed by acids or bases. Although, chalcones having simple structures of α and β-unsaturated ketone that easily to be synthesized, numerous innovative techniques and methods

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have lately been identified due to their intriguing bioactivities and the creation of different catalysis or reaction circumstances. The following is a summary of the synthetic techniques, basic approaches, catalysis, and conditions employed for chalcone synthesis.

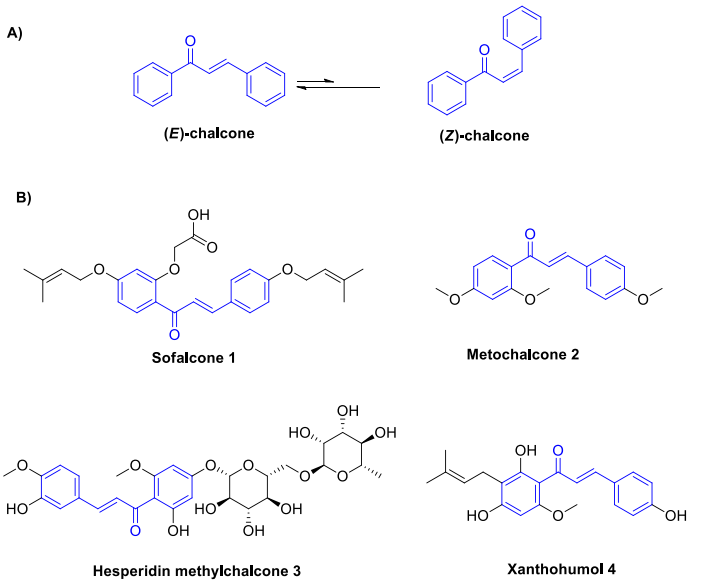


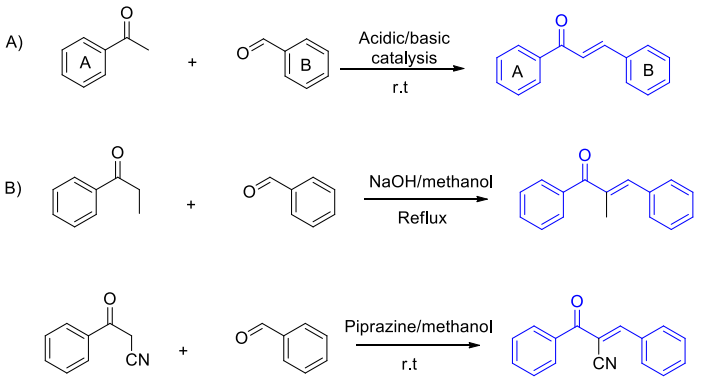
Figure 1: A) Chalcone general structure showing predominance of *trans*-form. B) Structures of approved chalcones.

2.1. Claisen−Schmidt condensation reaction

Claisen−Schmidt is named after reactions [21-22], which illustrate the method of condensation between benzaldehydes and methyl ketones in the existence of catalysts to produce chalcones. The Claisen-Schmidt reaction is one of the most conventional reactions in organic chemistry.[23] **Scheme 1A** Both strong acids and bases catalysts were utilized. The primary disadvantage of this reaction is its slow rate; it often takes several days to complete. In addition, the desired product, as well as byproducts and occasionally starting compounds, could all be present in the complicated mixture formed by the reaction. Moreover, the varied yield percent (10-100%) depends on the nature of reactants and the type of used catalyst.[23] The basic catalysis is predominantly favored for chalcone synthesis.[24]The traditional Claisen−Schmidt condensation with basic catalysis using potassium or sodium hydroxides in methanol or ethanol at ambient temperature has been commonly used to synthesis hydroxyl-substituted chalcones in average with yields of (60−90%). In some circumstances, conditions may be modified according to reaction requirements, for example, temperature raising, which was proceeded in the case of the presence of α-carbon in the ketone that is hard to dehydrate if the substituted ketone with electrophilic groups. This reaction has proceeded with reflux, or it will take several days.[25-27] **Scheme 1B** On the other hand, moderate conditions were sufficient for the α-carbon ketones substituted with the nucleophilic groups.[28] Recently, several reviews have been reported for chalcones synthesis with Claisen−Schmidt Condensation and its modified catalysis and conditions [3,29].

2.2. Chalcones synthesis via other well-recognized strategies.

Since the Claisen−Schmidt reaction condensation process occasionally may produce a mixture of compounds that is hard be separated to obtain the desired chalcone compounds, other recognized reactions have been discovered for the assembly of chalcones, such as Suzuki, Heck, and Sonogashira coupling reactions, Wittig and Julia−Kocienski olefination reactions, and Friedel-Craft acylation reactions. In addition, reductive annulation, one-pot, and Fries' rearrangement methods.



Scheme 1: A) Traditional Claisen−Schmidt condensation. B) Examples of modified temperature conditions.

2.2.1 Cross-coupling methods.

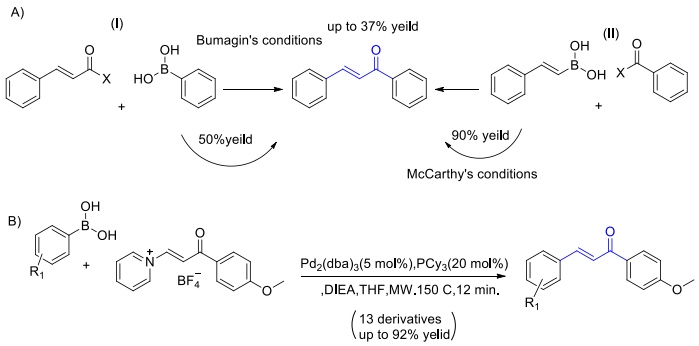
2.2.1.1. Suzuki cross-coupling methods.

Suzuki cross-coupling is an effective palladium-catalyzed reaction for creating carbon-carbon bonds. Suzuki reaction has primarily introduced for the synthesis of chalcones in 2003.[30]There are two plausible approaches for chalcone synthesis *via* the Suzuki reaction. Coupling-Based on the retrosynthetic analysis- has two plausible approaches for the chalcones synthesis; [30] coupling between cinnamoyl chloride and phenylboronic acid **Scheme 2A, I** and coupling between benzoyl chloride and phenyl-vinyl boronic acid **Scheme 2A, II.** As illustrated in **Scheme 2A**, the reaction yield is affected by the combined reaction conditions. Regarding the first approach, Bumagin's conditions, containing; (acetone: water, 3:1 as a solvent, 3%PdCl2 as a catalyst, and sodium bicarbonate as the base) provide a relatively low yield up to 37%.[31] Whereas McCarthy's conditions, including;(anhydrous toluene for solving, tetrakis TPP (triphenylphosphine) palladium as catalyst, and cesium carbonate as the base) afford approximately 50 and 90% yields, respectively related to the mentioned two approaches.[32] Suzuki reaction has been applied recently for producing chalcones with versatile substitutions on the phenyl rings; for example, the Suzuki−Miyaura reaction was used by Buszek *et al* for the synthesis of chalcone with high yields up to 92% from *N*-vinyl pyridinium tetrafluoroborate salt[33] **Scheme 2B**

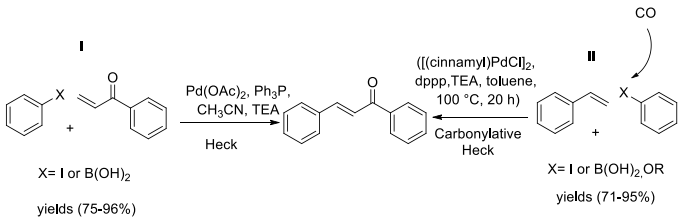
2.2.1.2. Heck coupling reactions.

Considering chalcone structurally as a stilbene, chalcone derivatives have been synthesized by traditional Heck reaction of aryl iodides or boronic acids with unsaturated ketones catalyzed by palladium in alkaline conditions to produce chalcone

compounds in high yields (75-96%).[34-35] **Scheme 3, I** In addition, the Heck carbonylative coupling method has been extended to produce chalcones in excellent yields up to 95% by using optimized palladium catalytic conditions.[34-37] Scheme 3, II



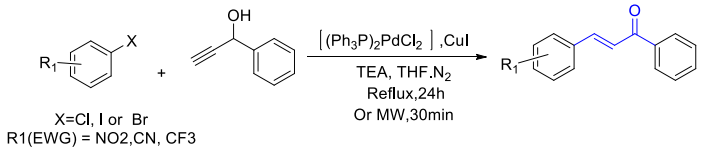
Scheme 2: chalcone synthesis via A) Suzuki coupling different approaches B) Suzuki−Miyaura reaction applications.



Scheme 2: Chalcone synthesis via Heck coupling and carbonylative Heck approaches

2.2.1.3. Sonogashira coupling isomerization.

Sonogashira coupling is described as the combining of alkynes to phenyl halides substituted with an electron-withdrawing group in the existence of palladium catalysis and a catalytic quantity of cuprous iodide (CuI) by reflux in a mixture of (TEA) and THF up to 24 hours under an inert atmosphere of nitrogen[38]. Many targeted chalcones were produced with good to excellent yield under these parameters [39-42]. Nevertheless, Sonogashira coupling involves significant drawbacks, such as long reaction periods, a large amount of base, and the requirement for electron-deficient aromatic halide.To address these problems, a microwave-aided coupling isomerization process was reported for chalcones production in high yield in less than 30 minutes [43]. **Scheme 4**



Scheme 3:Chalcone synthesis via Sonogashira coupling approach.

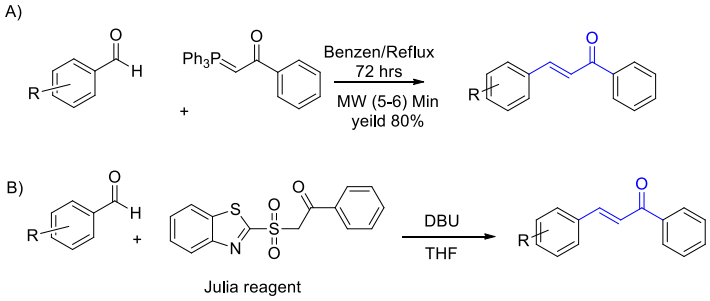
2.2.2. Olefination reactions

2.2.2.1. Wittig olefination reaction

The Wittig olefination reaction is a simple method for the synthesis of alkene derivatives. Chalcones are a suitable alkene model for the Wittig olefination approach. **Scheme 5A** Wittig strategy was applied for chalcone synthesis from benzaldehyde and triphenyl-benzoyl -methylene phosphorane by refluxing in benzene for 72 hours or in THF for 30 hours.[44-45] In case of proceeding under microwave radiation, the reaction rate was accelerated to produce chalcones in good yields within (5-6 minutes)[46].

2.2.2.2. Julia-Kocienski's olefination reaction.

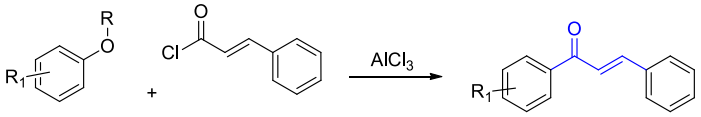
Julia−Kocienski olefination reaction was also reported for the synthesis of chalcones from suitable aldehyde and Heteroaryl-sulfonyl phenylethane-one in the presence of a base.[47-48] Scheme 5B The best-used condition was 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in the presence of non-polar solvents and Julia reagent containing hetero aryl benzothiazole**.**



Scheme 4: Chalcone Synthesis via olefination coupling A) Wittig reaction B) Julia−Kocienski reaction.

2.3. Friedel−Crafts Acylation of cinnamoyl chloride.

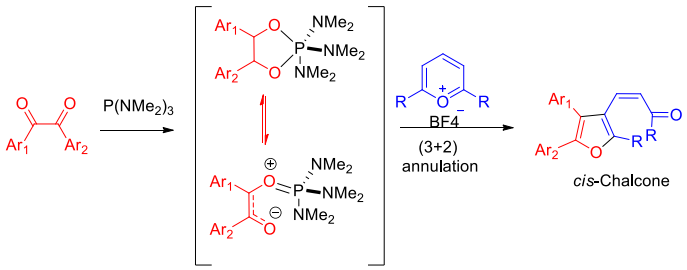
Friedel−Crafts Acylation was early used by Shotter et al. in 1978 for the synthesis of four chalcones from cinnamoyl chloride and four aromatic ethers. Aluminum chloride- strong Lewis acid- was used for catalyzing this reaction [49]. **Scheme 6** The use of Friedel−Crafts acylation for chalcone production has been limited.



Scheme 5: Chalcone synthesis via Friedel−Crafts Acylation

2.4. Reductive annulation method.

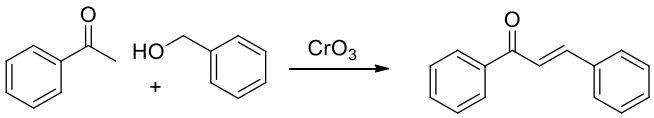
Reductive (3 + 2) Annulation of Benzils by Pyrylium Salts, a stereoselective method for synthesis of cis chalcone. *trans*-Chalcones are often produced more than cis-chalcones because they have lower chemical stability. As a consequence of this occurrence, *cis*-chalcones have fewer uses than *trans*-chalcones. *cis*-Chalcones bearing furanyl rings have been created using the reductive (3 + 2) annulation of pyrylium salts with benzil in the existence of $P(NMe_2)_3$ [50]. **Scheme 7**



Scheme 6: Reductive (3+2) annulation method for synthesis of cis-chalcones.

2.5. One-pot method.

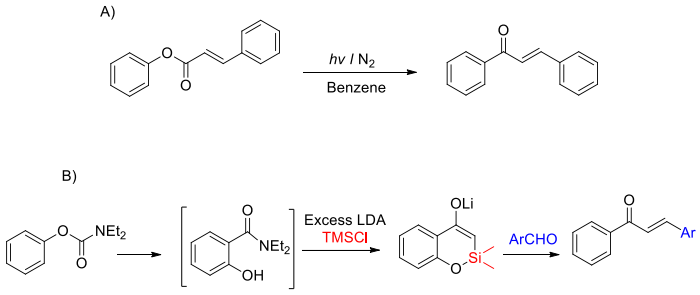
A one-pot reaction where the starting ingredients are directly mixed in the presence of an oxidizing agent has been recorded for chalcone synthesis. The one-pot production is considered because no further purification is required after one step. Catalyzed by chromium trioxide, benzyl methanol has been oxidized to benzaldehyde, which is then condensed with acetophenone to form chalcones.[51] **Scheme 8**



Scheme 7: One-pot chalcone synthetic approach

2.6. Fries' rearrangement methods.

Starting with phenyl-cinnamate, 2-hydroxy substituted chalcones were early prepared by Photo-Fries rearrangement under nitrogen atmosphere in benzene as solvent.[52] **Scheme 9A**. Similarly, starting with phenyl-diethyl-carbamate, Anionic Fries rearrangement has recently been employed in a one-pot reaction for producing a series of chalcones. This reaction was catalyzed by lithium di-isopropyl amide (LDA) and Chloro-trimethyl silane (TMSCl).[53] **Scheme 9B**.



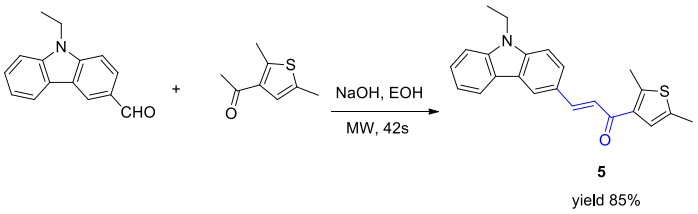
Scheme 8: Fries' rearrangement chalcone synthetic approaches.

2.7. Miscellaneous Approaches.

Among the significant limitations of the alkaline base-catalyzed synthetic procedures for chalcone production is that the workup of these techniques demands up to 3.0 equivalents quantities of catalyst in addition to another equivalent amount of mineral acid for neutralization. Chalcone synthesis, like many other uniformly promoted organic reactions, is challenged for its severely harmful environmental effect due to the massive volume of liquid waste formed. In response to the environmental issue, strategies for chalcones production employing these alkaline bases under ecologically friendly (green) experimental parameters have been developed [54-55].

2.7.1. Microwave-aided approach.

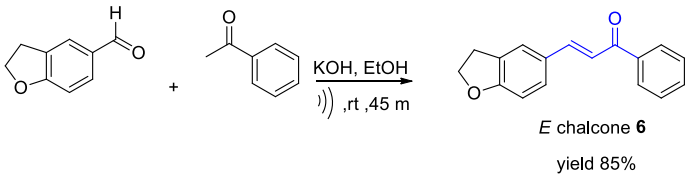
Microwave-aided chemical formulation is an effective method for heating in the organic synthetic process.[56-57] Microwaves operate as high-frequency electric forces and will typically heat any substance having mobile electronic charges, like polarized molecules inside a liquid or conductive ions within a solid [58] This approach provides a simple, clean, rapid, efficient, and cost-effective way for synthesizing a large variety of organic compounds. Compared with conventional methods, microwave-aided chalcone synthetic methods resulted in a considerable acceleration of reaction rate and improved yields.[59] Several chalcones have been synthesized with the aid of microwave radiation either by using solvents [60-62] or in solvent free conditions.[63] For example, chalcone compound 5 has been synthesized recently in excellent yield (85%) by microwave heating for 42 seconds [64]. **Scheme 10**



Scheme 9: Microwave-aided approach for chalcone 5 synthesis.

2.7.2. Ultrasound-aided approach.

Chalcone synthesis under Sonication conditions, as a source of heat, is another green synthetic approach. The ultrasound technique is thought to be environmentally benign.[65] It is interesting to note how reaction time was significantly decreased compared to conventional procedures. The estimated reaction time for that approach ranges from 3 to 72 hours,[66-67], whereas reported ultrasound-aided methods produced chalcones within a few minutes.[68] Versatile chalcones have been recently synthesized using an ultrasound-aided approach.**[69-72]** In addition, this approach has been used for the stereoselective synthesis of a series of dihydro benzofuran chalcone derivative **6** at room temperature.[73] **Scheme 11**



Scheme 10: Stereoselective synthesis of chalcone **6** using ultrasound-aided approach.

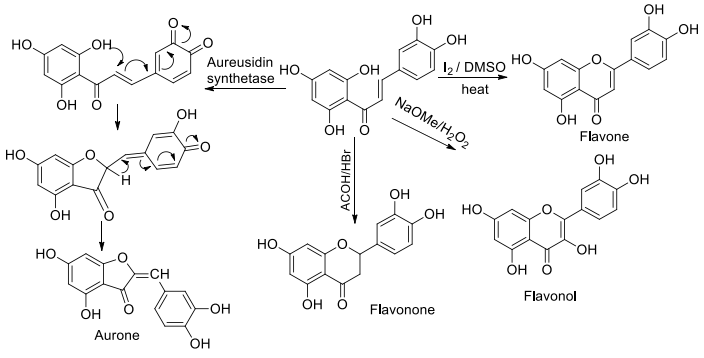
In conclusion, the mentioned traditional and unconventional approaches have been established for constructing carbon−carbon bonds under moderate conditions with satisfactory yields, producing various beneficial chalcone derivatives that have potential importance in areas of synthetic and medicinal chemistry.

3. Physical and chemical properties.

Chalcones can be found naturally almost in all parts of various plants. The naturally existing chalcones are mainly crystalline compounds with hues ranging from yellow to orange to brown. Chalcones have higher stability than flavonoids. Chalcones possess good solubility in alcoholic, diluted, or concentrated acids or alkali liquids and organic solving agents like acetone, chloroform, and DCM. They appear bright red or orange red in alkaline solutions. All chalcones pass the Wilson test, indicating pink coloration with concentrated H_2SO_4. In addition, chalcones exposed to ethanol ferric chloride became violet, indicating the existence of unbound hydroxyls.[74]

3.1. Chalcones isomerization.

Chalcones and flavonoids are structurally related. different flavonoids are formed by the isomerization of chalcones.[75-76] When chalcones are heated with iodine crystals in DMSO, their related flavones are formed.[77] Also, flavanones are readily formed by cyclizing chalcones with a mixture of hydrobromic and glacial-acetic acids. Side products of demethylated and debenzylated compounds may be produced during this isomerization process.[55,78] Similarly, chalcones are transformed easily into their related flavonols by oxidation in an alcoholic sodium hydroxide solution with H_2O_2.[79] Moreover, the production of aurones by oxidizing chalcone intermediates in the existence of aureusidin synthetase is an additional important isomerization step.[80] **Scheme 12**



Scheme 11: Chalcone isomerization into flavone, flavonol, flavonone and aurone.

3.2. Chalcones are Michael acceptors.

The chemical composition of chalcones influences or regulates their biological function. [81-82] Michael acceptors are recognized to include an electrophile, which is implicated in several physiological procedures and controls crucial signaling pathways. The chalcone α,β -unsaturated carbonyl active group, is acting as a Michael acceptor; that contributes to forming covalent bonds with thiol groups or other related nucleophiles *via* Michael addition. **Figure 2A** Chalcones, for example, can alter Keap1-Nrf2-ARE via forming a covalent bond with cysteine. It is worth addressing the different functional groups of chalcone phenyl rings in the creation of novel therapeutic compounds since they impact the electronegativity of the ring and hence the electron affinity of the α,β -unsaturated ketone system, as well as the high affinity and bioactivity of chalcones.[83] According to recent reports, chalcones stimulate the Nrf2 signaling pathway, boost the production of the Nrf2-regulated antioxidant defense system, promote anticarcinogenic proteins, and increase the levels of multidrug inhibition proteins. Antioxidant chalcone compound **7** was reported as a powerful Nrf2 activator in both in-vitro as well as in animals. Additional investigations revealed that this chalcone's stimulation of Nrf2 was unaffected by reactive oxygen species or redox alterations.[84] Similarly, compound **8** has recently confirmed as Nrf2 activator and expression inducer of the Nrf2-related enzymes.[85] Because chalcones are mild electrophiles, they become less liable to have harmful off-target actions and are unlikely to lead to carcinogenicity or mutagenicity. Moreover, their minimal toxicity, structure variety, molecular rearrangement capability, and the existence of α,β-unsaturated carbonyl group make them attractive therapeutic candidates for Nrf2-dependent disorders [86]. **Figure 2B**

The NLRP3inflamosome, another important pathway, has recently been found to be potentially inhibited by a series of natural and synthetic chalcones by utilizing their Michael addition properties. Stimulation of the NLRP3 inflammasome resulted in the production of activated pro-inflammatory mediators catalyzed by caspase 1, leading to pyroptosis. Chalcones have been investigated as a possible scaffold for the creation of NLRP3 inhibitors. **Velutone F 9**, natural chalcone, and its synthetic analog compound **10** have recently been reported as potent NLRP3 inhibitors through operating the Michael acceptor properties.[87] It was interesting to utilize chalcone scaffolds for developing drugs because of their reasonable molecular weight, facile manipulation of lipophilicity, and relatively inexpensive [88]. **Figure 2C**

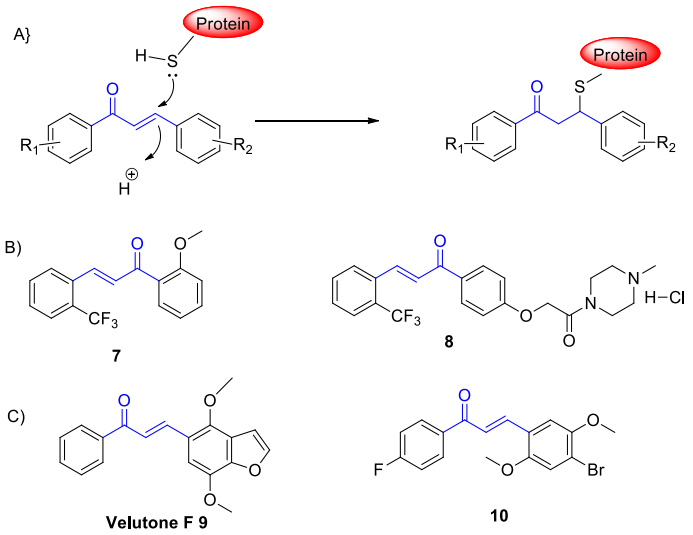


Figure 2: A) Michael addition properties of chalcones. B) Structures of Nrf2 activator chalcones **7** and **8**. C) Structures of NLRP3inflamosome inhibitor chalcones Velutone F **9** and **10**.

5. Chemical derivatization of chalcones.

In addition to its fundamental role in medicinal chemistry as bioactive structure, chalcone scaffold have been reported as synthetic precursor for generating various effective heterocyclic compounds. The chalcone-derived heterocyclic compounds can be classified into five membered and six membered derivatives. Five membered compounds such as pyrazoline and iso-oxazole derivatives. Six membered compounds including pyrimidine, cyano-pyridine, and cyno-pyran derivatives. In addition to bi-cyclic compounds including synthetic flavonoids and aurone derivatives[89].

5.1. Five membered Chalcone-based derivatives.

5.1.1. Chalcone-based pyrazolines.

Simply, many pyrazoline compounds have been derived from chalcones *via* condensation with hydrazine, phenylhydrazine, hydrazide, thiohydrazid, semi-carbazide, and thio-semicarbazide derivatives using ethanol and sometimes in existence suitable catalysts such as sodium hydroxide or glacial acetic acid.[90] **Figure 3 A** Recently, versatile chalcone-based pyrazoline derivatives have been reported as beneficial compounds for treating different diseases, for example, anticancer compound **11**[91], antimalarial-antibacterial compound **12**[92], and anti-inflammatory compound **13** [93]. **Figure 3 B**

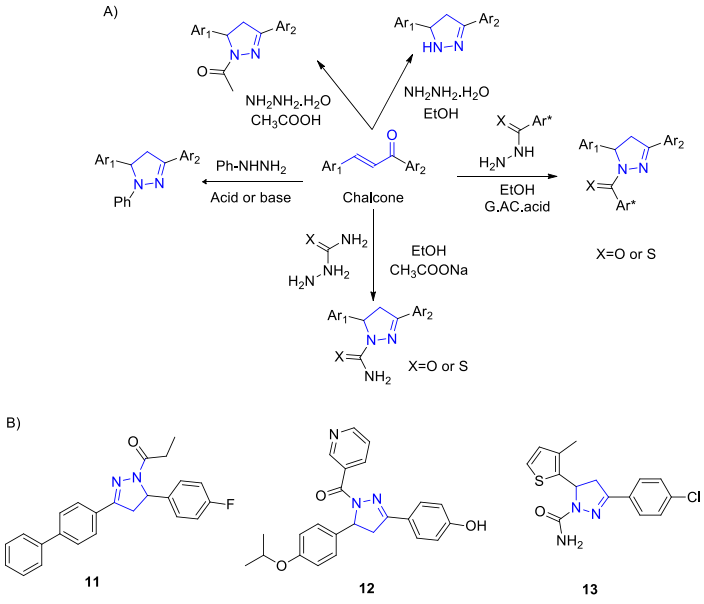


Figure 3: A) Chalcone-based pyrazolines synthetic approaches B) Structures of recently reported biologically active chalcone-derived pyrazoline compounds.

5.1.2. Chalcone-based isoxazoles.

Like pyrazolines, chalcone-based isoxazole derivatives have been synthesized *via* condensation with hydroxylamine hydrochloride in ethanol in the existence of sodium acetate or by using tosyl-hydroxylamine in methanol and K_2CO_3 aqueous solution. **Figure 4 A** Chalcone-based isoxazoles have several biological activities, for example anticancer compound **14[**94], antibacterial compound **15[**95], and anti-inflammatory-antiulcer compound **16.**[96] **Figure 4 B**

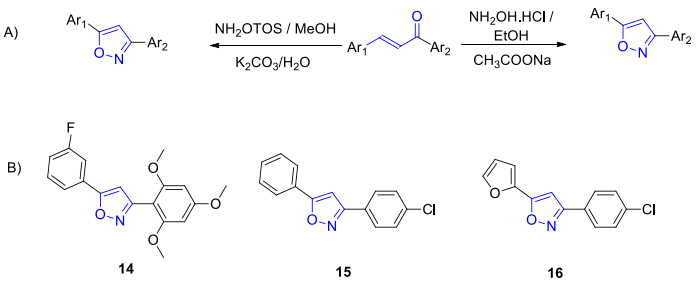


Figure 4: A) Chalcone-based isoxazoles synthetic approaches B) Structures of recently reported biologically active Chalcone-derived isoxazole compounds.

5.2. Six membered derivatives.

5.2.1. Chalcone-based Pyrimidines.

In the existence of strong bases such as KOH or NaOH, numerous chalcone derivatives have been condensed into pyrimidine compounds. Condensation of chalcones with guanidine yields amino pyrimidine,[97] whereas condensation with thiourea generates thiopyrimidine.[98] In addition, chalone refluxing with urea affords pyrimidinone.**[99] Figure 5 A** Chalcone-based pyrimidines compounds have recently gained great importance in medicinal chemistry because they exhibit diverse biological action, for example, anticancer compound **17**[100], antituberculosis compound **18[**101], and anti-diabetic compound **19**[102]. **Figure 5 B**

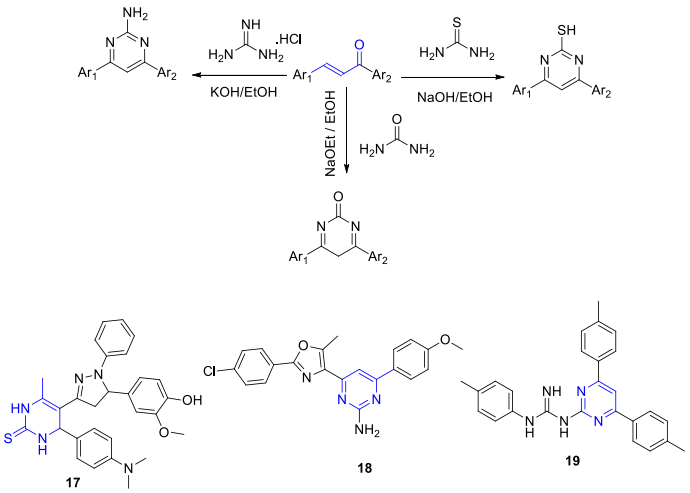


Figure 5: A) Chalcone-based pyrimidines synthetic approaches B) Structures of recently reported biologically active Chalcone-derived pyrimidine compounds.

5.2.2. Chalcone-based cyano-pyridines and cyano-pyrans.

In ethanol, chalcones reflux with malononitrile in basic conditions produces cyanopyridines.[103] Similarly, stirring of chalcones with malononitrile at ambient temperature using piperidine as catalytic base yields amino substituted cyano-pyrans. [104] **Figure 6 A** Recently, this strategy has been employed for the synthesis of numerous bioactive compounds, for example,

choline esterase inhibitor cyano-pyridine compound **20** [105] and anticancer cyno-pyran compound **21**.[106] **Figure 6 B**.

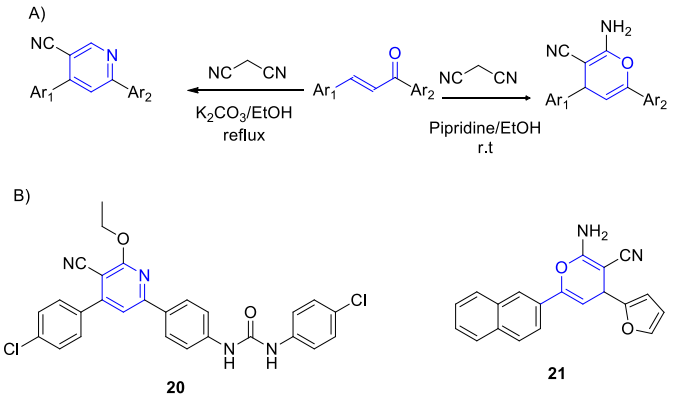


Figure 6: A) Chalcone-based Cyano-pyridine and cyano-pyrans synthetic approaches B) Structures of recently reported biologically active Chalcone-derived cyano-pyridine and cyano-pyran compounds.

Conclusion

Chalcone scaffold has a great importance in organic and medicinal chemistry due to its ease of synthesis *via* different methods and varied biological activities. Therefore, this review discussed the recent applications of chalcones' synthetic strategies including the famous Claisen Schmidt condensation; cross-coupling methods such as Suzuki Cross-coupling, Heck coupling, and Sonogashira coupling, as well as olefination reactions such as Wittig and Jula-Kocrenski reactions. In addition, Friedel-Crafts acylation of Cinnamoyl chloride, reductive annulation, and *Fries'* rearrangement approaches are used for the chalcones construction. Other eco-friendly methods as microwave and Ultra-sound assisted synthetic procedures, are also utilized for efficient chalcones synthesis. Moreover, this review also focused on the synthetic strategies of some important cyclized derivatives from chalcone, such as pyrazoles, isoxazoles, pyrimidines, cyano pyridines, and cyanopyranes. The most important physical and chemical properties of chalcones have been summarized. This review can help organic and medicinal chemists to select the best synthetic pathways for the synthesis of potential biologically active chalcone or chalcone derivatives.

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