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A Comprehensive Review on Chalcones: Preparation Methods, Reactions and Their Biological Activities

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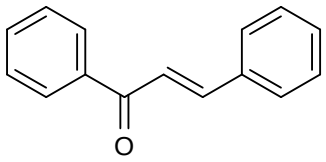
ABSTRACT: Despite their discovery in the early nineteenth century, chalcone compounds have evolved and played a significant role in medical and industrial applications. The most important feature of these compounds is that they contain two active groups (C=O and C=C), which give high biological effectiveness to pharmaceutical compounds. In both their synthetic and natural forms, chalcones have demonstrated a variety of biological properties, including antifungal, antibacterial, antioxidant, antimitotic, antimalarial, and antiviral properties. This review included preparation methods, cofactors used, chemical reactions, and biological applications for the last years.

KEY WORDS: Chalcones: Preparation methods, Reactions, Biological activities.

INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-ones) are crucial molecules that belong to significant categories of natural compounds and act as fundamental units for the synthesis of different types of flavonoids, which are highly prevalent in plants [1]. It is called a chalcone in chemical terms when two aromatic rings are joined together by a three-carbon alpha-beta-unsaturated carbonyl system [2]. Researchers have utilized chalcones as a foundation to create compounds with noteworthy pharmacological characteristics [3]. In certain Coreopsis and Asteraceae taxa, the pigments that make up chalcones, dihydrochalcones, and aurones shift from yellow to orange in color. These substances are present in many different plant tissues in addition to flowers. The interest in consuming plants containing chalcones increased due to the phenol groups' ability to scavenge free radicals [4]. The chemistry of chalcones continues to pique scientists' interest in the twenty-first century, yielding a variety of intriguing pharmacological properties such as antimicrobial [5], antiulcer [6], antioxidant [7], anti-inflammatory [8], analgesic [9], antimalarial [10], anti-gout [11], antihistaminic [12], anticancer [13], antileishmanial [14], antiviral [15], and antidiabetic effects [16].



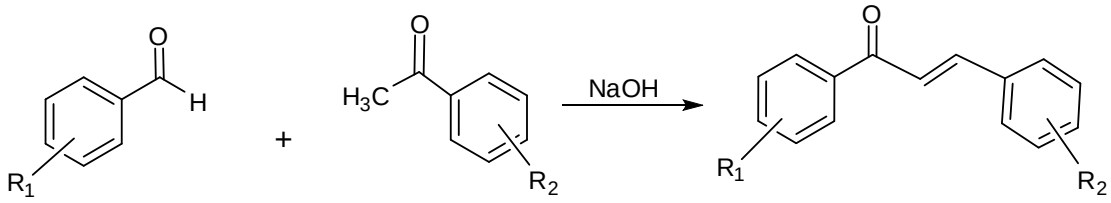
1,3-diphenyl-2-propen-1-one

1. PREPARATION METHODS OF CHALCONES

In general, aryl ketones and aromatic aldehydes are condensed in the presence of appropriate condensing agents to produce chalcones.

1.1. Claisen-Schmidt's condensation:

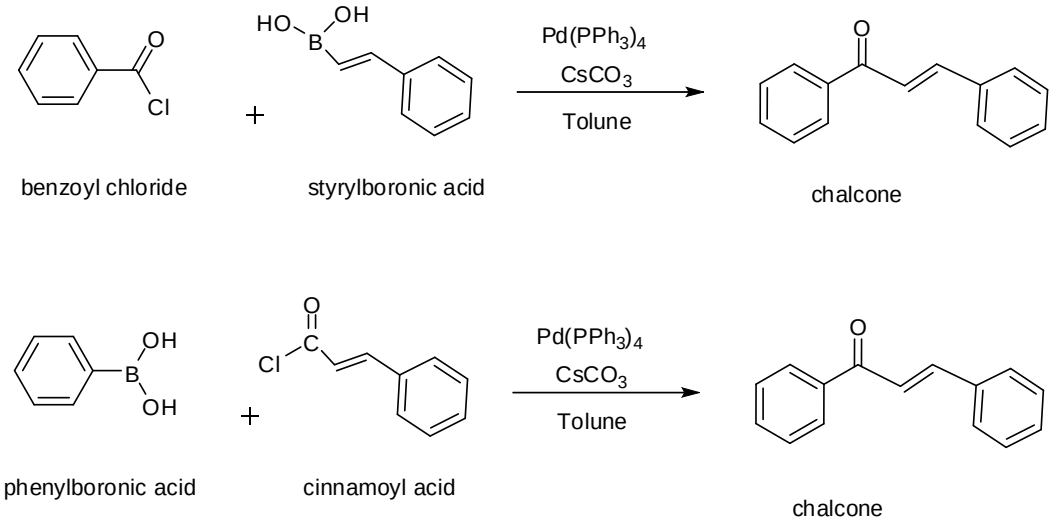
This process for making chalcone involved condensing a ketone with an aldehyde while alcoholic alkali or aqueous alkaline bases were present, (1) [17].



Scheme (1) Claisen-Schmidt's condensation

1.2. Suzuki–Miyaura's coupling reaction

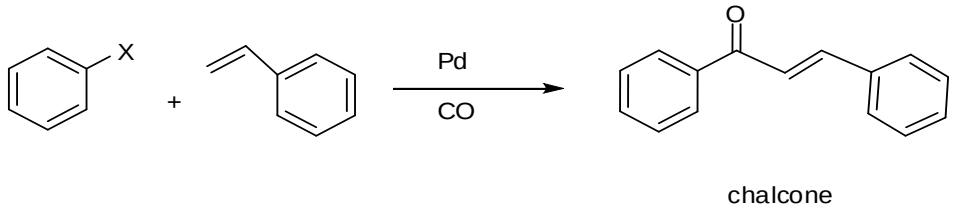
Using Pd $(PPh_3)_4$, $CsCO_3$, anhydrous toluene, and either benzoyl chloride and styryl boronic acid or phenyl boronic acid and cinnamoyl chloride using $Pd(PPh3)_4$, $CsCO_3$, and anhydrous toluene, this coupling process occurs. (2) [18].



Scheme (2) Suzuki–Miyaura's coupling reaction

1.3. Carbonylative Heck's coupling reaction

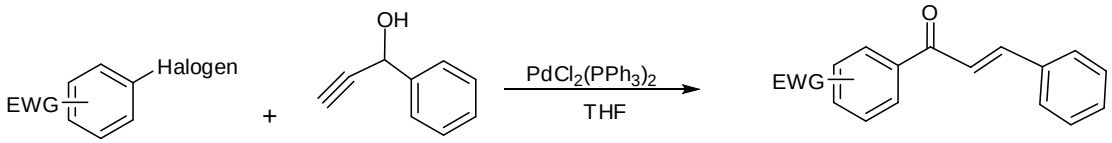
Chalcones are produced by vinylating aryl halides (like phenyl halides) with styrene in the presence of carbon monoxide, wherein palladium acts as a catalyst and undergoes carbonylative coupling, (3) [19].



Scheme (3) Carbonylative Heck's coupling reaction

1.4. Sonogashira's isomerization coupling

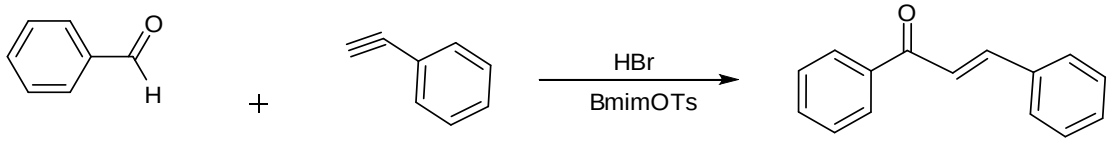
Chalcones are produced in this reaction by the microwave coupling of an electron-deficient group (such as phenyl halide) and prop-2-yn-1-ol with a catalyst ($PdCl2(PPh_3)_2$) and a solvent (such as tetrahydrofuran; THF), (4) [20].



Scheme (4) Sonogashira's isomerization coupling

1.5. Miscellaneous reaction

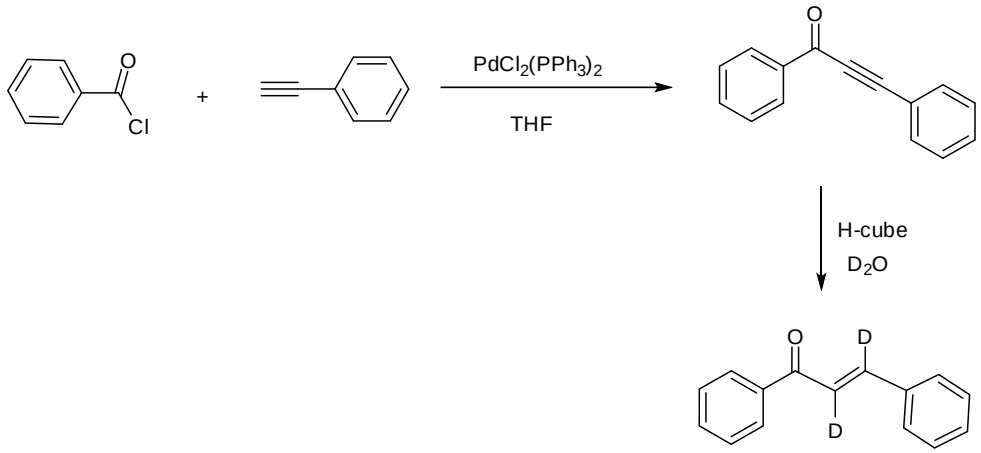
Chalcone was produced by reacting benzaldehyde and phenylacetylene in hydrogen bromide and ionic liquids such as 1-butyl-3-methyl-1H-imidazolium 4-methylbenzenesulfonate (BmimOTs) for 12 hours at 100 °C, (5) [21].



Scheme (5) Miscellaneous reaction

1.6. Continuous-flow deuteration reaction

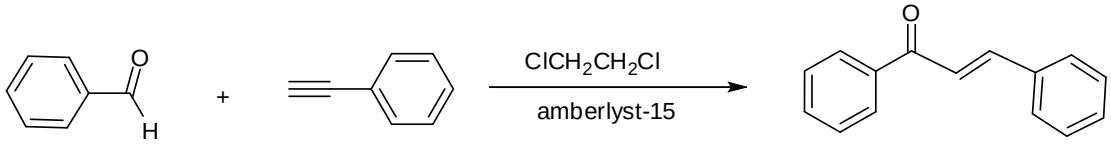
The basic method for synthesizing ynones is described in the literature. It involves reacting benzoyl chloride and phenylacetylene under Sonogashira's conditions, and then deuterating the product in an H-Cube system by substituting D_2O for H_2O as the



Scheme (6) Continuous-flow deuteration reaction deuterated source, (6) [21].

1.7. Solid acid catalyst-mediated reaction

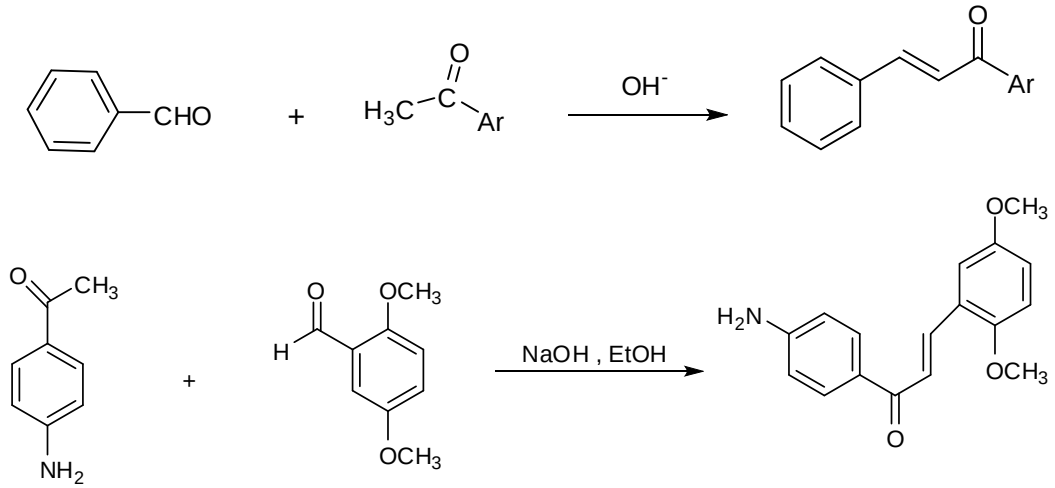
Chalcone was produced by heating 1,2-dichloroethane with benzaldehyde and phenylacetylene in a microwave and employing an ion-exchange resin such as amberlyst-15, a solid acid catalyst, (7) [22].



Scheme (7) Solid acid catalyst-mediated reaction

1.8. Aldol reaction

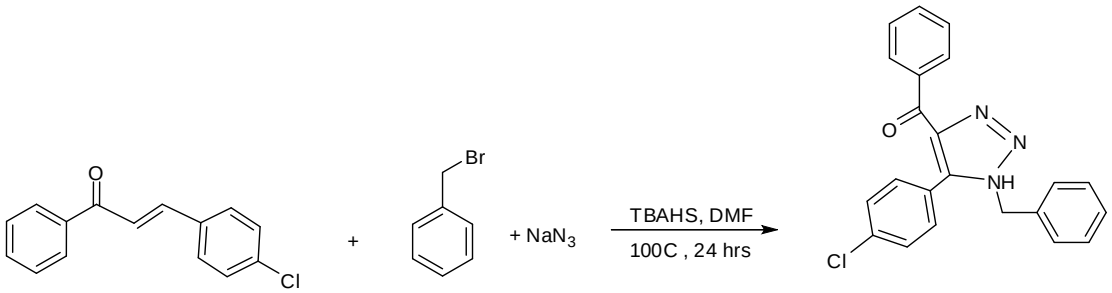
In an ethanolic basic media, benzaldehyde treatment of ketones produces chalcone [23]. By reacting 4- aminoacetophenone with 2,5 dimethoxybenzaldehyde in the current 40% NaOH solution as a catalyst in ethanol, Hery et al. synthesized anmine chalcone derivative secheme (8)[24] .



Scheme (8) Aldol reaction

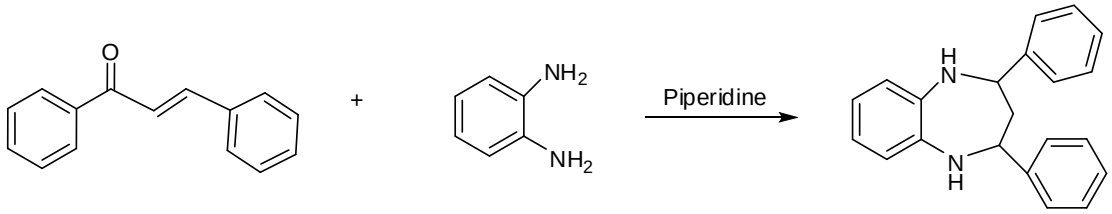
2. REACTIONS OF CHALCONE

When chalcone derivatives are treated with (azidomethyl) benzene (an aryl alkylazide), sodium azide is treated with (bromomethyl) benzene under realistic conditions, yielding good amounts of [1-benzyl-4-benzoyl-5(4-chlorophenyl)-1-H-1,2,3-triazol, which was synthesized by N. Singh et al [25], Scheme (9).



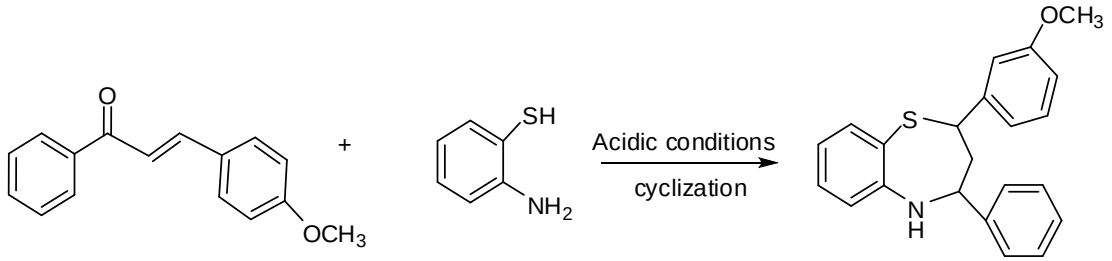
Scheme (9) Synthesized of 1,2,3-triazol derivatives

2,4-diphenyl-1,5-benzodiazepine was produced through the reaction of chalcone with *o*-phenylenediamine in the presence of piperidine as a catalyst. Benzodiazepines have been made using this method, Scheme (10) [26].



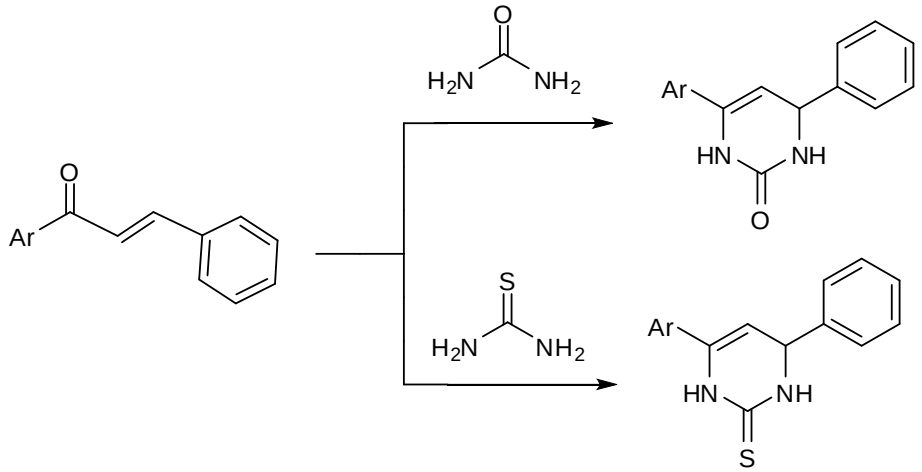
Scheme (10) Synthesized of 2,4-diphenyl-1,5-benzodiazepine

Chalcone, (E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, reacted with 2-aminothiophenol in an acidic environment to yield a derivative of benzothiazepine, Scheme (11) [27].



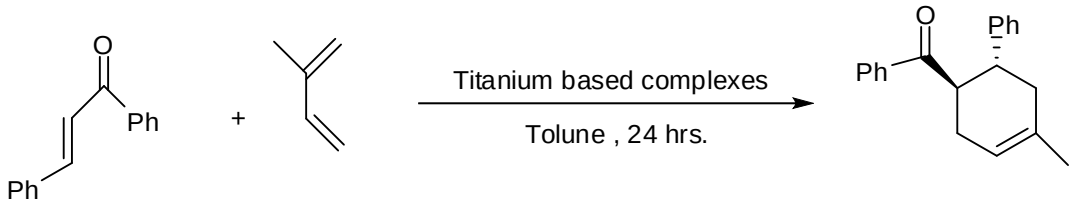
Scheme (11) Synthesized of Benzothiazepine

In an acidic solution, chalcones interacted with urea and thiourea to produce 6-phenyl-4-arylpyrimidin-2(1H)-one and 6-phenyl-4-arylpyrimidine-2(1H)-thione, respectively, Scheme (12) [28].



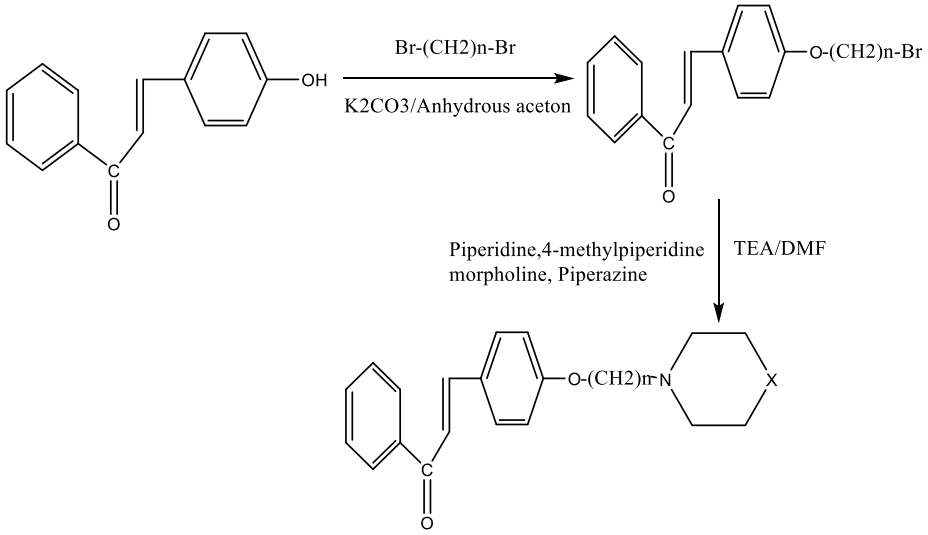
Scheme (12) Synthesized of Arylpyrimidin derivatives

By using chiral titanium complexes, the asymmetric Diels-Alder reaction between chalcone and isoprene has been achieved. Notably, a 95% regioselectivity and an enantiomeric excess of up to 61% have been attained. It is not necessary to install a chiral auxiliary beforehand in order to prepare the chiral titanium complexes. The asymmetric Diels–Alder reaction between chalcone and isoprene is demonstrated for the first time in this study, Scheme (13)[29].



Scheme (13) Diels-Alder reaction

When (E)-4-hydroxy chalcones and dibromoalkanes are heated in dry acetone with anhydrous potassium carbonate present, O-alkylation takes place [30]O-Alkylation reaction of hydroxy chalcones with dibromoalkanes scheme (14).



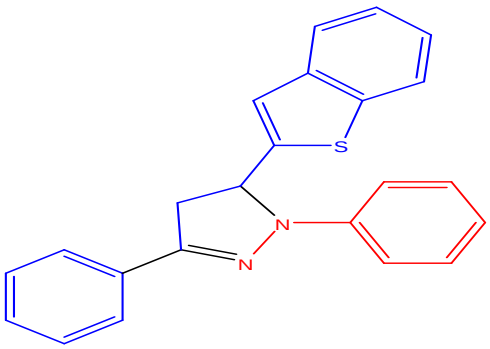
Scheme (14) O-Alkylation reaction of hydroxy chalcones with dibromoalkanes

3. BIOLOGICAL ACTIVITIES OF CHALCONES

Chalcones are a commonly utilized model in medicinal chemistry to facilitate drug discovery. They are often found in many plant parts, including seeds and flowers, and have a basic structure. Many chalcone derivatives are synthetic because of their easy and convenient synthesis. These substances exhibit a wide range of biologically significant behaviors that may be used therapeutically to treat various illnesses [31].

3.3. Chalcone as antimicrobial

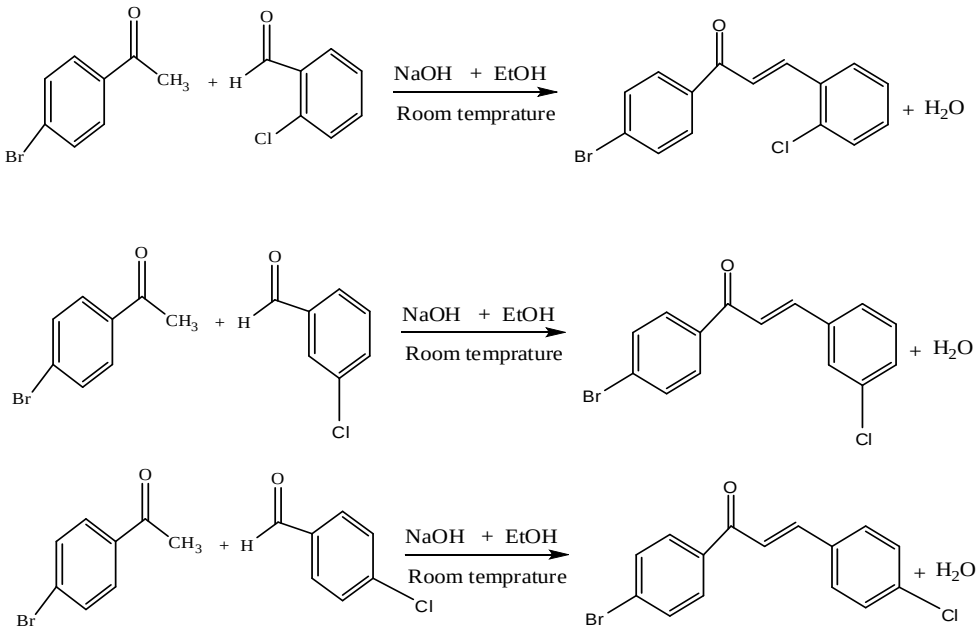
By reacting phenyl hydrazine with our previously described chalcone via a cyclization pathway in the presence of acetic acid, a series of pyrazoline derivatives were produced. The results of an investigation into the effects of various solvents, temperature, and reaction time on the production of pyrazoline are provided. For the synthesis of derivatives of pyrazolines, the synthetic applicability of several solvents, such as benzene, THF, ethanol, and acetic acid, was assessed. Even after five hours, no product had formed when the process was first initiated in benzene at room temperature with equal amounts of both substrates. Similarly, no product production was seen in THF either [32].



Pyrazoline

3.4. Chalcone as antioxidants

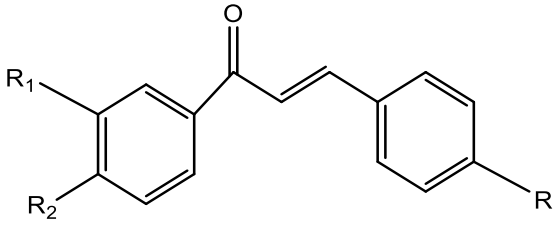
Jalal et al. [33], synthesized some chalcone derivatives as antioxidant Agent's scheme 15.



Scheme (15) In vivo studies

3.5. Chalcone as antiepileptic

Anees et. al . [34] A series of chalcones derivatives were evaluated for antiepileptic property in scheme (16).

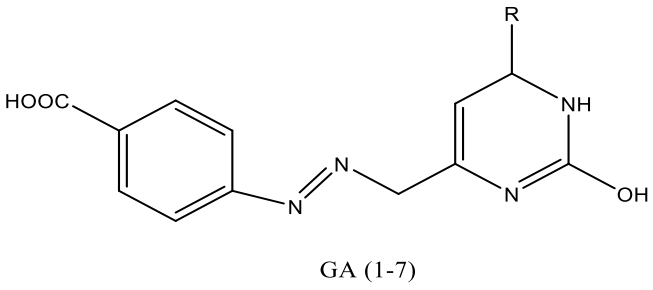


R=H, R_1= H, R_2= OCH3
R=H, R_1=Cl, R_2= H
R=OCH3, R_1=H, R_2=OCH3
R=CH3,R_1= Cl, R_2=H
R=Br, R_1=H, R_2=Cl

Scheme (16) Reaction scheme for synthesis of chalcone

3.6. Chalcone as antihypertensive agents

Chalcone derivatives were synthesized, consisting of pyrimidine as the basic moiety, and tested to be potent antihypertensive agents [35].



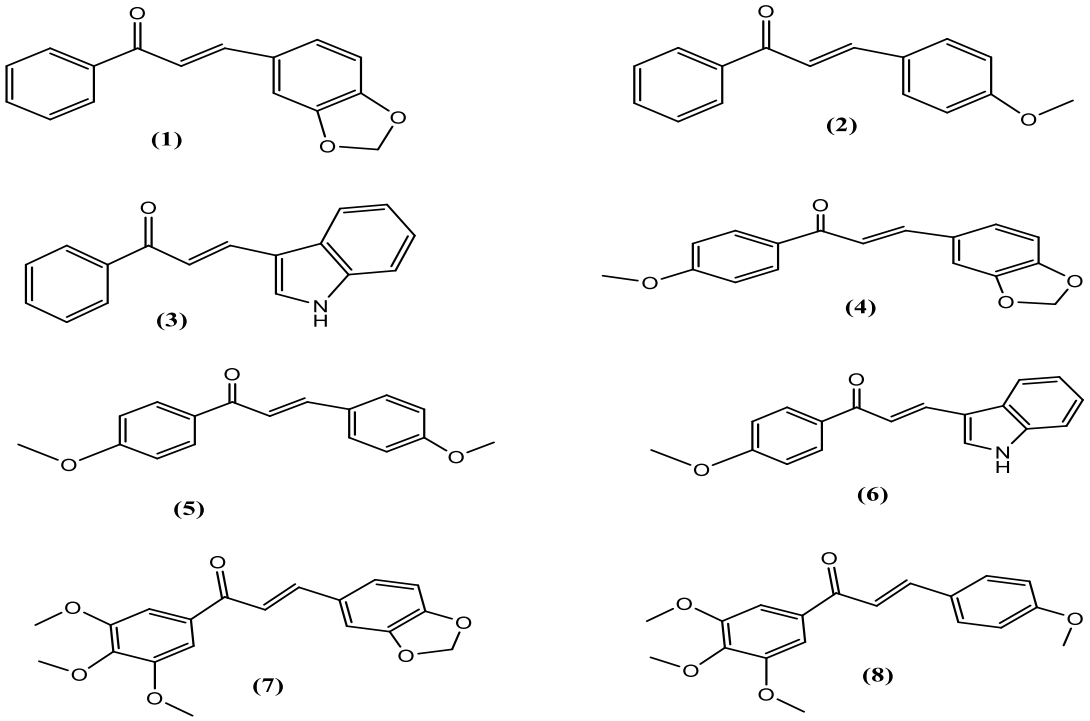
GA (1-7)

Compound	R
1	C_6H_5
2	2-OH C_6H_5
3	4-OH C_6H_5
4	2-NO_2 C_6H_5
5	4-OCH_3 C_6H_5
6	3- NO_2 C_6H_5
7	2-Cl C_6H_5

Scheme (17) Reaction scheme for synthesis of chalcone containing pyrimidine

3.7. Chalcone as Sunscreen Agent

Lucia *at el*., Synthesized synthesized eight chalcone derivatives through Claisen–Schmidt condensation, scheme (18), [36].



Scheme (18) Chemical structure of chalcone 1-8

CONCLUSION

Chalcone is a simple molecule with two aryl rings separated by an unsaturated carbonyl group (α, β). Chalcones can be made in a number of ways, for as via condensation or combining several chemicals together. However, because they include functional groups (C=O and C=C), chalcones are engaged in a variety of reactions. Chalcones, on the other hand, have great success in a variety of biological applications, including antifungal, antibacterial, antiviral, antioxidant, antimitotic, and antimalarial.

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