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SYNTHESIS OF SOME CHALCONE DERIVATIVES AND ITS ANTIOXIDANT ACTIVITIES

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Abstract

Recent years have seen an increase in interest in chalcones and compounds derived from them. Chalcones have been the subject of several studies, and their results are encouraging for the development of novel pharmaceuticals. The medicinally significant and beneficial chalcone species contains the flavonoid -CO-CH=CH-, a highly reactive ketoethylenic system. In plants, flavonoids are constructed from chalcones (1, 3-diphenyl-2-propen-1-one). Two or more aromatic rings and a three-carbon ß-unsaturated carbonyl system characterise them. Nevertheless, reports have also surfaced of the synthesis of a wide variety of chalcones in laboratory settings. The pharmacological potencies of chalcone and its derivatives are mainly due to their extremely reactive a, ß-unsaturated carbonyl system. Chalcones and their derivatives have a wide range of pharmacological effects. These effects include anti-inflammatory, antioxidant, antileishmanial, antifungal, anticancer, antibacterial, antiulcer, antiprotozoal, antitumor, antimalarial, antidiabetic, anthelmintic, insecticidal, antitigout, antihistaminic, antiviral, antimycobacterial, and many more positive effects. The synthesis of chalcones can be accomplished in a variety of ways, including the following: one pot

synthesis, solvent-free synthesis, ultrasound technique, Aldol condensation, Claisen-Schmidt's condensation, and many more. In this overview, we will look at the different ways chalcones and derivatives can be made, as well as their anti-antioxidant properties.
Keywords: Chalcone, Antioxidant, Pharmacological activity, Synthesis

Introduction

Any research that aims to identify new drugs must make molecular diversity a top priority. Obtaining the chemicals of interest might be accomplished through either natural or chemical synthesis. Unknown chemotypes, molecular scaffolds, pharmacophores, and structural fragments with potential medicinal chemistry applications may be present in naturally occurring substances[1]. Therefore, natural goods are always thought of as great resources for coming up with new medical discoveries. Researchers have lately become interested in microfragments or scaffolds with a molecular weight of about 300 Da because of their remarkable properties[2]. More specifically, these fragments possess the capacity to engage in efficient molecular interactions with specific biological receptors, hence enabling them to perform pharmacological effects[3]. The field of fragment-based drug design (FBDD) highly values these characteristics, therefore keep that in mind. All of these wonderful features may be found in flavonoids, which are a fantastic source. Flavonoids are among the most abundant polyphenols, and they are highly regarded among the numerous secondary metabolites that may be discovered in plants. There is a wide variety of subclasses of flavonoids, which include chalcones, flavanones, isoflavones, aurones, neoflavones, and biflavones[4]. There have been approximately 7,500 flavonoids with a variety of molecular identities that have been reported up until this point. It has been established that chalcones are a precursor for the production of flavonoids and that they play an important role throughout the flavonoid system[5].

In Greek, "chalcos" means "bronze," and this is where the English term "chalcone" gets its start. When describing a mineral's hue in its unprocessed form, this term is employed[6]. The chalcone chemical scaffold, which goes by a few names like chalconoid or 1,3-diaryl-2-propen-1-one, can exist in two distinct forms. In terms of thermodynamic stability, the trans isomer outshines the other option[7]. Figure 1 shows the phenyl ring connected to the carbonyl group, which is called the A ring here. The carbonyl group's connection to the benzene ring is known as the B ring, in contrast.

Chalcones have an α,β-unsaturated structure formed by the combination of three carbon units. They have been the subject of much study, especially in the domains of infectious and non-infectious diseases; their hydrophobic and hydrophilic properties have at least one possible explanation in their name, 1,3-diphenylprop-2-en-1-one. It should be noted that both cis and trans chalcones are present, with the former being more thermodynamically stable. It has been noted that chalcones possess biological characteristics[8].

Furthermore, the chalcone family has attracted a great deal of attention from synthetic and biosynthetic points of view, in addition to the wide range of fascinating biological functions that it possesses[9]. The use of plants and herbs for the treatment of a wide range of medical conditions, such as inflammation, diabetes, cancer, and chalcones, has a history that extends back thousands of years[10]. For the purpose of conducting clinical studies, a number of medications that are based on chalcones have been given the go-ahead. In Figure 1, two examples are the choleretic pharmaceutical metochalcone and the antiulcer and mucoprotective medicine sofalcone. Both of these medications are from the same class[11]. In spite of this, the profound biological impacts of chalcones and the specific processes by which they exert their influence are still not well understood[12].

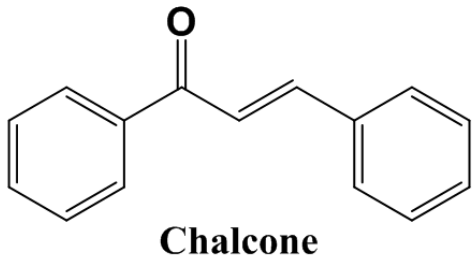


Fig 1: Structure of Chalcone

Chalcones from natural sources

Convergent synthesis involves combining the phenyl propane and acetate methods in order to create chalcones[13]. There are three phases of enzymatic reactions that take place during the formation of phenylalanine from coumaroyl-CoA. Additionally, the Krebs tricarboxylic acid cycle is dependent on the carboxylation of acetyl-CoA in order to make malonyl-CoA[14]. There is a further classification of the chalcones based on the structural characteristics that they possess[15]. As an illustration, the chemicals that are commonly discovered in plants are either hydroxylated or methoxylated structures[16]. Less frequently encountered are the glycosylated and prenylated forms, as well as the geranylated derivatives of chromene and dihydroquinone-based chalcones. In the past, therapeutic applications of herbs that contained chalcone were employed for the treatment of a wide variety of ailments. There are a number of species that contain significant quantities of this substance. Some of these plants are *Butea monosperma*, *Desmodium gangeticum*, *Humulus lupulus*, *Helichrysum rugulosum*, *Neoraputia magnifica*, *Angelica keiskei*, *Piper hispidum*, *Tarenna attenuata*, and *Calythropis aurea*[17-19].

Methodology

Search Strategy

A comprehensive investigation was carried out on the scientific databases Pubmed, Scopus, Scielo, and Science Direct, utilising the keywords Chalcones, biological activities, and antioxidant activities.

Chalcone chemistry and its derivatives

Chalcone and its derivatives are utilised in numerous well-established medicinal traditions, including homoeopathy and traditional Chinese medicine. There are numerous other such practices as well. Both benzaldehydes and active methylene ketones are normally produced through a reaction that takes place in a homogeneous environment. This reaction can be carried out using either the Claisen-Schmidt condensation or, more recently, the aldol condensation, which are two ways that have been successfully established. Despite this, recently developed methods of producing chalcones offer a variety of advantages, which vary according to the catalyst, solvent, base, and reaction conditions that are utilised.

Claisen-Schmidt Condensation

The Claisen Schmidt condensation procedure can generate the required α,β-unsaturated ketone by making use of a heterogeneous acid catalyst. To do this, a ketone is joined to an aldehyde through a carbonyl group that is free of hydrogen atoms in the α-position. Using this technology, chalcone can be synthesised in a controlled environment. The fact that acetophenone and benzaldehyde have identical molecular weights makes this a real possibility. The Claisen Schmidt condensation calls for a 10% to 60% concentration of an aqueous-alcoholic alkali. When acetophenone and benzaldehyde react, this is done to speed up the dehydration process. On one hand, the reaction can go on for 12–15 hours at 50°C, or for a whole week at 20–25°C.

The heterogeneous acid catalyst has several benefits when making chalcones, including a faster reaction time, less expensive method, more pure end product, and less unwanted byproducts. Ionic liquids (ILs) are produced using this condensation approach by employing a multi-sulfonic acid group ion liquid as the catalyst. The continuous catalytic activity, low catalyst usage, simple filtration, and strong catalytic activity of ILs have made them very popular (Figure 2). Nevertheless, if the reaction conditions favour the Cannizzaro reaction, the product yield will fall. Starting with just two molecules of aldehyde, this redox process yields primary alcohol and carboxylic acid[20].

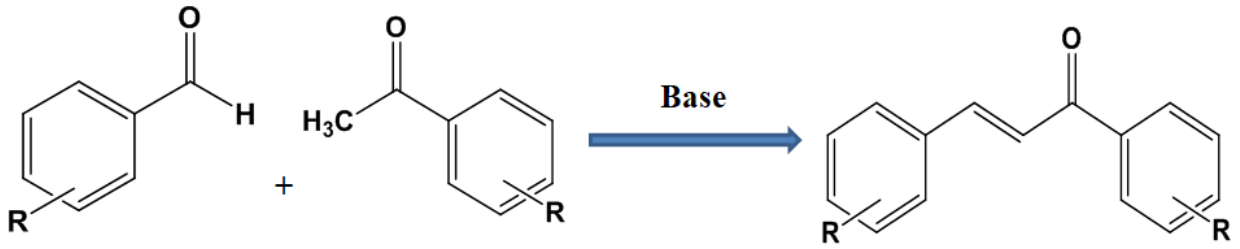


Figure 2: Claisen-Schmidt condensation

Aldol condensation

Another well-known synthetic process that follows the Claisen-Schmidt condensation is the Aldol condensation. When aldehydes are not present, the solid-state reaction, also called the aldol condensation reaction, can take place with the help of a base, like potassium hydroxide, and heat (200–350 degrees Celsius). The reactants in this reaction are benzylidene-diacetate instead of aldehydes. A mixture of catalysts (calcium, barium, or strontium hydroxides or carbonates) and a low-boiling-point liquid (water) can be distilled at a constant temperature. Using microwave radiation instead of solvents speeds up other synthetic reactions; these reactions also provide fluorescence emission profiles that can be utilised as biological indicators. This is possible because microwave radiation is a form of high-energy microwave radiation. Through the reaction of a ketone with an aldehyde that possesses an acidic heterogeneous catalyst-activated carbon and a carbonyl group that does not contain any hydrogen atoms in the α position, it is possible to reduce the amount of impurities, as well as the amount of time and money required for the reaction. The phase transfer method is an additional way that can be utilised to synthesise chalcones that contain heterocyclic rings. In this approach, the chalcone skeleton chain is extended by a third ring. The following reaction occurs when acetophenone and 1-phenyl-3-aryl-4-formyl pyrazole are exposed to microwave radiation; tetrabutylammonium bromide is used as a catalyst. Figure 3 also shows the presence of an inorganic alkaline solution[21].

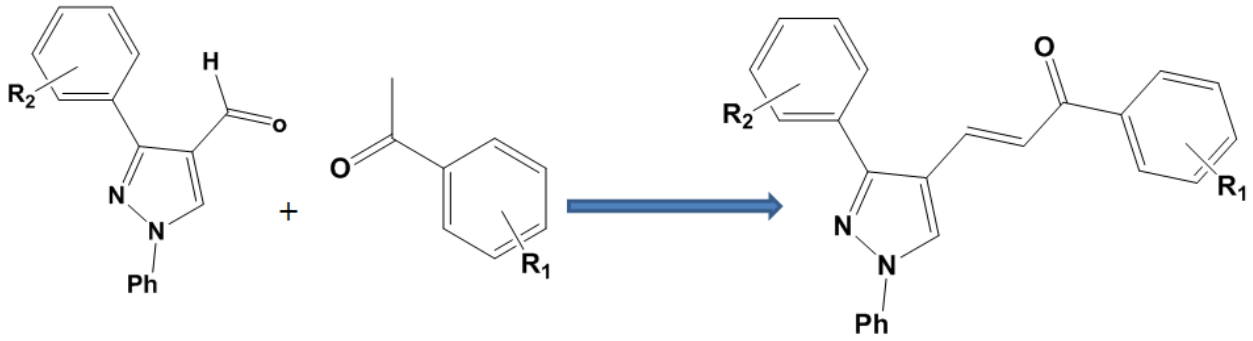
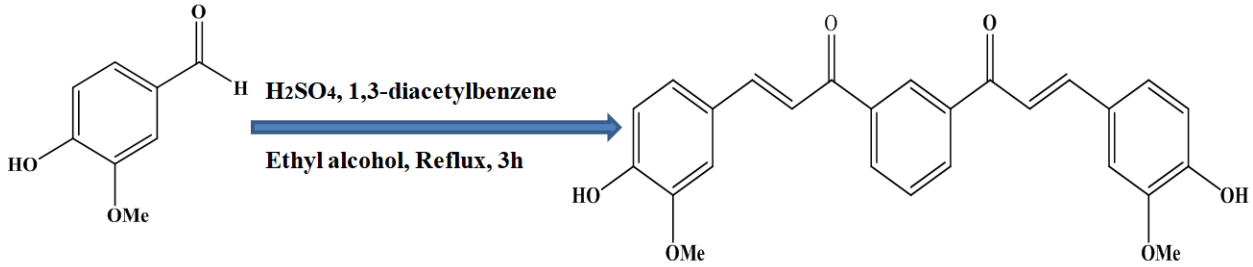


Figure 3: Using a phase transfer catalyst, a heterocyclic ring-containing chalcone

Synthesis of 1,3-Diacetylbenzene and 1,4-Diacetylbenzene derivatives by a synthetic process

The potential biological and structural uses of chalcone derivatives 1-3 were the focus of this investigation. These compounds were generated when 1,3-and/or 1,4-diacetylbenzene, 1,3,5-triacetylbenzene, and 4-hydroxy-3-methoxybenzaldehyde underwent a condensation process. Acetic acid, concentrated hydrochloric acid, phosphoric acid, and sulfuric acid were utilised in the one-step procedure. Using a mixture of concentrated sulfuric acid and ethanol yielded the best results[22].



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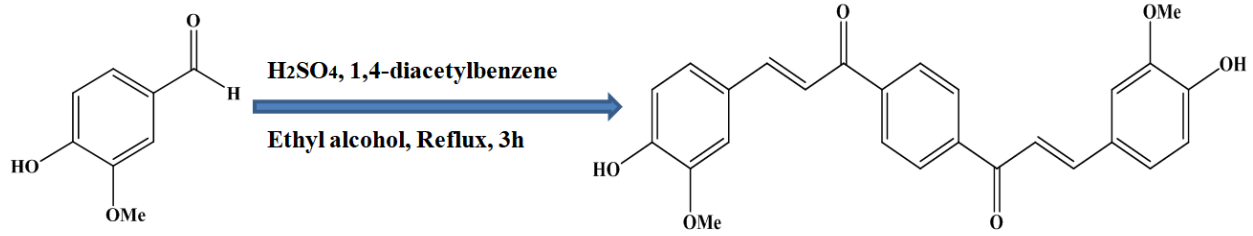

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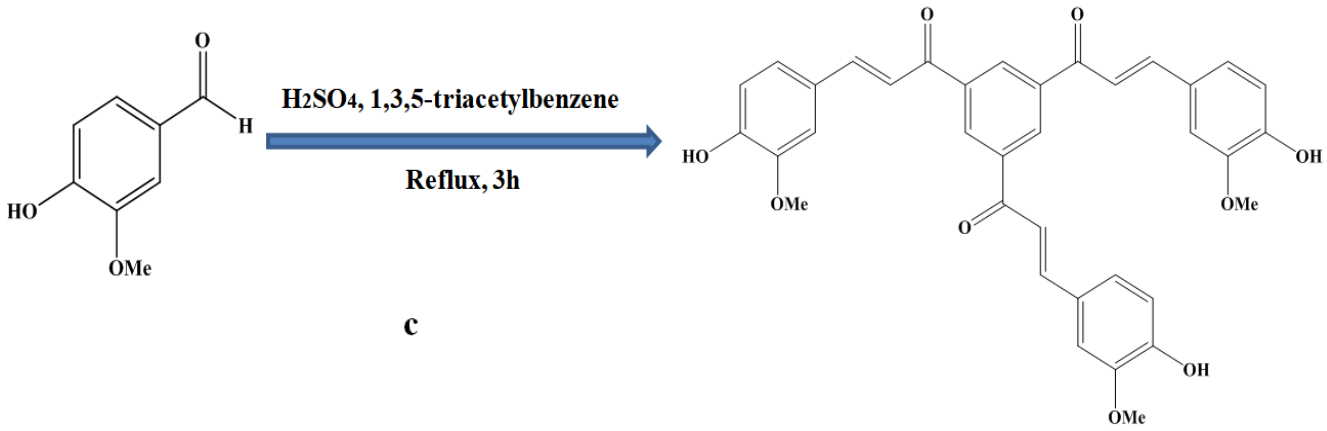

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Figure 4: Synthesis of Chalcone derivatives from 1,3-Diacetylbenzene and 1,4-Diacetylbenzene and 1,3,5-triacetylbenzene

A One-Pot Approach to the Synthesis of Chalcone

The chalcone derivative 4 was created by reacting phenylmethanol 4 with acetophenone using CrO3 as an oxidising agent[23].

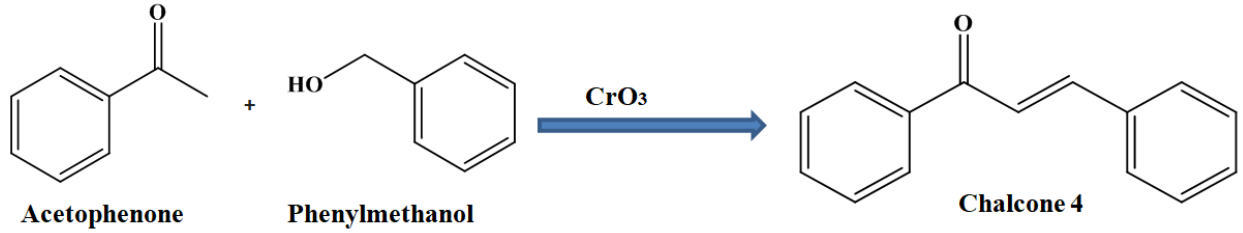


Figure 5: One-pot synthesis of Chalcone 4

Synthesis of Chalcone using solid acid catalyst

Following the application of a catalytic quantity of heterogeneous acid in 1,2-dichloroethane as a solvent, benzaldehyde and phenylacetylene were subjected to microwave irradiation in order to generate the corresponding chalcone 4.

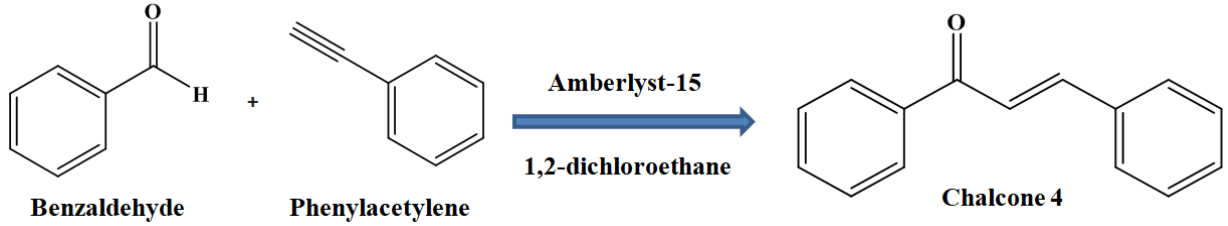


Figure 6: Synthesis of Chalcone using solid acid catalyst

Synthesis of Chalcones using Greener approaches

Microwave-assisted method

The microwave-assisted synthesis of chalcones was developed so that the disadvantages of the traditional methods may be avoided. When using the microwave-assisted technique, the reaction is often able to occur more quickly in the majority of instances. As an illustration, it is possible to generate a diminutive quantity of heteroaromatic chalcones without the use of solvents in a span of three to five minutes[24]. A thick paste is created by combining the catalysts, which,

depending on the conditions, can either be acidic or basic. This paste is then mixed with the starting materials. After that, the catalysts can be eluted in order to separate the product into a form that is soluble. It has been possible to synthesise a number of chalcones by employing microwave irradiation and using K2CO3 as the starting material. Additionally, chalcones that include pyrazoline moieties have been successfully created in higher amounts when they are exposed to acidic conditions[25].

Ultrasound-irradiated synthesis

Furthermore, the ultrasonic irradiation method is an additional way that does not necessitate the use of solvents in order to develop it[26]. Ultrasonic irradiation reduces the amount of time required to produce the product while simultaneously increasing the amount of product that is produced[27]. This is accomplished by raising the pace of the reaction. It was shown that the reaction could be completed in around 10 seconds when thiophene-based chalcones were synthesised with cesium carbonate as the base. Through the utilisation of a catalyst that was based on zeolite, it was also possible to generate chalcones without the need of any solvents, with a yield that was greater than 95%[28].

Grinding technique

Additionally, chalcones can be synthesised by utilising this approach, which does not require the utilisation of solvents[29]. The reagent, acetophenone, and aromatic aldehydes should be mixed together in an equal proportion in a porcelain mortar, and then the mixture should be ground for roughly ten minutes. In the process of adding cold water, filtration makes it possible to separate the product of interest from the rest of the mixture. The compounds were synthesised with a yield ranging from 85 to 95% after a series of chalcones were synthesised using a grinding technique, various benzaldehydes, and 2-acetyl-2-naphthol[30].

Antioxidant activity of Chalcone derivatives

Using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, the in-vitro antioxidant activity of the three chalcones that were synthesised was evaluated. This examination was carried out in accordance with the approach that was described by Mulula et al[31]. For the purpose of evaluating the antioxidant activity, methanol was used to produce concentrations of 2, 4, 6, 8, and 10 µg/mL of the chalcones that were synthesised. These concentrations were designated as test solutions[32]. The DPPH solution was prepared in methanol at a concentration of thirty milligrammes per millilitre. One millilitre of this solution was then combined with nine millilitres of test solutions that included synthetized chalcones at varying concentrations of two, four, six, eight, and ten micrograms per millilitre with this solution. An ultraviolet spectrophotometer was used to determine the absorbance at 517 nm after the darkness had been present for 30 minutes[33]. The participants in the control group were given the equal amount of DPPH and methanol to mix together. The graph was constructed using the average of the three results obtained from each test, which were carried out three times. A comparison was made between the absorbance values of the test solutions and those of the control blank solution in order to ascertain the percentage of inhibition[34]. Yakuchinones A and curcumin-related enones are two examples of chalcones that have been investigated and discovered to possess a variety of pharmacological effects. These qualities include the inhibition of prosurvival transcription and the antioxidant action[35].

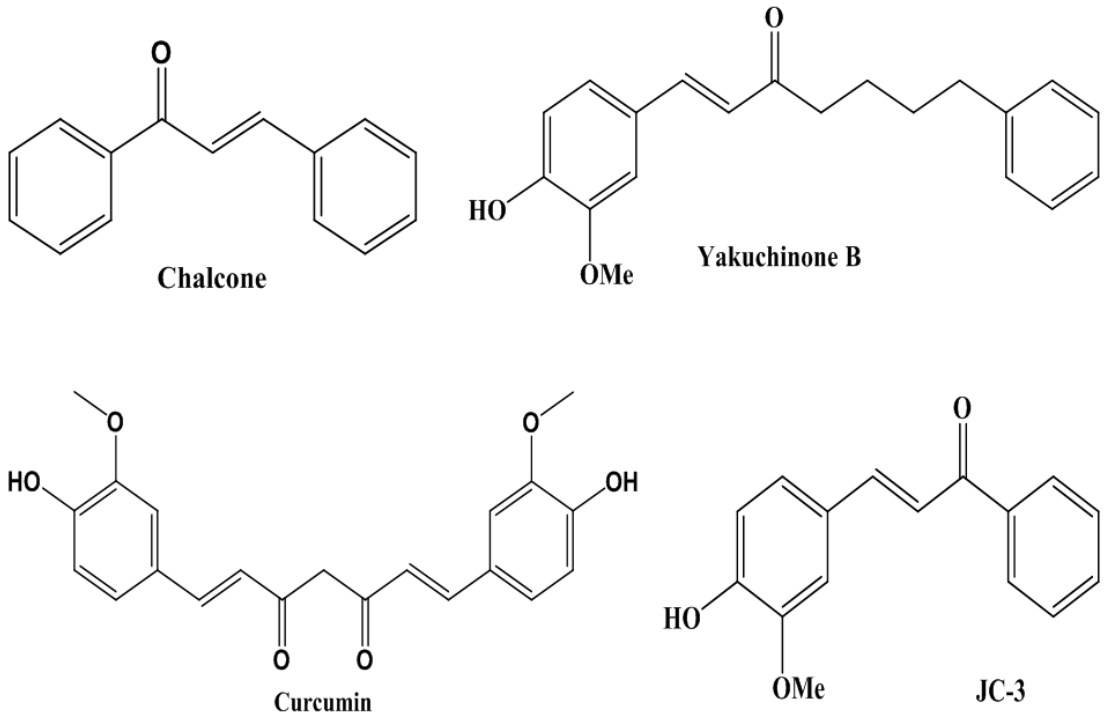
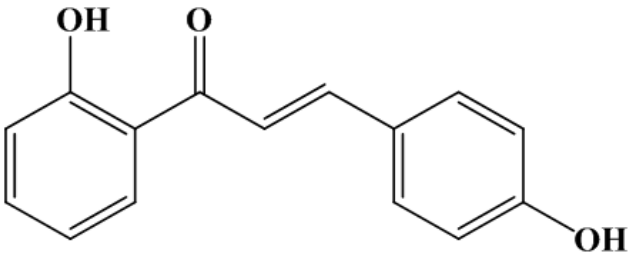
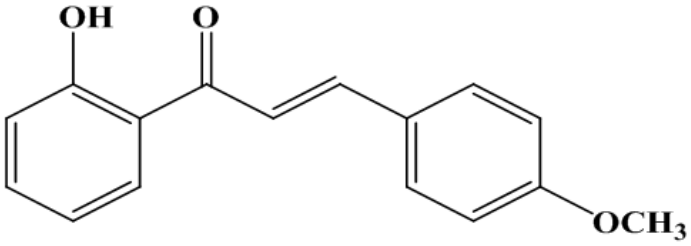


Figure 7: Chalcone, Yakuchinone B, Curcumin, JC-3 these all compounds shows antioxidant activity

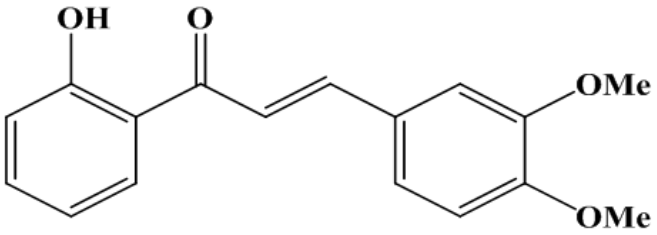
This is due to the fact that oxidants such as peroxynitrite, nitric oxide, hydrogen peroxide, and hydroxyl are responsible for cell death in humans. The free radical scavenging activity of three distinct chalcones 1, 2, and 3 (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one, (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one, and (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one—was determined by measuring the compounds' ability to reduce the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH)[36]. A standard called ascorbic acid is used. In the visible light spectrum, DPPH has a strong absorption band at 517 nm when it is a free radical[37]. Three synthetic chalcones and the reference were tested for antioxidant activity, and the findings are shown in Table 1 and Figure 8[38]. All three of the synthesised chalcones demonstrate remarkable antioxidant activity, according to their respective IC50 values: (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1), (E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2), and (E)-3-(3, 4-dimethoxyphenyl)-1-(2-hydroxyphenyl) prop-2-en-1-one (Chalcone 3). The ascorbic acid concentration, on the other hand, was 2.17 µg/mL[39,40].



(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one



(E)-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one



(E)-3-(3, dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one

Figure 8: (E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1), (E)-1-(2- hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2) and (E)-3-(3, 4-dimethoxyphenyl)-1-(2- hydroxyphenyl) prop-2-en-1-one (Chalcone 3).

Compounds	**IC50 (µg/ml)**
(E)-1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (Chalcone 1)	8.22
(E)-1-(2- hydroxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one (Chalcone 2)	6.89
(E)-3-(3, 4-dimethoxyphenyl)-1-(2- hydroxyphenyl) prop-2-en-1-one (Chalcone 3)	3.56
Ascorbic acid	2.17

Conclusion

In the chemical process, chalcones can be used to synthesise and transform a wide variety of molecules that have a variety of different structures. Because the compounds possess desirable properties, they have the potential to serve as viable building blocks for molecule-targeting therapeutics. This review brings together the most recent knowledge that has been gathered regarding chalcone synthesis. Further, it demonstrates the adaptability of these scaffolds in terms

of their ability to be utilised in the development of various kinds of compounds through the utilisation of various synthetic methods and moieties. An examination of the antioxidant capabilities of a few chalcone derivatives is presented throughout this article. Despite the fact that it is not difficult to synthesis, there will be a need for new methods of doing so in the future. The identification of their targets, the examination of molecular mechanisms of action, and the exploration of unique biological aspects are all going to be made possible as a result of this.

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