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Review on Substituted Chalcones

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Abstract- Chalcones and their analogues have emerged as a subject of significant attention in contemporary times. A multitude of scholarly articles have been disseminated, attesting to the ongoing potential of chalcones in the realm of novel pharmaceutical inquiries. Scholars have conducted investigations into novel methodologies for the production of chalcone derivatives, leading to the discovery of a diverse range of pharmacological and biological impacts. The chalcone derivatives have demonstrated significant capabilities in various areas, including antimicrobial, antifungal, anti-mycobacterial, antimalarial, antiviral, anti-inflammatory, antioxidant, antileishmanial, anti-tumour, and anticancer activities. The present paper provides an overview of the production and pharmacological characteristics of chalcone derivatives.

Indexed Terms- Chalcone, Synthesis, Pharmacological properties

I. INTRODUCTION

The compound seen in Figure 1 is commonly referred to as chalcone, a term introduced by Kostanecki and Tambor[1]. This compound is alternatively referred to as benzalacetophenone and benzylidene acetophenone. Chalcones are a class of compounds that are classified under the flavonoid family[2-4]. The open-chain flavonoids under consideration possess two aromatic rings that are connected by an aliphatic three-carbon chain. The molecule known as chalcone is a very adaptable chemical that possesses an α, β-unsaturated ketone structure. This structure includes a reactive keto-ethylenic group, denoted as –CO–CH=CH–, which serves as a chromophore responsible for the colour observed in chalcone compounds. The specific colour exhibited by these compounds is contingent upon the presence or absence of other auxochromes.

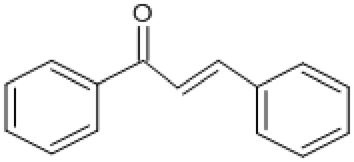
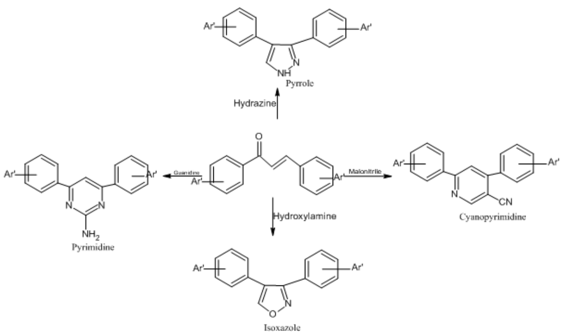


Figure 1: Structure of chalcone

Chalcone is characterised by the presence of conjugated double bonds that exhibit complete delocalization. Additionally, it consists of two aromatic rings that possess a π-electron system. These structural features contribute to chalcone's very low redox potential and enhance its propensity to perform electron transfer processes. Chalcones are commonly found in a variety of edible plants[5], such as vegetables, fruits, spices, tea, and other natural food sources. Chalcones have the potential to serve as precursors for the synthesis of flavonoids and isoflavonoids[6]. These entities serve as synthons, enabling the targeted synthesis of a variety of analogues and new heterocycles with medicinal properties[7-9]. Several chalcone derivatives have been found to possess antibacterial[10], antifungal[11], antimalarial[12], antiviral[13], anti-inflammatory[14], antileishmanial[15-16], anti-tumour[17], and anticancer[18-19] activities. The presence of the α, β-unsaturated carbonyl system in chalcones confers biological activity[20], whereas the absence of this carbonyl system renders them physiologically inert, hence maintaining stability in both cis and trans forms. Chalcones have the potential to be used in the synthesis of various heterocyclic rings via ring closure processes, as depicted in Scheme 1.



Scheme 1: Responses of chalcones to ring closure

Chalcones have been used in the synthesis of many heterocyclic ring systems, such as cyanopyridines, pyrazolines, isoxazoles, and pyrimidines, along with their numerous derivatives[21-25]. Various techniques can be employed in the synthesis of chalcones, with the Claisen-Schmidt condensation being the most favourable approach[26-29]. This process involves the reaction of equal amounts of aryl methyl ketone and aryl aldehyde in the presence of alcoholic alkali. In general, alkaline substances such as potassium hydroxide (KOH), sodium hydroxide (NaOH), lithium hexamethyldisilazane (LiHMDS), and barium hydroxide ($Ba(OH)_2$), together with naturally occurring phosphates, are commonly selected as appropriate media for the process of manufacture[30-35].

- Nomenclature

Different nomenclature approaches have been proposed for chalcones at different points in time. The naming pattern, as depicted in Figure 2, has received acceptance from Chemical Abstracts, a publication by the American Chemical Society.

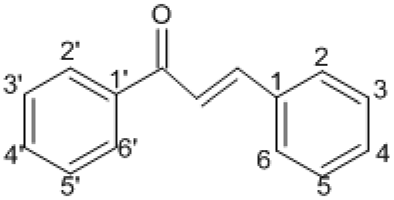


Figure 2: Numbering as per chemical abstract

The system employed by the British Chemical Abstracts and Journal of the Chemical Society is illustrated in Figure 3.

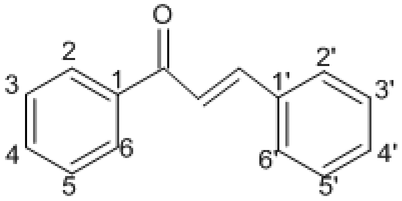


Figure 3: Numbering as per British Chemical abstract

- Methods of preparation

Condensing agents for synthesis

Alkali as a condensing agent

Alkali, which is frequently employed as a condensing agent in the synthesis of chalcones, is used in the form of an aqueous solution with concentrations ranging from 30% to 70%.

Hydrochloric acid serves as a condensing agent.

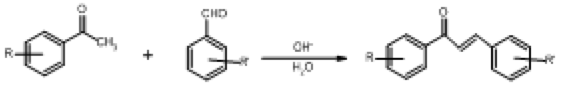
In some preparations of chalcones from aromatic ketones, the utilisation of dry hydrochloric gas as a condensing agent in an appropriate solvent, such as ethylacetate at a temperature of 0°C, has been seen. A solution of hydrochloric acid gas in methanol at a temperature of 0°C has been used in previous studies.

Other condensing agents

Raval and Shah employed[30] phosphorus oxychloride as a condensing agent for the synthesis of chalcones. In their study, Szell and Sipos[31] conducted a condensation reaction between 2-hydroxy-5-nitroacetophenone and benzaldehyde using anhydrous aluminium chloride ($AlCl_3$). In their study, Kuroda and Matsukuma synthesised[32] chalcone using the condensation process of acetophenone obtained from anisole and various polymethoxy benzenes, with specific methoxy-aldehydes, under the influence of anhydrous aluminium chloride.Furthermore, many condensing agents have been employed in the production of chalcones, including amino acids, aqueous solutions of borax, perchloric acid, piperidine, boron trifluoride, alkali metal alkoxides, magnesium tert-butoxide, and organocadmium compounds.

- Claisen-Schmidt reaction

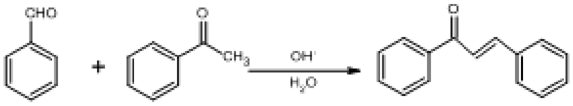
Various methodologies for the production of chalcones have been documented in scholarly literature. Among these, the most practical technique involves the Claisen-Schmidt condensation (Scheme 2), wherein equimolar amounts of substituted acetophenone and substituted aldehydes are reacted in the presence of aqueous alcoholic alkali[33-36].The Claisen-Schmidt process often employs alkali concentrations ranging from 10% to 60%. The reaction is conducted at approximately 50 degrees Celsius for a duration of 12 to 15 hours, or at room temperature for a period of one week. In the given circumstances, it is observed that a Cannizzaro reaction occurs, hence diminishing the overall yield of the intended product[37]. To prevent the occurrence of disproportionation in aldehydes, a substitution method including the utilisation of benzylidene-diacetate has been documented.



Scheme 2: Chalcones by Claisen-Schmidt condensation

- Aldol condensation reaction

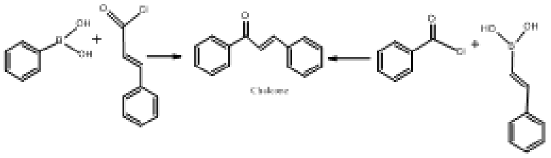
The Claisen-Schmidt reaction utilises acetophenone and benzaldehyde as the starting materials for this particular reaction, as depicted in Scheme 3. During the initial stage, acetophenone undergoes treatment with a base, such as KOH, resulting in its conversion into a more reactive state known as its enolate form. Subsequently, the aforementioned compound undergoes a reaction with benzaldehyde, resulting in the formation of an intermediate. Upon subjecting this intermediate to heat, a molecule of water is eliminated, leading to the formation of chalcone[38-39].



Scheme 3: Chalcones by Aldol condensation

- Suzuki reaction

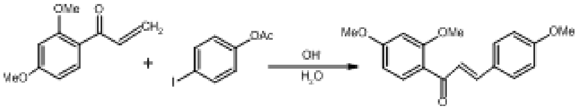
Chalcones can be synthesised by the Suzuki reaction, as demonstrated in Scheme 4. The overall procedure involves the interaction between phenylboronic acid (I) and cinnamyl chloride (II), or between benzoyl chloride (III) and phenyl vinyl boronic acid (IV).



Scheme 4: Chalcones by Suzuki coupling

- Heck reaction

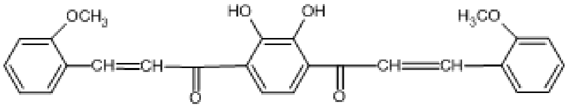
Chalcones and several other flavonoids can be synthesised through the coupling of an aryl vinyl ketone with an aryl iodide using the Heck reaction conditions, as depicted in Scheme 5[40].



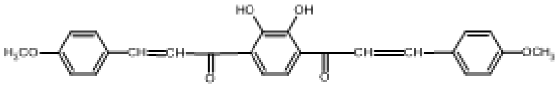
Scheme 5: Chalcones by Heck coupling

- Preparation of bis-chalcone

Venkatraman and Nagrajan (1973) synthesised[41] bis-chalcone by employing dihydroxy-diacetylbenzene and anisaldehyde in the presence of an alkali medium (Figures 4 and 5).



Figures 4: Preparation of bis-halcones



Figures 5: Preparation of bis-halcones

- Reaction of benzaldehyde with phosphonate carbanion

The reaction between benzaldehyde and phosphonate carbanion obtained from diethyl phenacyl phosphonate typically results in the formation of chalcones[42].

- Preparation of chalcones using Schiff bases

The reaction of aryl-aminoketones, which are produced from Schiff bases, in the presence of acid, leads to hydramine cleavage. This cleavage results in the formation of primary aromatic amine and chalcones as the final products[43].

- Preparation of chalcones from organometallic compounds

Several studies have documented the production of chalcones through the utilisation of organometallic compounds, including acetylenic Grignard reagents, cadmium derivatives, and cinnamyl chloride in an ether medium. Additionally, phenyl magnesium bromide and cinnamonitrile have been employed in the presence of ammonium chloride and methylmagnesium iodide, along with benzaldehyde[44].

- Microwave-assisted synthesis of chalcones

In their study, Mistry and Desai (1994) employed a microwave-based methodology for the synthesis of chalcones.Various heterogeneous catalysts, such as potassium carbonate, barium hydroxide, p-Toluenesulfonic acid, KF-Al_2O_3, zirconium tetrachloride, piperidine, and aqueous alkali, have been employed in the microwave-assisted synthesis of chalcones and their analogues[45-46].

- Chalcone synthesis using ultrasound irradiation

Potassium carbonate, basic Al_2O_3, amino-grafted zeolite, $Ba(OH)_2$, pulverised KOH, and KF-Al_2O_3 are examples of heterogeneous catalysts that have demonstrated excellent utilisation in the production of chalcones and their analogues when subjected to ultrasonic irradiation[47-49].

- Solvent-free synthesis of chalcones

The study conducted by Rothenberg et al. demonstrated that solid-state processes are facilitated by the presence of a liquid melt. This finding suggests that the presence of a liquid phase, which may arise from the combination of reactants or one of the reactants alone, is a necessary condition for the reaction to take place. The observed increase in reaction speeds can be attributed to the high concentration of reactants in these solvent-free yet liquid environments. The mixture of benzaldehyde and acetophenone exhibited a melting phenomenon before the addition of NaOH. Upon the application of mechanical force by grinding, the solid NaOH transformed, resulting in the formation and subsequent separation of the solid product of chalcone from the liquid mixes. As a consequence, the liquid mixtures exhibited a pasty consistency.

- One-pot synthesis of chalcones

A recent study conducted a one-pot synthesis of chalcones[50] utilising CuI/carbon sphere (CSP) nanocomposites, which exhibited remarkable selectivity under environmentally friendly circumstances.The synthesis of CuI/CSP nanocomposites involved refluxing a mixture of CuI and CSP in ethanol. The CSP samples were synthesised by the hydrothermal carbonization process of glucose at a temperature of 180°C. The copper iodide (CuI) was subsequently immobilised onto the polysaccharide surface of the chiral stationary phase (CSP) by combining equal amounts of CuI and CSP in ethanol and subjecting the mixture to standard reflux conditions. Major products with high yields ranging from 75% to 93% were produced in the presence of 3-methylpiperidine, piperidine, pyrrolidine, and piperazine. These products are e-selective heterocyclic chalcones.

- Importance of chalcones

Chalcones exhibit a strong association with flavones, aurones, tetralones, and aziridines. Chalcone derivatives have been utilised in several fields, such as artificial sweeteners, scintillators, polymerization catalysts, fluorescent whitening agents, and organic brightening agents. Chalcone has been identified as a stabilising agent that offers protection against various forms of degradation, including heat, visible light, ultraviolet radiation, and ageing. The compound tetrahydroxy-4-propoxy-dihydrochalcone-4-b0-neohesperdoside has been employed as an artificial sweetener with a sweetness potency that is 2200 times more than that of glucose. The keto-ethylenic functional group present in chalcone exhibits reactivity towards several chemicals, such as phenyl hydrazine and 2-amino thiophenol. Chalcones have proven to be valuable tools in the investigation of the molecular structure of various natural compounds, including hemlock tannin, cyanomaclurin, phloretin, eriodictyol and homoeriodictyol, as well as naringenin. The provided text refers to a range of pages in a scholarly source.

CONCLUSION

In conclusion, the presented text provides a comprehensive overview of chalcones, starting with their structural characteristics, nomenclature, and methods of preparation. Chalcones, commonly referred to as benzalacetophenone or benzylidene acetophenone, belong to the flavonoid family and are characterized by an α, β-unsaturated ketone structure with conjugated double bonds and a low redox potential. The text highlights the adaptability of chalcones and their potential as precursors for the synthesis of flavonoids and isoflavonoids.

The pharmacological significance of chalcones is emphasized, showcasing their diverse biological activities, including antibacterial, antifungal, antimalarial, antiviral, anti-inflammatory, antileishmanial, anti-tumour, and anticancer properties. The α, β-unsaturated carbonyl system in chalcones is identified as a key structural feature responsible for their biological activity. The text further explores various methods of chalcone synthesis, such as the Claisen-Schmidt condensation, aldol condensation, Suzuki reaction, and Heck reaction, providing a detailed insight into each process.

Additionally, the text discusses alternative methods like the use of condensing agents, Claisen-Schmidt reaction, aldol condensation, Suzuki reaction, Heck reaction, preparation of bis-chalcone, reactions involving phosphonate carbanion and Schiff bases, synthesis from organometallic compounds, and innovative techniques like microwave-assisted and ultrasound-assisted synthesis, solvent-free synthesis, and one-pot synthesis using nanocomposites. The importance of chalcones is underscored by their association with various compounds, their utility in different fields, and their potential applications as stabilizing agents and artificial sweeteners. Overall, the text provides a comprehensive and detailed exploration of the synthesis, properties, and applications of chalcones, making it a valuable resource for researchers and scholars in the field.

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