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AN OVERVIEW ON CHEMISTRY AND VARIOUS BIOLOGICAL ACTIVITIES ON MESOIONIC CHALCONES

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ABSTRACT
Privileged structures have been widely used as an effective template in medicinal chemistry for drug discovery. Chalcone is a common simple scaffold found in many naturally occurring compounds. Many chalcone derivatives have also been prepared due to their convenient synthesis. These natural products and synthetic compounds have shown numerous interesting biological activities with clinical potentials against various diseases. This review aims to highlight the recent evidence of chalcone as a privileged scaffold in medicinal chemistry.These chalcone derivatives have shown important antimicrobial, antifungal, anti-mycobacterial, antimalarial, antiviral, anti-inflammatory, antioxidant, antileishmanial. This review highlights the synthesis and pharmacological properties of chalcone derivatives.

INTRODUCTION
The framework 1,3-diphenylprop-2-en-1-one in Fig.1 is well known by the genericterm chalcone,a name coined by Kostanecki and Tambor.[1] It is also known asbenzalacetophenone and benzylidene acetophenone. Chalcones belong to theflavonoid family.[2–4] These open-chain flavonoids have two aromatic rings thatare linked by an aliphatic three-carbon chain. The versatile molecule chalcone is ana,b-unsaturated ketone that contains the reactive keto-ethylenic group –CO–CH=CH–, a chromophore responsible for the color in chalcone compounds,depending on the presence of other auxochromes.

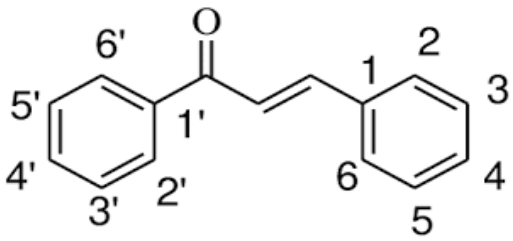


Fig. 1: 1,3-diphenylprop-2-en-1-one.

Chalcone has conjugated double bonds with absolute delocalization and twoaromatic rings that possess an p-electron system, which gives them relatively low redox potential and a greater chance of undergoing electron transfer reactions.Chalcones are naturally abundant in edible plants,[5] including vegetables, fruits,spices, tea and natural foodstuffs. Chalcones can be designed as precursors forflavonoids and isoflavonoids.[6] They act as synthons by which a range of analogsand novel heterocycles with pharmaceutical structures can be targeted.[7–9]

Various chalcone derivatives show antimicrobial, antifungal, antimalarial, antiviral,anti-inflammatory, antileishmanial anti-tumor and anticancer properties,[10,19] The a,b-unsaturated carbonyl system in chalcones makes them biologically active[20] and exclusion of the carbonyl system makes them biologically inactive,ensuring stability in both cis and trans forms. (Fig. 2).

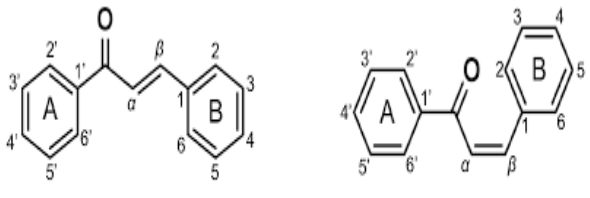


Fig. 2: Structural and numerical representations of chalcone scaffold.

Despite medicinal applications of chalcones, their wide bioactivity spectrum indicates a potentially promiscuous target profile, which presents a challenge for clinical development. This is largely attributable to the electrophilic nature of the œ,ß,-unsaturated carbonyl system. This moiety is capable of forming irreversible bonds with biological macromolecules, resulting in a number of toxic effects, such as allergenic reactions, carcinogenicity, and mutagenicity [18]. On the other hand,

this reactivity may be affected both by the decoration of the aromatic rings, and also, even more effectively, by _œ-X-substitution of the double bond of the enone system.[21] Therefore, the design and synthesis of new analogs are particularly important for the future development of clinically useful chalcone derivatives.

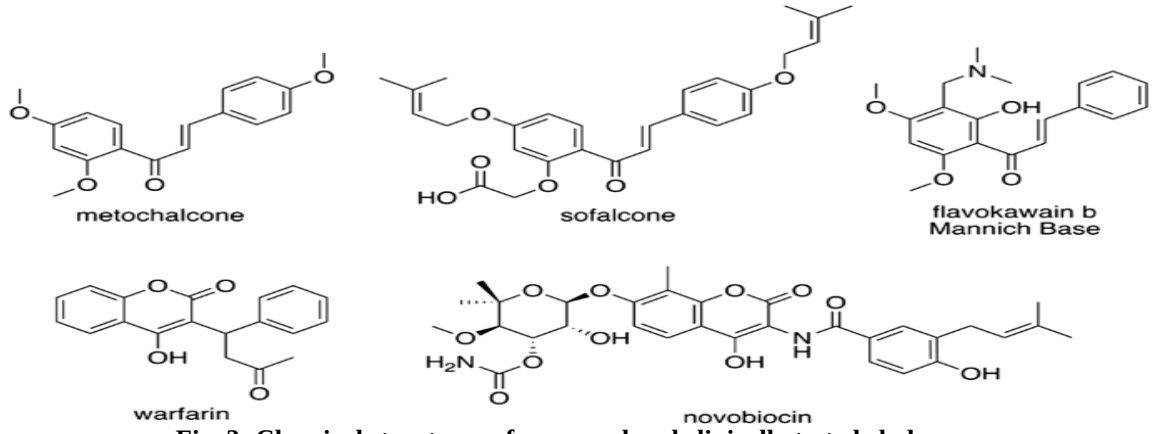


Fig. 3: Chemical structures of approved and clinically tested chalcones.

Here, we aimed to review recent data on computer-assisted design and synthesis of new chalcone derivatives with improved pharmacodynamics, pharmacokinetics, and toxicological profiles; major challenges in the field; and possible solutions to existing pitfalls.

Chalcones from Natural sources

Chalcones are the core of many biologically interesting compounds from natural sources and have attracted substantial research attention for decades. How many natural chalcones have been isolated and structurally elucidated and the answer to this question depends on how broadly the net is cast. As in many articles, the term "chalcone" refers generically to chemicals with an α,β-unsaturated ketone system. Thus, the chalcone family has extensive structural diversity and can be roughly classified into two categories: simple/classical chalcones and hybrid chalcones with the core scaffold of 1,3-diaryl2-propen-1-one. Bichalcones, such as rhuschalcone from Rhus pyroides, contain two chalcone moieties in a single structure. Dihydrochalcones, such as the fleminchalcones from Flemingiaphilippinensis, are a class of compounds with a reduced α,β-unsaturated double bond. Chalcone mimics (e.g., piperlongumines) and fused chalcones (e.g., oxyfadichalcones) are not structurally traditional chalcones, although they have a similar α,β-unsaturated ketone system or fused forms derived from chalcones by special biosynthesis pathways. When searching for the classical chalcone in the well-known chemical databases, more than 92 000 chalcones can be found in SciFinder and over 1000 of them have biological data reported in PubChem (accessed August 2016). Therefore, the number of natural chalcones may ultimately not be countable with certainty.[22-26]

Fluorescent Properties of Chalcones

Because of its conjugated system, chalcones with proper electron-pulling and electron-pushing functional groups on the benzene ring(s) can be fluorescent,[27–30] making them potential chemical probes for mechanistic investigations and imaging/diagnosis. As a fluorescent compound, the photophysical parameters, which include the absorption (Abs λm) and emission (Emi λm) wavelengths, extinction coefficient (ε), and quantum yield (ϕ), are critical for biological applications. The dynamic range of detection is determined by the Abs λm and Emi λm values. The fluorescence brightness, which is the product of ε and ϕ at the maximum absorption wavelength, is associated with the detection sensitivity. Some nonstructural factors are also critical to the fluorescent intensity, such as the solvents and the biological components/additives. The dimethylamino group is a widely used substituent in fluorescent probes and has also been introduced into fluorescent chalcone compounds. 4-Dimethylaminochalcone was first reported by Jiang et al. as a fluorescent probe for detecting micelle formation.Very recently, the authors have synthesized a small library of fluorescent chalcones to systematically characterize the structural effects on their intrinsic fluorescence and evaluate the influence of several biologically relevant environmental factors.[27] The 4-dimethylaminochalcone compounds exhibited similar-absorptions, with an Abs λm between 390 and 460 nm and an Emi λm between 450 and 620 nm. The ε and ϕ values were between 28 000 and 38 000 and 0 and 0.40, respectively. Several compounds showed good fluorescence brightness, with values exceeding 6000 M−1 cm−1, which is comparable to that of commercial fluorophores (e.g., Cy 3.18–6000 M−1 cm−1). A structure–fluorescence relationship (SFR) study demonstrated the following: for the chalcone moiety, the molecular planarity played a critical role in the fluorescence, e.g., introducing a methyl group to the α-position of the unsaturated ketone resulted in the loss of fluorescence; for the A ring, weak electron-donating groups (e.g., a methoxyl group) were favorable to the quantum yield, while electron-withdrawing (e.g., a nitro group) or strong electron-donating (e.g., a dimethylamino group) substituents significantly decreased it; for the B ring, disubstituted amino groups were essential for fluorescence, such as piperidine,

piperazine, dimethylamino, and diethylamino groups; and for the α,β-unsaturated ketone system, the extension of the double bond decreased the fluorescence and caused a red shift of the maximum emission wavelength. The fluorescence–environment relationship (FER) showed that the fluorescent intensity of chalcone-based compounds depends highly on the solvent polarity, the pH, and the interactions with proteins or detergents. In aprotic solvents, chalcone's fluorescence decreases as the solvent polarity decreases, although the fluorescence is completely lost in protic solvents, such as water or EtOH, at neutral pH. However, it could be partially recovered by the addition of BSA, Triton-X100, or Tween-20. A similar result was obtained by another study, in which 4′-N,N-dimethylamino-4-methylacryloylamino chalcone containing both electron-withdrawing and electron-donating groups was synthesized as a fluorescent sensor for determining the water content in organic solvents. The fluorescent intensity of compound decreased with an increase in the water concentration in acetone, ethanol, and acetonitrile solutions. Such a sensor was useful for water determination with a low detection limit (<0.01%). The loss of fluorescence in a protonic solvent is potentially due to the formation of hydrogen bonds between the solvent and the nitrogen of chalcone's dialkylamino group, keeping the nitrogen lone pair electrons out of the conjugate system and leading to the nonfluorescent property. Nevertheless, fluorescent chalcones have been explored for their potential to detect different diseases.[28] Compound was designed based on a phosphorylated chalcone hybridized from 4-dimethylaminochalcone to visualize alkaline phosphatase through emission color changes in living cells. Stark et al. reported a series of chalcone analogues (4) that could be used to image human histamine H3 receptors (hH3R) in stably transfected HEK-293 cells. Fluorescent chalcones have also been applied to image stem cells. For example, Lee et al. designed a novel library of 160 fluorescent chalcone amide compounds. Two amides were introduced into these chalcones on each side of the scaffold to enhance the fluorescence emission intensity. Interestingly, CDg4 (5) was applied as a novel green fluorescent probe for detecting mouse embryonic stem cells (mESCs), where its molecular binding target was identified as the glycogen of the stem cell colony surface. These investigations have provided new possibilities for using nonradioactive alternatives in novel binding assays and as visualization tools.

Synthesis

Biosynthesis

Chalcone synthase (CHS), the first type III polyketide synthase (PKS) superfamily discovered in the 1970s, is a ubiquitous enzyme in higher plants. CHS has also been detected in several lower plants, such as the liverwort Marchantia polymorpha. [38] All other members in this family are labeled "CHS-like" enzymes. CHS is responsible for the biosynthesis of different chalcones. The CHS superfamily enzymes are associated with the biosynthesis of diverse secondary metabolites, including flavonoids, stilbenes, and aurones. Joseph P. Noel and coworkers developed an important framework for the biosynthetic mechanism by crystallizing CHS from the legume Medicago sativa, a process that provided clear structural information about chalcone biosynthesis.[40] CHS exists as a homodimer, and the size of each monomer is approximately 42–45 kDa.81 Cys164, Phe215, His303, and Asn336 are the key residues of the active site and have been conserved among all CHS members and CHS-like enzymes. CHS produces chalcones by transferring a coumaroyl moiety from one 4coumaroyl-coenzyme A (CoA) to Cys164 as the first step. Subsequently, three malonyl-CoA thioesters form an intermediate via a polyketide reaction. After the generation of a thioester-linked tetraketide, a regiospecific Claisen-type cyclization occurs and forms a new ring system to generate naringenin chalcone. Naringenin chalcone is converted into 6′-deoxynaringenin chalcone (isoliquiritigenin,) in the presence of chalcone reductase (CHR) and CHS. Other plant secondary metabolites, such as stilbenes, phloroglucinols, resorcinols, and benzophenones, could be biosynthesized in a similar manner with the corresponding catalytic enzymes. Flavonoids and isoflavonoids are produced by CHS and chalcone isomerase (CHI), respectively, using naringenin chalcones as the substrates. Naringenin chalcones are also the building blocks for the biosynthesis of aurone compounds by a plant catechol oxidase, aurone synthase (AURS). These conversions from chalcones to flavanones or aurones could also be realized by chemical reactions, such as the Algar–Flynn–Oyamada reaction.[29] Chalcones serving as precursors have generated a range of plant metabolites, revealing interesting biological activities, which will be discussed in the following sections. Taking such experience from nature, simple chalcones have been synthetically hybridized with other templates, such as stilbenes.

Chemical Synthesis

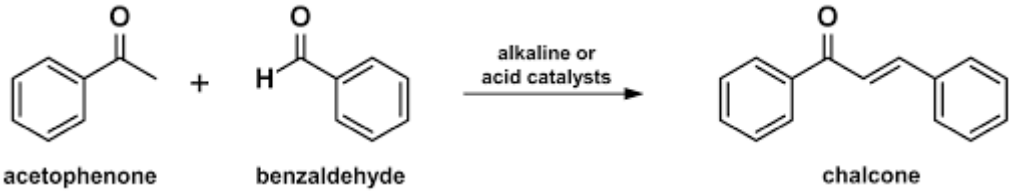
Synthesis of Chalcone Scaffolds

Chalcones have a simple chemistry which enables a multiplicity of substitutions with easysynthesis. Currently, a variety of methods and schemes are available for the synthesis of chalcone derivatives. In each of these methods, the most important part is condensation of two aromatic systems (with nucleophilic and electrophilic groups) to yield the chalcone scaffold. Despite the multiplicity of substitutions allowed, we describe below the reaction scheme using the standard scaffold of chalcones (1,3-diphenyl-2-propen-1-one).

Claisen-Schmidt Condensation

Amongst all methods, the Claisen-Schmidt condensation (Scheme 1) is one of the most common. In this reaction, chalcones are formed by condensation of benzaldehyde and acetophenone derivatives conventional Claisen-Schmidt reaction is typically carried out in the liquid phase, but certain reactions can take place in the solid

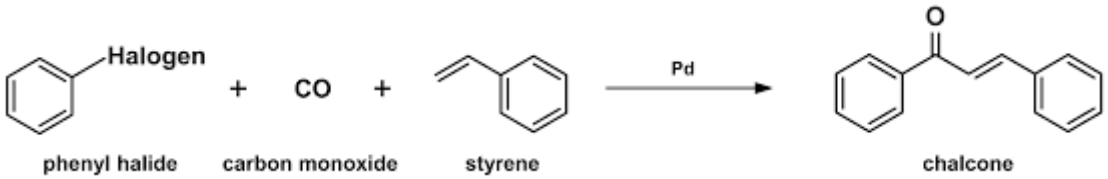
phase (e.g., acetophenone derivatives are primarily bound to the reactions an take place in the solid phase (e.g., acetophenone derivatives are primarily bound to the resin and then treated with benzaldehyde derivatives) or solvent-free phase (e.g., condensation in the presence of catalyst triazabicyclodecene). In addition, the use of microwaves in liquid and solvent free Claisen-Schmidt reactions reduces synthesis time and yields good amounts of chalcones.[30]



Scheme 1: The Claisen-Schmidt condensation.

Carbonylative Heck Coupling Reaction

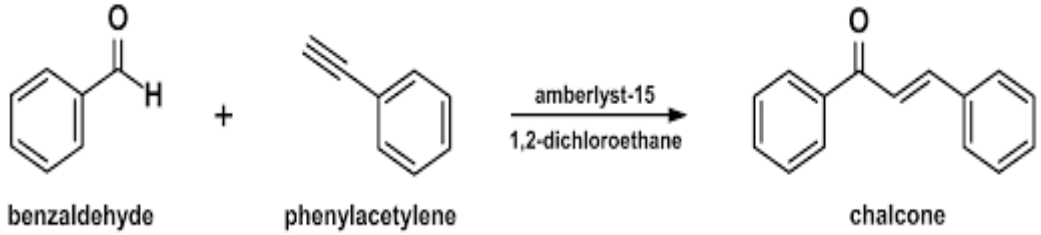
In the carbonylative Heck coupling reaction (Scheme 2), chalcones are synthesized by carbonylative vinylation of phenyl halide with styrene in the presence of carbon monoxide and using palladium (Pd) as catalyst.



Scheme 2: Carbonylative Heck coupling reaction.

Coupling Reaction

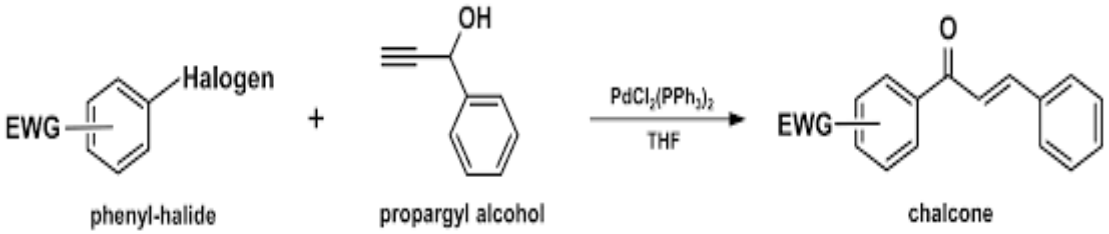
Chalcones also are synthesized by a coupling reaction (Scheme 3) between benzaldehyde and phenylacetylene in the presence of HBr and ionic liquids, such as 1-butyl-3-methyl-1*H*-imidazolium 4-methylbenzenesulfonate (BmimOTs) for 12 h at 100 °C.



Scheme 3: Coupling reaction.

Sonogashira Isomerization Coupling

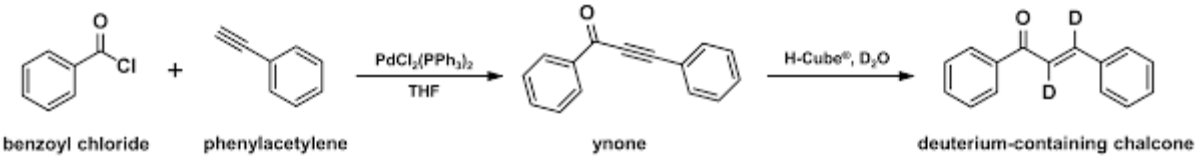
In the Sonogashira isomerization coupling reaction (Scheme 4), chalcones are synthesized through a reaction between the equimolar concentration of electron-deficient phenyl-halide and propargyl alcohol employing microwave irradiation and using PdCl2(PPh3)2 as catalyst and THF as a solvent.



Scheme 4: Sonogashira isomerization coupling. EWG: electron withdrawing group.

Continuous-Flow Deuteraction Reaction

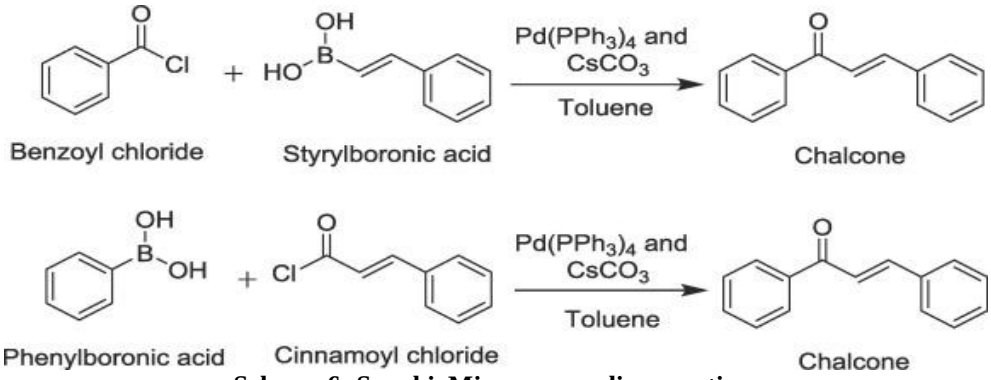
In the continuous-flow reaction (Scheme 5),ynones are initially prepared by literature procedures through the coupling of benzoyl chlorides with phenylacetylenes under Sonogashira conditions (see above). Then, deuterations are carried out in an H-Cube® system with replacement of the H2O hydrogen source to D2O deuterium source.



Scheme 5: Continuous-flow deuteraction reaction.

Suzuki–Miyaura Coupling Reaction

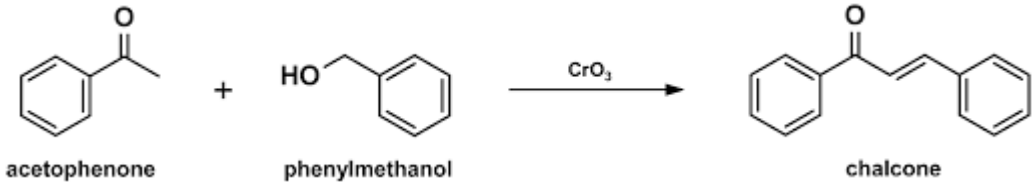
In the Suzuki–Miyaura coupling reaction (Scheme 6), chalcone synthesis involves the coupling of benzoyl chloride with styrylboronic acid employing Pd(PPh3)4, CsCO3 and anhydrous toluene or coupling of phenylboronic acid with cinnamoyl chloride employing Pd(PPh3)4, CsCO3, and anhydrous toluene.



Scheme 6: Suzuki–Miyaura coupling reaction.

One-Pot Synthesis

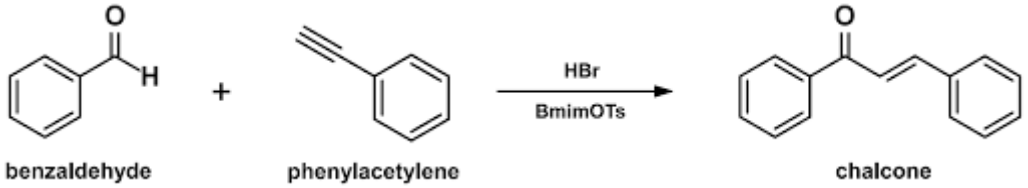
The one-pot synthesis (Scheme 7) is a simple, yet efficient green method which allows synthesis of chalcones in just one reactor. This method provides several advantages, such as increased reaction efficiency, and avoidance of the lengthy purification process of the intermediate chemical compounds, thereby saving resources and time. The reaction consists of a mixture of phenylmethanol and acetophenone in the presence of the oxidizing agent CrO3. In this reaction, CrO3 plays the vital role of generating the benzaldehyde from phenylmethanol, which further reacts with the acetophenone to produce the desired chalcone.



Scheme 7: One-pot synthesis of chalcones.

Solid Acid Catalyst Mediated Reaction

Chalcones have also been synthesized by employing a heterogeneous solid acid catalyst (Scheme 8). The reaction consists of the addition of an equimolar quantity of benzaldehyde and phenylacetylenein 1,2-dichloroethane solvent irradiated in a microwave and employing ion exchange resin amberlyst -15 as heterogeneous solid acid catalyst.

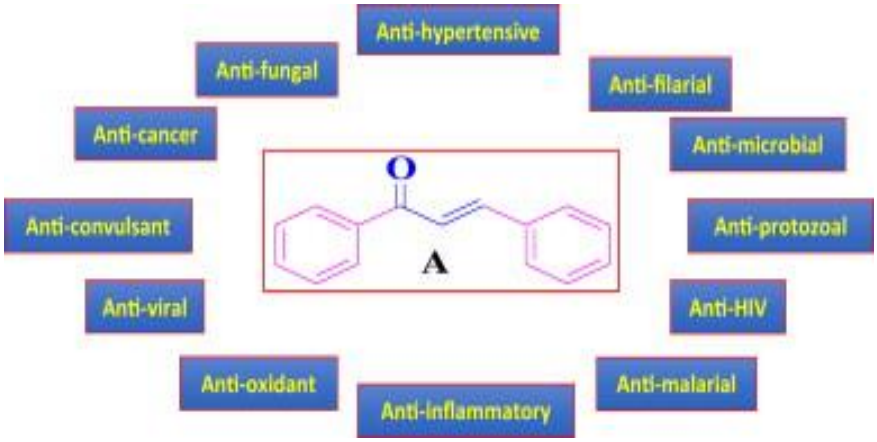


Scheme 8: Solid acid catalyst mediated synthesis.

Importance of chalcones

Chalcones have a close relationship with flavones, aurones, tetralones andaziridines. Chalcone derivatives find application as artificial sweeteners, scintillators, polymerization catalysts, fluorescent whitening agents and organic brightening agents. Chalcone is a stabilizer against heat, visible light, ultraviolet light and aging 3,20,40,60-Tetrahydroxy-4-propoxy-dihydrochalcone-4-

b0-neohesperdoside has been used as a synthetic sweetener which is 2200 times sweeter than glucose. The keto-ethylenic group found in chalcone is reactive towards several reagents including phenyl hydrazine and 2-amino thiophenol. Chalcones areuseful in elucidating the structure of natural products such as hemlock tannin,cyanomaclurin, phloretin, eriodictyol and homoeriodictyol, and naringenin. Chalcones show diverse biological activity including insecticidal, anticancer, anti-inflammatory, bactericidal, fungicidal, antiviral, anti-tumor, antimalarial and antiulcer effects Studies in the literature show that licochalcone and oxygenated chalcone have potent antileishmanial properties Chalcones exhibiting powerful activity against human malaria parasites have also been reported. Many researchers have noted the various pharmaceutical propertiesof chalcones and their analog. Studied the antibacterial activity of various substituted chalcones, and Vincenzo et al. reported the anti-inflammatory activity of certain chalcone derivatives. Aldose reductase inhibitor activity of chalcone derivatives has also been reported. Noted anticancer activity of chalcones, and reported chalcones as aglucosidase inhibitors. Antiplasmodial activity of ferrocenyl chalcones was studied. Bhatt and co-workers investigated the cytotoxicproperties of chalcones and their pyrazole derivatives.



Anti-inflammatory activity

(E)-1-(2-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one (Fig. 4), which is a chalcone derivative, and confirmed bioactivity in vitro for its inhibitory effect on chemical mediators released from mast cells, macrophages, neutrophils and microglial cells, with good results.

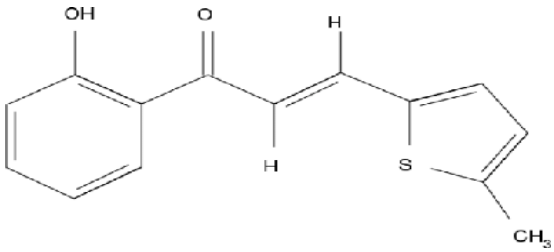


Fig. 4: (E)-1-(2-hydroxyphenyl)-3-(thiophen-2-yl)prop-2-en-1-one.

Dihydro xanthohumol (Fig. 5), which was isolated from the fruit of Mallotusphilippensis,[169] exhibited anti-inflammatory activity.

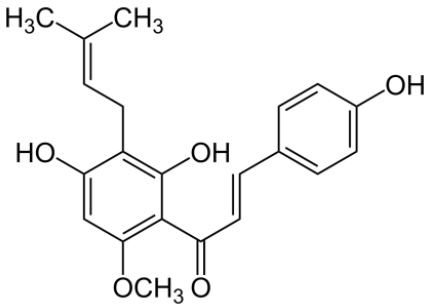


Fig. 5: Dihydro xanthohumol.

Antimicrobial activity

The antimicrobial activity of chalcones has been reported in many research papers. The existence of a reactive a,b-unsaturated keto function in chalcones will undergoconjugate addition with a nucleophilic group in an essential protein, thuscontributing to antimicrobial activity. Alterations can be made depending on thetype and position of the substituents present on the aromatic rings. Synthesis of novel benzimidazolyl chalcones (Fig. 6) to produce antimicrobial agents through condensation of N-(4-(1Hbenzo[d]imidazol-2-yl) phenyl) acetamide with aromatic aldehydes in the presenceof aqueous KOH at room temperature.

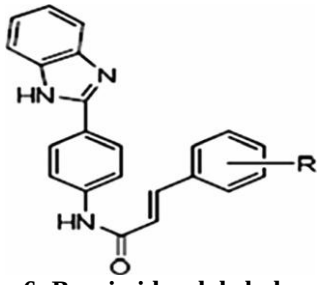


Fig. 6: Benzimidazolyl chalcones.

A number of **nitrofuryl chalcones** were prepared and tested for their antibacterialActivity. Staphylococcus aureus at a concentration of1 lg/ml was inhibited by the compound (Fig. 7), which was the most efficientamong all derivatives synthesized.

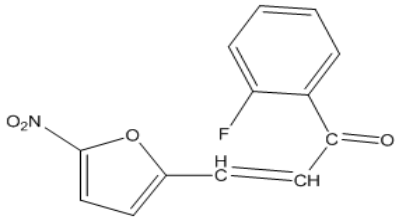


Fig. 7: nitrofuryl chalcones.

Anti-OxidantActivity

The many free radicals and oxygen species produced during biological processes can damage DNA, proteins and lipids via their oxidation, and have been implicated in the initiation of several degenerative processes related to aging, cancer and atherosclerosis. Hence the removal of free radicals from biological systems is vital to cell sustainability. Antioxidants are well known as free radical scavengers and tend to trap free radical species, specifically inhibiting or delaying the oxidation of oxidizable substrates in the chain reactions.

Phenylated Chalcone (Fig. 8) that exhibited antioxidant activity.

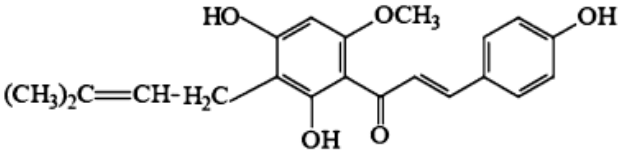


Fig. 8: Phenylated chalcone.

20-Hydroxychalcones (Fig. 9) prepared and[188] demonstrated antioxidant activity.

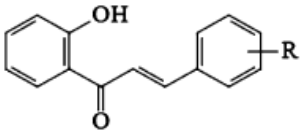


Fig. 9: 20-Hydroxychalcones.

Antileishmanial activity

Antileishmanial activit 20,60-dihydroxy-40-methoxychalcone (Fig. 10) that exhibited significant antileishmanial activity.

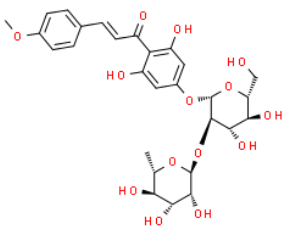


Fig. 10: 20,60-dihydroxy-40-methoxychalcone.

Synthesized a di-hydrochalcone (Fig. 10) having antileishmanial activity.

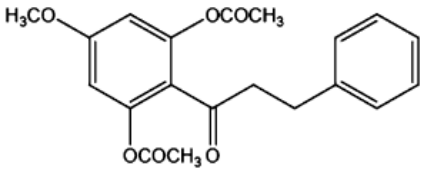


Fig. 10: di-hydrochalcone.

Antimalarial activity

Antimalarial activity Advanced and more efficient antimalarial drugs are greatly needed, as malaria parasites are increasingly resistant to the available drugs. In 1994, Chen. first reported the potential for chalcones as antimalarial agents.

The synthesis of phenylurenyl chalcones (Fig. 11) that exhibited anti-malarial activity.

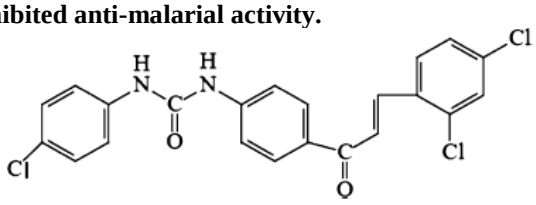


Fig. 11: Phenylurenyl chalcones.

CONCLUSION

Chalcones are versatile scaffolds for synthetic modification and exhibit diverse pharmacological properties. Due to their better bioavailability and high tolerance in the body, research on chalcones and derived compounds is gaining interest worldwide for the development of pharmacological compounds. A number of molecules containing a chalcone moiety are currently available in the market or in clinical trials. This reviewarticle updates recent developments regarding synthetic and pharmacological properties of chalcones by various synthetic methods containing different biological activities.

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