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A review on recent advances and potential pharmacological activities of versatile chalcone molecule

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ABSTRACT

Chalcone is an aromatic ketone and precursors of open chain flavonoids and isoflavonoids present in edible plants and their derivatives have attracted attention due to many potential pharmacological activities. Chalcone are also known as benzalacetophenone and phenyl styryl ketone. Modifications in their structure have offered diverse pharmacological activities that have proven useful for the development of new medicinal agents having improved potency and lesser toxicity. They are also the intermediates in the Auwer's synthesis of flavanoids and in the biosynthesis of flavanoids. Chalcone can be synthesized by various method but the two main methods are Aldol condensation method and Claisen Schmidt method. This review provides an overview of the pharmacological activities of natural and synthetic chalcone derivatives.

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Capsule Summary: The recent advances and potential pharmacological activities of versatile chalcone molecule are reviewed in this article.

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INTRODUCTION

A group of compounds having different substitution patterns on the two aromatic rings of 1,3- diphenyl-2-propen-1-one which is known as chalcone and it is linked by a three carbon α , β -unsaturated carbonyl system. It is an important class of natural product and belongs to the flavonoid family which have been reported a wide spectrum of biological activities (Matos et al., 2015; Wang et al., 2015; Jantan et al., 2014; Abdellatif et al., 2014; Lee et al., 2014; Singh et al., 2014; Drutovic et al., 2014; Lahsasni et al., 2014; Thillainayagam et al., 2014; Mohamed et al., 2012; Dimmock et al., 1999; Go et al., 2005; Nowakowska and Kedzi. 2008). They are also defined as the product of condensation of substituted or simple aromatic with substituted or simple acetophenone in the presence of alkali. Some of the

derivatives of chalcone are used as drugs, sunscreen agents and sweeteners (Li et al., 2002; Karthikeyan, et al., 2007). In the synthesis of heterocyclic compounds chalcone are the well-known intermediate (Rateb, 2007; Forkmann et al., 1999). Synthesis of the chalcone is the one step reaction and the synthesis of the alpha beta unsaturated compounds is the main structural component in natural occurring and biological essential substance. There are several strategies for the synthesis of these based on the formation of the carbon-carbon bond directly reported to the Aldol Condensation and Claisen-Schmidt Condensation occupies the important position (Bukhari et al., 2012; Wang et al., 2012; Tran et al., 2012; Zhang et al., 2012; Luo et al., 2012; Kerher et al., 2003; Yarishkin, 2008). There are various methods to synthesize chalcones. Most widely used method is base catalyzed and acid catalyzed method. In base catalyzed such as potassium hydroxide, barium hydroxide,

lithium hydroxide and sodium hydroxide are used whereas in acid base catalyzed it includes aluminium trichloride, dry hydrochloric acid, titanium trichloride and ruthenium trichloride. The most important catalyst were used are solid sodium hydroxide and aqueous sodium hydroxide. Palleros was introduced the first solid sodium hydroxide method in 2004 (Anderson. 2001). It is an aromatic ketone that forms a variety of biological compounds. Some chalcones are able to block the voltage-dependent potassium channel (Patil et al., 2009). They are also the intermediate in the biosynthesis of flavonoid. It is also an intermediate in the synthesis of Auwers Synthesis (Prakash et al., 2005). Now the Auwers synthesis is a series of organic synthesis of forming flavonol from coumarins.

Chalcones (*trans*-1,3-diaryl-2-propen-1-ones) (1), a biosynthetic product of the shikimate pathway, belonging to flavanoid family are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, 1,4-diketones, and flavones. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. There are also some reports of acid-catalyzed aldol condensations, e.g. AlCl_3 , BF_3 , dry HCl , $\text{ZrH}_2/\text{NiCl}_2$ and RuCl_3 (for cyclic and acyclic ketones). Chalcones and its derivatives have attracted increasing attention due to numerous pharmacological applications. They have displayed a broad spectrum of pharmacological activities, among which antimalarial (Motta et al., 2006; Awasthi et al., 2009; Cheng et al., 2000; Lim et al., 2007), anticancer (Achanta et al., 2006; Romagnoli et al., 2008; Echeverria et al., 2009; Szliszka et al., 2010; Ilango et al., 2010), antiprotozoal (antileishmanial and antitrypanosomal) (Lunardi et al., 2003), anti-inflammatory (Yadav et al., 2010; Zhang et al., 2010), antibacterial (Hamdi et al., 2010; Bhatia et al., 2009), antifilarial (Awasthi et al., 2009), antifungal (Bag et al., 2009; Lahtchev et al., 2008), antimicrobial (Yayli et al., 2006), larvicidal (Begum et al., 2010), anticonvulsant (Kaushik et al., 2010), antioxidant (Vasil'ev et al., 2010; Sivakumar et al., 2010; Vogel et al., 2008) activities have been reported. They have also shown inhibition of the enzymes, especially mammalian α -amylase (Najafian et al., 2010), cyclo-oxygenase (COX) (Zarghi et al., 2006) and monoamine oxidase (MAO) (Chimenti et al., 2009). They have shown antimitotic activity too (Romagnoli et al., 2008). Chalcones are α,β -unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituents. Rings are interconnected by a highly electrophilic three carbon α,β -unsaturated carbonyl system that assumes linear or nearly planar structure (Awasthi et al., 2009; Lim et al., 2007). They contain the ketoethylenic group ($-\text{CO}-\text{CH}=\text{CH}-$) (Ilango et al., 2010). Chalcones possess conjugated double bonds and a completely delocalized π -electron system on both benzene rings. They can be readily synthesized by the Claisen-Schmidt reaction which is very easy and simple to conduct as well as inexpensive (Siddiqui et al., 2010).

Chalcones (1,3-diaryl-2-propen-1-ones) and their heterocyclic analogues, belong to the flavonoid family, which possess a number of interesting biological properties. Chalcones are one of the major classes of naturally occurring compounds. A large number of synthetic routes have been reported for the synthesis of chalcones, the most classical and general being the Claisen-Schmidt condensation. Chalcones and their derivatives have a huge importance in medicinal chemistry, displaying a wide range of important pharmacological activities. Several chalcones have been approved for clinical use or tested in humans. Clinical trials have shown that these compounds reached reasonable plasma concentration and are well-tolerated. For this reason they are an object of continuously growing interest amongst the scientists. However, much of the pharmacological potential of chalcones is still not utilized (Singh et al., 2011; Rahman, 2011).

In this reaction the first step is acid catalyzed aldol condensation between 3-oxypentanone and benzaldehyde to form α -hydroxy chalcone. Alkenes product is brominated to give dibromo adduct which re-arranges flavonol by the reaction with potassium hydroxide. Chalcones are found abundant in edible plants and it is considered to be precursor of iso-flavonoid and flavonoid (Prasad et al., 2005). It is also considered as the precursor of biologically important heterocycles such as pyrazolines (Raghavan and Anuradha, 2002), 1,4-diketones (Bohn, 1998), benzothiazepine (Sogawa et al., 1994) and flavones. Chalcone are also obtained from the natural source, whereas some of its derivatives have been found to inhibit several enzymes in cellular system, such as protein tyrosine kinase and xanthine oxidase (Nerya et al., 2004). Biosynthetically chalcone can be synthesized by these methods which are as follows: chalcone synthase, chalcone isomerase, Naringenin-chalcone synthesis and auronones. Chalcone synthase a class of organic compound that is synthetically found as intermediate, such as in the production of pigments and mainly found in the plants as natural defense mechanism. Cloning of chalcones synthase from the moss revealed an important transition from the chalcone synthase present in microorganisms to those present in higher plants (Nerya et al., 2004). Petunia plants, a chalcone synthase gene is famous for being the first gene in which RNA interference phenomena were exist. Pigments were produced in light pink or violet colour flowers produced or introduced a transgene for the chalcone synthase. Both native and transgenic gene, express the enzyme and results in more deeply coloured flower known as phenotype. Plants which are transgenic were mottled with white flower led to the introduction of transgene had down regulated or silenced chalcone synthase expression (Jiang et al., 2006). Further investigation indicates that the down regulation is due to the post transcriptional inhibition for chalcone synthase gene expression and increase the rate of the messenger RNA degradation (Napoli et al., 1990).

In auronones, a chalcone group is enclosed with 5 membered rings instead of 6 membered rings. Auronones are the plant flavonoid which provide yellow colour to the

ornamental plants, such as cosmos and snapdragon. There are two isomers of aurones i.e. E and Z configurations. Most of the aurones are in Z configuration which is most stable then E configuration (Nakayama, 2002).

Chalcone isomerase

Chalcone isomerase in enzymology is an enzyme which catalyzes the chemical reaction. This enzyme is also known as chalcone-flavanone isomerase which converts chalcone into flavanone. The name of this enzyme is flavanone lyase or decyclizing. It participates in the biosynthesis of flavonoid. Class of this enzyme is intramolecular lyase and it belongs to the family of isomerases (Van Blokland et al., 1994).

Naringenin-chalcone synthesis

It is also an enzyme which catalyzes the chemical reaction. There are two substrate of this enzyme are 4-coumaroyl- CoA and malonyl-CoA, whereas its 3 products are naringen chalcone, CoA and carbon dioxide. Name of this class of enzyme is 4-coumaroyl-CoA malonytransferase/cyclizing and malonyl-CoA. Other name is flavonoid synthase, chalcone synthase, chalcone synthase, CHS and DOCS. It also participates in the biosynthesis of flavonoid (Moustafa and Wong, 1967).

Aurones

It is a flavonoid and a heterocyclic chemical compound (Ayabe et al., 1988). Its molecule consist of benzylidene linked at position 2 and a benzofuronone associated with it. They are naturally occurring compounds mainly found in the species of Glycyrrhiza, Humulus, Scutellaria and Angelica. The substitution patterns or specific functional groups on the chalcone template with particular activity profile. Mainly functional groups exert their strong influence on the physiochemical properties of the molecule. By the great extent of functionalities present in the moiety properties like lipophilicity and hydrogen bonding characteristics gave good activity of the compound and is associated with optimization of these properties. Some functional groups are associated with the inherent reactivities like radical quenching associated with phenolic group. Addition of heteroaryl group at position 5 of ring B in chalcone increased the lipophilic character of the compound. Replacement of carboxylic group in chalcone 1 by boronic group. Boronic acid is a weak and exist in a unionized state at pH 7.4. Boronic moiety disrupts the salt bridge in the same way as carboxylic acid. Boronic chalcones were demonstrated anti-proliferative activities and more selective against cancer cells. Chalcones having toluenesulfonylamino side chains were identified a new class of α -glycosidase inhibitors. α -glycosidase enzymes play an important role in processing glycoprotein and glycolipid inhibitors of this enzyme and are useful in anti-diabetic and anti-obesity agents. Amino chalcone showed the antiproliferative activity. Substituted chalcone with basic

groups like 2-amino was about 40 times more active the chalcone without 2-amino group such as 3'-methoxy-4, 5-methylenedioxychalcone. Another amino chalcone i.e., 3-(3-amino-4-methoxyphenyl)-1-(2,3,4-trimethoxyphenyl)prop-2-en-1-one exhibit potent activity against murine melanoma B16 cells while its nitro derivative or precursor had no activity. It was suggested that nitro chalcone were potentially useful for bioreductive prodrugs.

Preparation of chalcones

Preparation of chalcone by aldol condensation reaction: In aldol condensation reaction the most important synthetic route is that it gives the large molecules by the formation of carbon-carbon double bonds. In this the first step involves the acidbase reaction mechanism between the hydrogen located at alpha position carbonyl group and the strong base such as hydroxide ion which lead to the formation of enolate ion. And in the second step this enolate ion attacks carbonyl group of another molecule of the same ketone and aldehyde or the other reagent present in it. Take equimolar quantity of substitute acetophenone and benzaldehyde in adequate quantity of ethanol. Place the reaction mixture on the magnetic spin vane for 3-5 min to make sure that the reaction mixture is thoroughly mixed and no solid remains. If solid is remain then heat the mixture to dissolve it. Next add to the mixture of 10 ml of a concentrate sodium hydroxide solution drop wise by the help of burette. Stir the mixture on the magnetic vane for 25-30 minutes. Cloudiness appears before the solidification of the mixture and this cloudiness disappear with an obvious precipitation which led to the formation of chalcone, which can be separated out by the filtration and recrystallized in ethanol (Ducki, 2007).

Chemical synthesis

Chalcones were synthesized by the substituted acetophenone and benzaldehyde in the presence of NaOH in ethanol and reaction is called the Claisen- Schmidt condensation. The methyl group of the substituted acetophenone was deprotonated in the presence of to give the enolate, which attacked the electron deficient carbonyl carbon group of benzaldehyde by the nucleophilic addition reaction. In reaction the loss of water results in the formation of chalcone. Synthesis of chalcones was synthesized by reacting the aldehyde and acetophenone in the presence of aqueous NaOH. In this reaction, in the presence of base the methyl group of acetophenone was deprotonated and forms the enolate ion which attacked on the electron deficient carbonyl carbon of aldehyde by the nucleophilic addition reaction which led the loss of water from the reaction and resulted in the formation of chalcone (Pavia et al., 1990).

Microwave assisted synthesis

The Claisen Schmidt condensation reaction was also successfully carried out under microwave condition at the

temperature 130° C for 3 min. the better reason for the synthesis outcome is thermal or kinetic effects associated with microwave assisted synthesis. Specific microwave effects are also defined as the “accelerations of chemical transformations in the microwave field that cannot be achieved or duplicated by conventional heating, but essentially are still thermal effects”.

Synthesis of chalcone

A solution mixture of aldehyde (2 mmol) in methanol (5ml) was added drop wise in a stirred mixture of acetophenone (1 mmol) dissolved in 3% NaOH in methanol (20 ml). Solution mixture was stirred at 28 C for 12 hours and alternatively the reagents of the solution was reacted under the microwave at 130 C for 3 min. residue was dissolved in 1M HCl and extract it with ether after removing the solvent under reduced pressure. The aqueous layer was alkaline with saturated Na₂CO₃ solution which gives the precipitate. This precipitate was filter out and washed with water. The product is then recrystallized in methanol and water (Ducki, 2007).

Pharmacological activities of chalcones

It is an effective diuretic which removes the toxic waste from the body. Smooth bowel movement enhances detoxification. It helps to protect the organ from the destructive free radical and slows down the process of aging in human. It helps in cleansing of blood and promote blood circulation which is then helps in as follows: Reduces blood pressure, improves vision, regulates blood sugar, regulates cholesterol level, improves memory, enhances liver and kidney functions, aids in weight control, suppresses gastric acid secretion, beautifies skin and hair, relieves smooth muscle spasms in the arteries and bronchial tube, functions as an antibacterial and antiviral, strengthens the immune system, reduces allergy and sinus problems, prevents cancer, prevents osteoporosis and also various other useful functions (Nakayama et al., 2001).

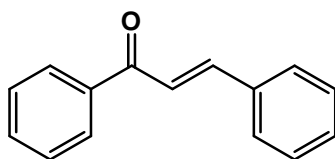
Antimalarial activity

Malaria is globally recognized as a serious problem of public health, mainly in the tropical and subtropical regions of the world. The increase of resistant malarial parasite strains represents the largest obstacle to antimalarial chemotherapy. A series of chalcone derivatives (1,3-Diphenyl-2-propen-1-one) as act as anti-*Plasmodium falciparum* agents (antimalarial agents) and inhibitory activity of chalcone derivatives on *P. falciparum* cysteine protease. The observed values of biological activity, high adjustment level, statistical significance and good predictive capacity, hydrophobic and steric properties seemed to play an important role in the activity. The results also indicated that molar refractivity and molecular length have positive contributions to the activity against chloroquine-resistant (W2) *Plasmodium falciparum* strains, while molecular weight against mefloquine-resistant (D6) strains as, (i) The C2–C3 double bond is essential for

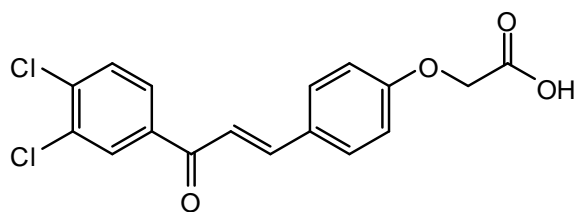
high inhibitory activity. It is not only a conjugated linker between A and B aromatic substituents, but it keeps extended the molecular conformation. In this way, the drug molecule seems to bind much better to the active site, which resembles a cleft on the surface of falcipain; (ii) Substitutions on the bridge portion of the chalcone series caused a pronounced decrease in the inhibitory activity, probably due to steric interactions; (iii) Chloro or fluoro substitution on the ring B and electron-donating substitution on the ring A increased the antimalarial activity; (iv) Quinoliny group in the ring B resulted in increased activity (Motta et al., 2006). Several chalcone analogues were evaluated as inhibitors of malaria parasite. Inhibitory activity was determined *in vitro* against a chloroquine-sensitive *P. falciparum* strain of parasites. The chalcone ‘3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl)prop-2-en-1-one’ (4) was found to be the most active with 50% inhibition concentration (IC₅₀) of 1.61 µg/ml. This inhibitory concentration was comparable to a prototype phytochemical chalcone, licochalcone, with an IC₅₀ of 1.43 µg/ml. The study suggested that small lipophilic nitrogen heterocyclic at ring B together with small hydrophobic functionality at ring A can enhance antimalarial activity. The results suggested that chalcones are a class of compounds that provides an option of developing inexpensive, synthetic therapeutic antimalarial agents in the future (Awasthi et al., 2009). In order to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of *P. falciparum*, a methodology for the solid phase synthesis of chalcone analogues in reasonably high yields. The chalcone derivatives with hydroxyl functionality on one of the aromatic rings and with some other appropriate substitutions on the other ring will be even more potent as antimalarials. They found that the chalcone ‘1-(2-chloroquinolin-3-yl)-3-(3-hydroxyphenyl)prop-2-en-1-one’ (5) was prepared (Cheng et al., 2000). A search for novel antimalarial agents from plants or via chemical synthesis, twenty derivatives of flavonoids and chalcones, four derivatives for each of flavones, flavanones, chalcones, dihydrochalcones, and 3'-chlorochalcones, and evaluated for *in vitro* antimalarial activity against *P. falciparum* strain FCR-3 and cytotoxicity against FM3A cells (a mouse mammary tumor cell). The aim was to derive predictive structure activity relationships to guide lead compound design. Among the chalcones tested, the most active compound was 3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-phenyl)propan-1-one (6) showing 100% inhibition against *P. falciparum* at the final concentration of 5.4 µg/ml (EC₅₀ = 1.0 µg/ml). The compound also showed strong cytotoxicity against FM3A cells, a model of the host, with relatively low EC₅₀ values (>3.3 µg/ml) and low selectivity index (>3.3) indicating that the compound have non-selective antimalarial activity (Lim et al., 2007).

Anticancer activity

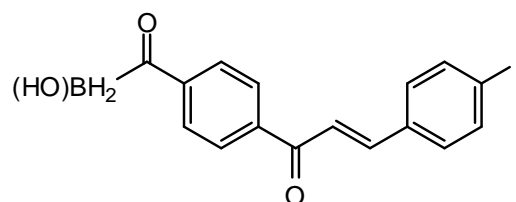
A series of boronic chalcones were tested for their anticancer activity and mechanisms of action.



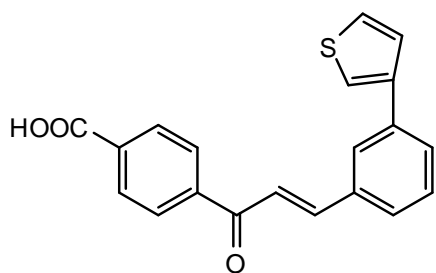
Chalcone (1)



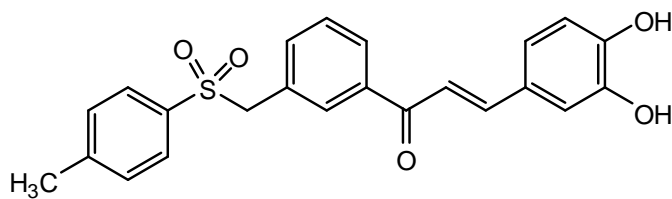
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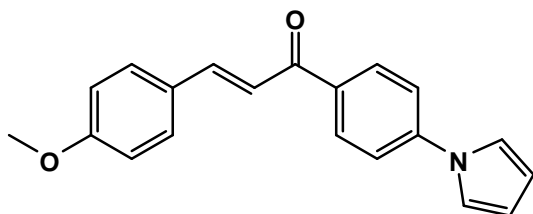
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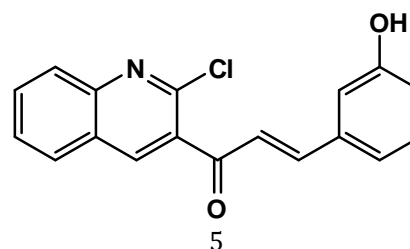
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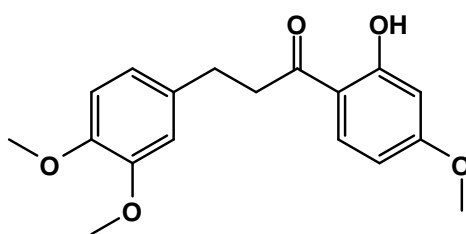
3b



4



5



6

Among the eight chalcone derivatives tested, the chalcone '3,5-bis-(4-boronic acid-benzylidene)-1-methylpiperidin-4-one' (7) exhibited most potent growth inhibitory activity with IC_{50} values of 1.5 and 0.6 μM in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and colony formation assay respectively. The cytotoxic activity of AM114 was shown to be linked with the

accumulation of p53 and p21 proteins and induction of apoptosis. Mechanistic studies showed that AM114 treatment inhibited the chymotrypsin like activity of the 20S proteasome *in vitro*, leading to a significant accumulation of ubiquitinated p53 and other cellular proteins in whole cells. *In vitro* studies showed that AM114 did not significantly disrupt the interaction of p53 and murine double minute 2

protein. It was noteworthy that AM114 as a single agent was preferentially toxic to cells with wild type p53 expression, whereas combination of this compound with ionizing radiation significantly enhanced the cell killing activity of ionizing radiation in both wild type p53 and p53 null cells. Together, these results indicated that the boronic chalcone derivative AM114 induced significant cytotoxic effect in cancer cells through the inhibition of the cellular proteasome and provided a rationale for the further development of this class of compounds as novel cancer chemotherapeutic agents (Achanta et al., 2006).

A series of chalcone-like agents, in which the double bond of the enone system is embedded within a thiophene ring, were evaluated for antiproliferative activity and inhibition of tubulin assembly and colchicine binding to tubulin. The replacement of the double bond with a thiophene maintained antiproliferative activity and therefore must not significantly alter the relative conformation of the two aryl rings. The synthesized compounds were found to inhibit the growth of several cancer cell lines at nanomolar to low micromolar concentrations. In general, all compounds having significant antiproliferative activity inhibited tubulin polymerization with an $IC_{50} < 2 \mu M$. Several of these compounds caused K562 cells to arrest in the G2/M phase of the cell cycle. Turning to the effects of an electron-releasing group (ERG) on the phenyl moiety, they found that a *p*-methyl group caused only minor changes in antiproliferative activity. Reduced activity occurred when the methyl substituent was moved from the *para* to *ortho* position. The more active compounds were evaluated for their *in vitro* inhibition of tubulin polymerization and for their inhibitory effects on the binding of [³H]colchicine to tubulin (in the latter assay, the compounds and tubulin were examined at a concentration of 1 μM with the colchicine at 5 μM). For comparison, the antitubulin agent CA-4 was examined in contemporaneous experiments as a reference compound. Compounds '3,4,5-trimethoxyphenyl-(5-(thiophen-2-yl)thiophen-2-yl)methanone' (8) and '3,4,5-trimethoxyphenyl-(5-*p*-tolylthiophen-2-yl)-methanone' (9) were the most active (IC_{50} , 0.8 μM), having twice the potency of CA-4 (IC_{50} , 1.4 μM) (Romagnoli et al., 2008).

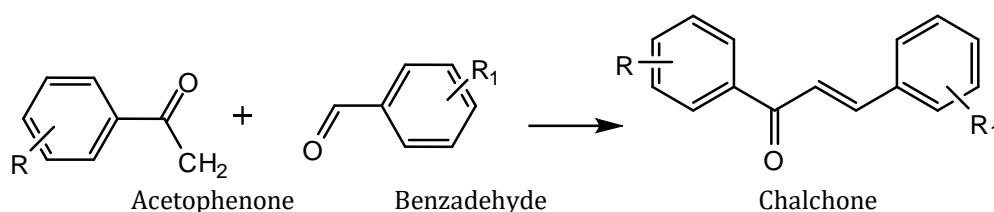
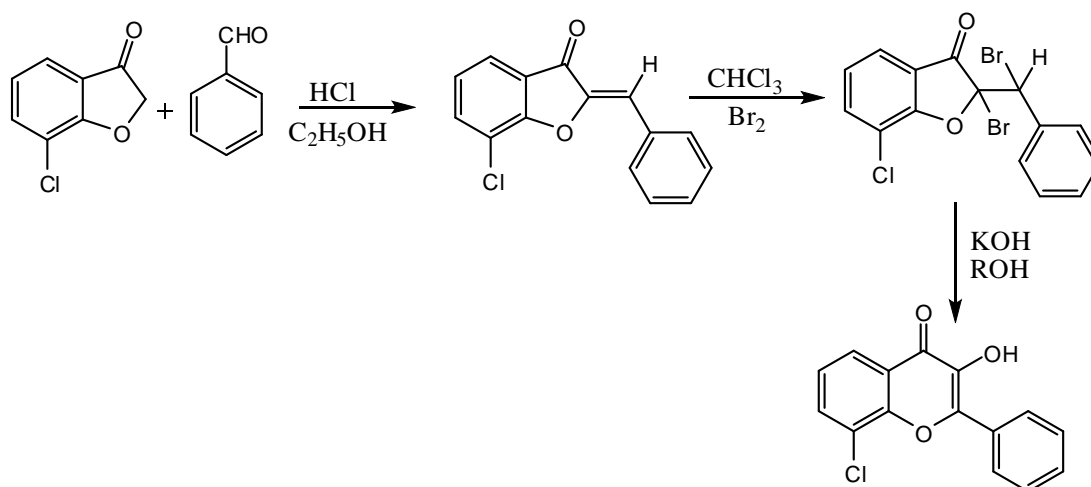
A relationship between the structural characteristic of synthetic chalcones and their antitumoral activity has also been studied. Treatment of HepG2 hepatocellular carcinoma cells for 24 h with synthetic 2'-hydroxychalcones resulted in apoptosis induction and dose-dependent inhibition of cell proliferation. The calculated reactivity indexes and the adiabatic electron affinities using the DFT method including solvent effects, suggested a SAR between the chalcone structure and the apoptosis in HepG2 cells. The absence of methoxy substituents in the ring A of synthetic 2'-hydroxychalcones, showed the major structureactivity pattern along the series and because of this, the chalcone '1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one' (10) was found to be the most active (Echeverria et al., 2009). Chalcones exhibit chemopreventive and antitumor effects. Tumor necrosis factor-related apoptosis-inducing ligand

(TRAIL) is a naturally occurring anticancer agent that induces apoptosis in cancer cells and is non-toxic to normal cells. Szliszka *et al* [8] examined the cytotoxic and apoptotic effect of five chalcones in combination with TRAIL on prostate cancer cells and evaluated the cytotoxicity by the MTT and Lactate Dehydrogenase (LDH) assays. The apoptosis was determined using flow cytometry with annexin V-FITC. Their study showed that all the five tested chalcones: chalcone (1), licochalcone-A (11), isobavachalcone (12), xanthohumol (13), butein (14) markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells and confirmed the significant role of chalcones in chemoprevention of prostate cancer. They showed for the first time that chalcones sensitize prostate cancer cells to TRAIL-induced apoptosis. The obtained results suggested that chalcones help anticancer immune defense in which endogenous TRAIL takes part. The TRAIL-mediated cytotoxic and apoptotic pathways may be a target to the chemopreventive agents in prostate cancer cells and the overcoming TRAIL resistance by chalcones may be one of the mechanisms responsible for their cancer-preventive effects (Szliszka et al., 2010). A series of chalcones and evaluated them for their *in vitro* cytotoxic activity by microculture Tetrazolium Test Assay method using two breast cancer cell lines MCF-7 and T47D. The IC_{50} value was calculated at the 0.1-100 μM concentration range. The assay was dependent on the activity of mitochondrial dehydrogenase enzymes that reduce yellow MTT to a blue formazan product and the activity of enzyme that is directly proportional to cell viability. The result showed significant cytotoxicity against both of the cell lines and value lied between 52-89 μM . All the compounds showed good cytotoxic activity and the compound 'N-(4-hydroxy-3-(3-(2/3/4-nitrophenyl)acryloyl)phenyl) acetamide' (15) showed better activity than other compounds, this may be due to presence of nitro group in the compound (Ilango et al., 2010).

Antiprotozoal activity

Ten chalcones were tested as leishmanicidal and trypanocidal agents against *in vitro* growth of *Leishmania braziliensis* and *Trypanosoma cruzi*. The results showed that the positions of the substituents seem to be critical for their antiprotozoal activities. The results also showed that some substitution-containing chalcones exhibited promising concentration-dependent (i.e., at high concentration) leishmanicidal and trypanocidal activities with no evidence of a cytotoxic effect on mouse macrophages. The chalcone (1), which has no substituent groups, revealed both pronounced leishmanicidal and trypanocidal activities even at low concentration with no evidence of a cytotoxic effect on mouse macrophages (Lunardi et al., 2003).

Anti-inflammatory activity

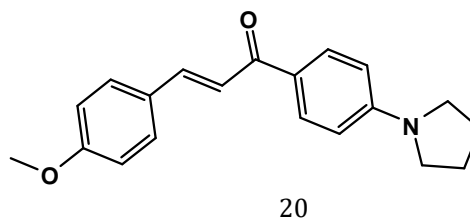
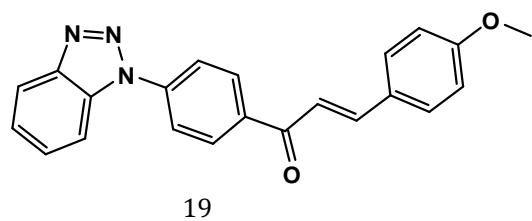
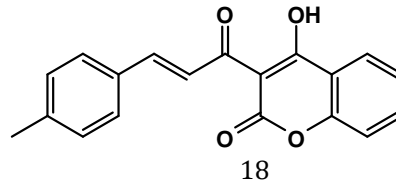
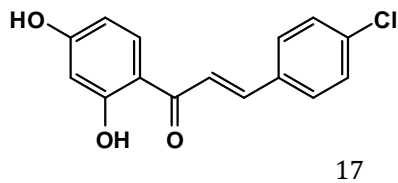
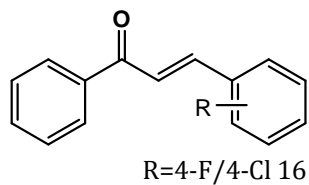
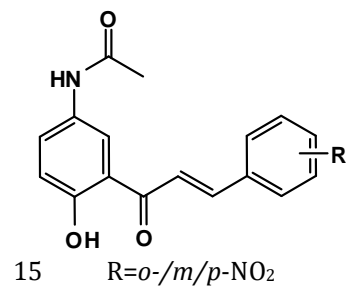
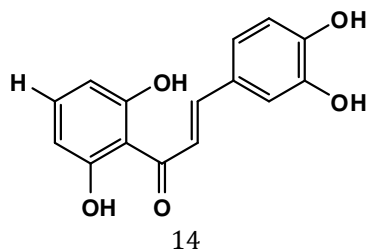
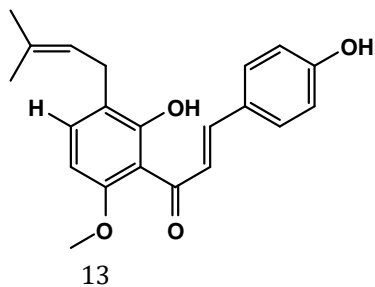
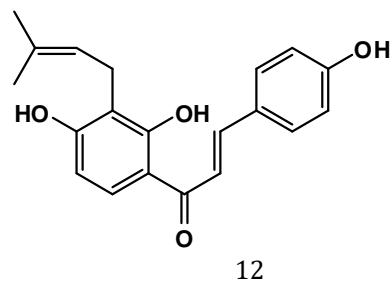
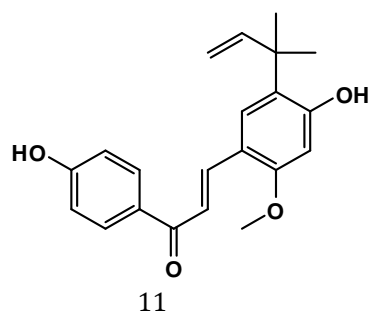
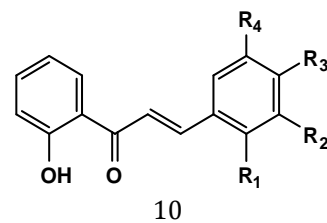
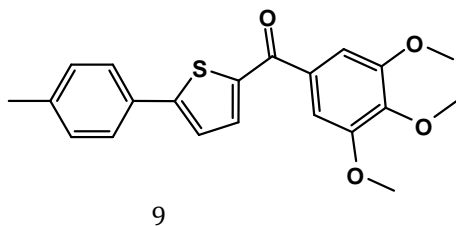
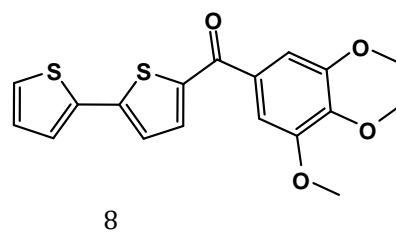
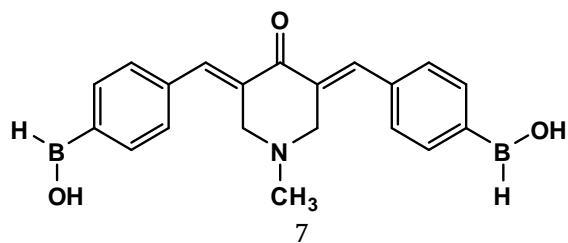
**Scheme 1:** Synthesis of chalcone**Scheme 2:** Auwer's synthesis

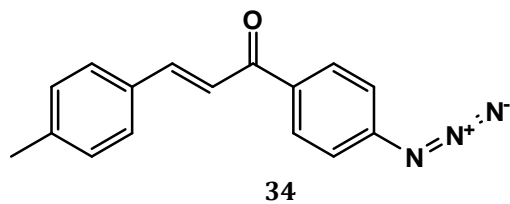
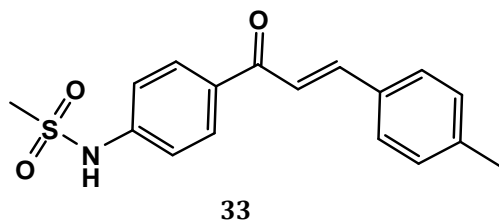
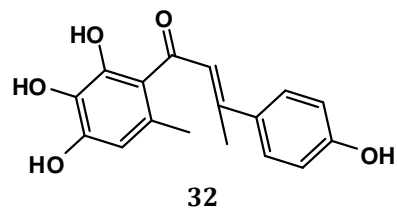
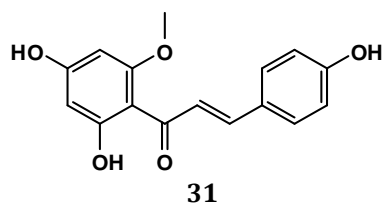
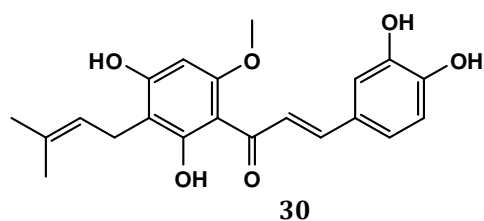
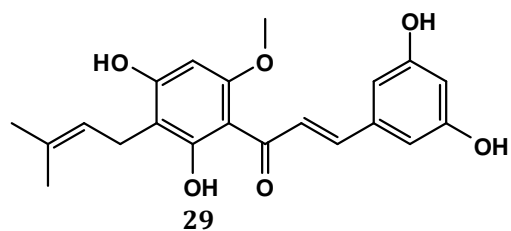
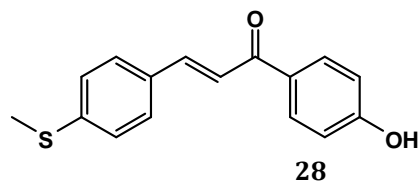
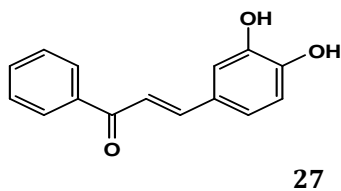
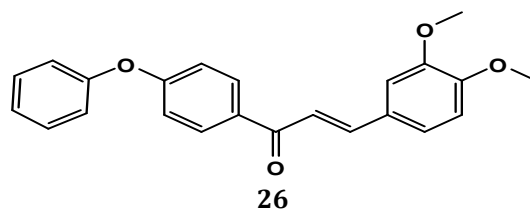
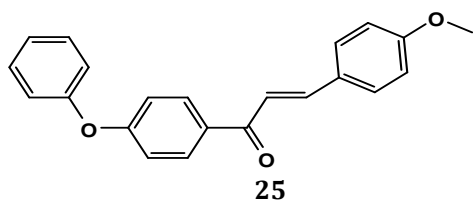
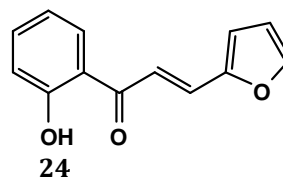
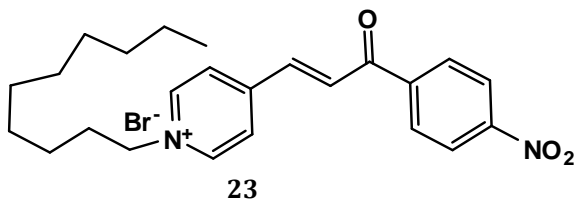
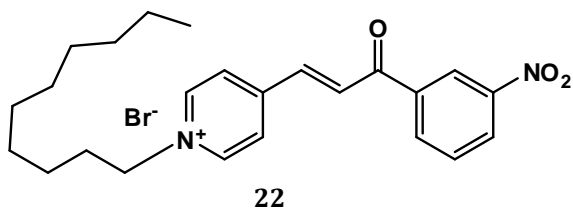
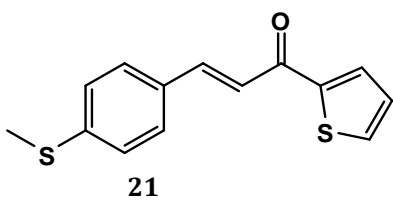
Chalcone derivatives contain α , β -unsaturated carbonyl moiety which is responsible for anti-inflammatory activity. A series of five chalcone derivatives and were subjected to anti-inflammatory screening using the carrageenan-induced rat hind paw edema model. Chalcone derivatives at dose 25 mg/kg by oral route inhibited significantly the formation of edema and showing significant anti-inflammatory activity. The compound '4-fluoro/4-chloro chalcone' (16) showed more activity comparable to standard drug indomethacin due to -F/-Cl groups present in the compound. Hence, the anti-inflammatory activity of chalcone derivatives was increased when electron withdrawing groups (EWG) were present on the chalcone moiety (Yadav et al., 2010). In an effort to develop potent anti-inflammatory agents, a series of substituted chalcone derivatives was synthesized and evaluated for anti-inflammatory activity through *in vivo* inhibition assay monitoring of their ability to inhibit xylene-induced ear edema in mice. Some of the tested compounds exhibited significant activity, and the compound '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one' (17) showed the highest anti-inflammatory activity (68% inhibition) comparable with or even slightly more potent than the reference drug ibuprofen (53%). Furthermore, the structure-activity relationship of these substituted chalcone derivatives demonstrated that the substituted 2',4'-dihydroxychalcone derivatives was stronger than that of 4'-hydroxychalcone. The position of the substituted group on

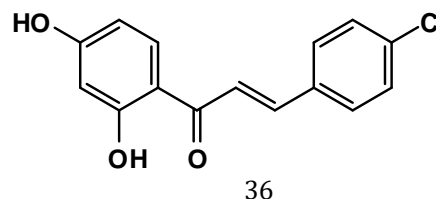
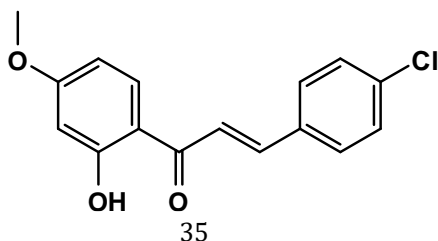
the phenyl ring greatly influenced the anti-inflammatory activity, with an activity order of -4-N(CH₃)₂>-4-OCH₃>-3-OCH₃-4-OH>-3,4-OCH₂O>-4-OH>-3,4-(OH)₂. The potency order of the two Cl-substituted derivatives being 4-Cl>2,4-Cl₂. the potency order of the two NO₂-substituted derivatives being 3-NO₂>2-NO₂. These results indicated that the character of the substitution on the ring A had a significant influence on the anti-inflammatory activity (Zhang et al., 2010).

Antibacterial activity

A series of new coumarin derivatives containing a chalcone moiety and evaluated for possible anti-oxidant and antibacterial activities. The coumarinic chalcone '4-hydroxy-3-(3-*p*-tolylacryloyl)-2H-chromen-2-one' (18) had been found to be the most active (IC₅₀ = 2.07 μ M). The derivatives were screened *in vitro* for their antibacterial activity against Gram +ve bacteria, *S. aureus* using the paper disc diffusion method for the antibiotic sensitivity technique. It showed that the activity against bacteria is moderate, but in addition, it was clearly demonstrated that this kind of compound could be an antibacterial agent. The activity depends on its chemical composition. The moderate active antibacterial effects observed showed that this kind of compound could be an antibacterial agent (Hamdi et al., 2010).







A series of chalcone derivatives were evaluated for antibacterial activity. All the compounds were screened for their antibacterial activities against four different bacterial strains *S. aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Dimethyl formamide was used as a solvent, and ciprofloxacin as the standard drug. QSAR equation revealed that selected electronic, steric and lipophilic parameters had good correlation with antibacterial activity. The findings suggested that the chalcone framework is an attractive template for structure optimization to achieve higher potency, lower toxicity, and a wider spectrum of antibacterial activity. Although more hydrophobic surface areas tend to favor antibacterial activity and Gram -ve and Gram +ve selectivity, the increase in the size of molecules may lead to a decrease in the antibacterial activity. The hydrophobic surface area should be increased without increasing the molecule size. An increase in the dipole and quadrupole moments leads to charge separation which increases biological activity (Bhatia et al., 2009).

Antifilarial activity

Chalcone derivatives were evaluated for their antifilarial activity on *Setaria cervi* using glutathione-S-transferase (GST) enzyme as a drug target. The compounds '1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one' (19) and '3-(4-methoxy phenyl)-1-(4-pyrrolidin-1-yl-phenyl)prop-2-en-1-one' (20) showed a significant suppression in GST activity of adult female parasite extract at 3 μ M concentration *in vitro*. However, GST activity was detected along with depletion in GSH level. More or less, all compounds showed a paralyzing effect on the motility and viability of parasites, ranging from 25% to 97% inhibition. The compounds '1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl) prop-2-en-1-one' and '3-(4-methoxyphenyl)-1-(4-pyrrolidin-1-ylphenyl)prop-2-en-1-one' exhibited major irreversible effects on viability and resulted in parasite death and also inhibited the GST activity by 84-100% *in vitro*. They reported for the first time the antifilarial activity of chalcones on GST of adult parasites. This study also strengthened their previous findings where GST was reported as a potential drug target for antifilarials. However, this was a preliminary *in vivo* and *in vitro* study in which living worms were incubated with chalcones. The results of 4-chloro and 4-methoxy-substituted chalcones strongly supported that small- and medium-sized highly

lipophilic or hydrophobic groups containing single or multiple nitrogen or oxygen in an acetophenone ring of chalcone have potent inhibitory effects on motility, viability, and GST activity of the parasite, supporting the antifilarial efficacy of chalcone. The most significant effect on parasites was exerted by methoxy-substituted chalcones, suggesting that these substituents can be used for further studies against filariasis (Awasthi et al., 2009).

Antifungal Activity

With the aim of developing potential antifungals, a series of chalcones incorporating sulfur either as part of a hetero-aromatic ring (thiophene) or as a side chain (thiomethyl group) and tested for their *in vitro* activity. Some of the compounds showed appreciable activity against a fluconazole-sensitive and fluconazole-resistant strain with the chalcone '3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one' (21) exhibiting the highest activity. Maximum activity was obtained with *p*-fluoro substitution on ring A. Activity was decreased with increasing halogen size. Presence of *p*-methoxy or hydroxy groups at the *o*-, *m*- or, *p*-position also resulted in good activity while the *p*-nitro group as well as the bulky *p*-phenyl substitution decreased activity as compared with the unsubstituted compound. The *m*- and *p*-disubstitution with methoxy led to increased activity while again the *p*-phenyl-substituted compounds exhibited considerably decreased activity. All compounds with the bromo thiophene ring in place of ring B exhibited less activity compared with those with the unsubstituted thiophene ring. Bromine substitution on the thiophene ring B decreased antifungal activity. Compounds with unsubstituted thiophene ring B and thiomethyl substitution at the *p*-position of ring A, exhibited good antifungal activity. Highest activity was found when both thiophene ring B and thiomethyl substitution at ring A were present together in the chalcone 3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one (Bag et al., 2009).

Antifungal evaluation and study on substituent effects of several chalcones. A lot of genetically defined strains belonging to different yeast genera and species, namely *Saccharomyces cerevisiae*, *Hansenula polymorpha* and *Kluyveromyces lactis*, were used as test organisms. Concerning the mode of the antifungal action of chalcones it was shown that DNA was probably not the main target for the chalcones. It was revealed that the yeast's intracellular

glutathione and cysteine molecules play significant role as defence barrier against the chalcone action. It was also shown that chalcones may react with some proteins involved in cell separation. The antifungal effects of the substituted chalcones were compared with those of the parent chalcone. The following correlations were observed: (i) Introduction of EW substituents (Cl, CN and NO₂ groups) in *p*-position in ring A yielded less active chalcones than the parent chalcone. (ii) Introduction of ED substituents (OH, CH₃ and OCH₃ groups) in *p*-position in ring A produced inactive chalcones. (iii) Presence of a single hydroxyl group was effective at *m*-position in ring A. Introduction of a single methoxy group at *m*-position in ring A led to inactive compound. (iv) The combination of *m*-hydroxyl and *p*-methoxy groups in ring A was effective. Loss of activity was observed with the interchange of the positions of the hydroxyl and methoxy groups and when the hydroxyl group was placed in *o*-position and the methoxy group was in *m*-position. (v) Introduction of *p*'-chloro atom in ring B was beneficial only for the chalcones with a single hydroxyl group at *m*- and *p*-positions. The *m*-position was more favourable than the *p*-position. Presence of *m*- and *p*-hydroxyl groups together led to the inactive chalcone. (vi) Elongation of the conjugated system by introduction of one additional double bond between the ketovinyl moiety and the ring A did not produce an active compound. Based on these observations, it was concluded that the electronic effects of the *p*substituents in ring A of chalcones are not crucial for displaying antifungal activity towards the tested fungi. This is contradictory to the antifungal effects, which chalcones with EW and ED substituents in ring A have shown against several *dermatophytes* and the yeast *C. albicans*. Besides, in this study the position of the hydroxyl group in ring A was found important for the chalcone activity as opposed to some other antifungal studies. Interestingly, the favored location for the hydroxyl group was the *m*-position in ring A (Lahtchev et al., 2008).

Antimicrobial activity

The *N*-alkyl derivatives and photochemical dimers of 3 *o*-, *m*-, and *p*-nitro substituted 4-azachalcones. The monomeric compounds showed good antimicrobial activity against test micro-organisms *E. coli*, *K. pneumoniae*, *Yersinia pseudotuberculosis*, *P. aeruginosa*, *Enterococcus faecalis*, *S. aureus*, *Bacillus cereus*, and *Candida tropicalis*. The most sensitive micro-organisms were Gram +ve bacteria. The compounds '1-decyl-4-(3-(3-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' (22) and '1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' (23) exhibited broad-spectrum antimicrobial activity. The MIC values (MBC) for the test micro-organisms were between <0.35 and 25 µg/ml. The synthesized compounds were also tested for their antioxidant activity based on their ability to scavenge the stable radical DPPH (2,2-diphenyl-1-picrylhydrazine). The monomers showed high anti-oxidant activity, while the dimerization products were less active.

The monomeric compounds exhibited higher radical scavenging potential in general, with low IC₅₀ values. The compound '1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' was found to have similar or even higher activity when compared to the standard anti-oxidants Trolox and vitamin C, respectively (Yayli et al., 2006).

Mosquito larvicidal activity

A series of chalcone analogues and some of their derivatives were synthesized and subjected to the mosquito larvicidal study (larvae of *Culex quinquefasciatus*), SAR and QSAR. The chalcones showed % mortality ranging from a very low value (10%) to a very high value (90%). Chalcones having EDG(s) on either ring A or ring B showed high toxicity to larva of the mosquito. EWG(s), especially at ring A, reduced the activity of chalcones. The activity was abruptly decreased due to replacement of ring B by CH₃, extension of conjugation or blocking of α,β-unsaturated ketone part of chalcones by derivation. QSAR studies of these compounds were performed using various spatial, electronic and physicochemical parameters. Genetic function approximation with linear and spline options was used as the chemometric tool for developing the QSAR models. The investigation had clearly shown that certain chalcone analogues had potent mosquito larvicidal activity. Most of the hydroxyl chalcones showed toxicity against the third instar larvae of *C. quinquefasciatus*. The favorable chemical structures were found to be a hydroxyl substituent in ring B at 2'-position which may be hydrogen bonded with the electron pair on α,β-unsaturated ketone moiety, thereby decreasing the electrophilicity of this part of the molecule. Presence of hydroxyl group at 2'-position of ring B and replacement of ring A (phenyl) by a furan ring also increased the larvicidal activity. Besides that 3-chlorine substitution in ring A was also another feature of favorable activity. Presence of methylenedioxy group at 3,4 positions of ring A also enhanced the larvicidal activity of chalcone-type compound. However, extension of conjugation and blocking of α,β-unsaturated ketone part of chalcones had bad effects toward the activity of these compounds. The chalcone '3-(furan-2-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one' (24) had shown 100% mortality and LC₅₀ was very low with a value of 19 µmole/dm³. QSAR analysis also suggested that charge distribution on molecular surface and surface area are important determinants of the larvicidal activity. The derived models suggested that for the good larvicidal activity positively charged surface areas of the compounds should be limited. Moreover, there should be a balanced distribution of +ve and -ve charges on the molecular surfaces of the compounds (Begum et al., 2010).

Anticonvulsant activity

Some new phenoxy chalcones were prepared and screened for their anticonvulsant activity using Maximal Electroshock Method (MES). Neurotoxicity study was performed using

rotarod method. It was found that substitution of 4-methoxy and 3,4-dimethoxy group in the substituted ring A of phenoxy chalcone showed significant anticonvulsant activity without neurotoxicity while hydrogen and chloro substitution does not showed the significant anticonvulsant activity. It was also found that the compounds '3-(4-methoxyphenyl)-1-(4-phenoxyphenyl)prop-2-en-1-one' (25) and '3-(3,4-dimethoxyphenyl)-1-(4-phenoxyphenyl)prop-2-en-1-one' (26) showed the most potent anticonvulsant activity without neurotoxicity (Kaushik et al., 2010).

Antioxidant activity

Six anti-oxidants from the class of chalcones (ArOH), compounds from which flavonoids are obtained in nature. The antiradical activity of chalcones and a number of related compounds was determined by a chemiluminescence method using the scavenging of peroxide radicals $\text{ROO}\cdot + \text{ArOH} \rightarrow \text{ROOH} + \text{OAr}\cdot$ (with the rate constant k_7) in a model reaction of diphenylmethane (RH) oxidation. The structures and energies of the reagents and intermediates were determined by semi-empirical quantum chemical (PM3, PM6) calculations. 3-(3,4-Dihydroxyphenyl)-1-phenylprop-2-en-1-one (27) and caffeic acid, which have a catechol structure, that is, two neighboring OH groups in phenyl ring A, exhibited high antioxidant activity ($k_7 \approx 107 \text{ l/mol/s}$) (Vasil'ev et al., 2010).

The chalcone derivatives and evaluated their antioxidant activity, and (QSAR). Antioxidant activity was evaluated through four different methods namely, superoxide radical-scavenging, hydrogen peroxide-scavenging, reducing power, and DPPH radical-scavenging assays at $50 \mu\text{g/ml}$ *in vitro*. The antioxidant potential of the compound was related to its (i) hydrogen or electron donation capacity, (ii) its ability to stabilize and delocalize the unpaired electron, and (iii) potential to chelate transition metal ions. These actions were achieved either by the hydrogen atom or single electron transfer. In the case of ferric reducing anti-oxidant power (FRAP), it was due to the single electron transfer and in the cases of superoxide radical-scavenging, hydrogen peroxide-scavenging, and DPPH radical-scavenging activities, it was due to the transfer of hydrogen atom. The antioxidant activity of the flavonoids was due to the inhibition of the enzyme responsible for the superoxide radical production, chelation of the metal ions and scavenging of ROS. Generally, compounds with $-\text{SCH}_3$ and $-\text{OCH}_3$ in the *para* position of the ring A and $-\text{OH}$ in the ring B were most active than others. The chalcone '1-(4-hydroxyphenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one' (28) was showing the highest superoxide radical-scavenging activity (>50%), reducing power activity (>46%), DPPH scavenging activity (>20%). In few cases, some of the compounds were more active than ascorbic acid or butylated hydroxytoluene. QSAR was developed correlating the antioxidant activity with the structural features of the compounds and the predictive capability of the models was estimated using internal and external validation methods. All

the predictions were within the 99% confidence level. Spatial, structural, and lipophilic properties of the compounds determined their antioxidant properties (Sivakumar et al., 2010).

A general strategy for the synthesis of 3'-prenylated chalcones and synthesized a series of prenylated hydroxychalcones, including the hop (*Humulus lupulus* L.) secondary metabolites xanthohumol, desmethylxanthohumol, xanthogalenol, and 4-methylxanthohumol. They investigated the influence of the ring A hydroxylation pattern on the cytotoxic activity of the prenylated chalcones in a HeLa cell line and revealed that non-natural prenylated chalcones, like 2',3,4',5-tetrahydroxy-6'-methoxy-3'-prenylchalcone (29) ($\text{IC}_{50} 3.2 \pm 0.4 \mu\text{M}$) as well as the phase I metabolite of xanthohumol, 3-hydroxyxanthohumol '1-(2,4-dihydroxy-6-methoxy-3-(3-methylbut-2-enyl)phenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one' (30) ($\text{IC}_{50} 2.5 \pm 0.5 \mu\text{M}$), were more active in comparison to xanthohumol ($\text{IC}_{50} 9.4 \pm 1.4 \mu\text{M}$). A comparison of the cytotoxic activity of xanthohumol and 3-hydroxyxanthohumol with the non-prenylated analogs helichrysetin ($\text{IC}_{50} 5.2 \pm 0.8$) and 3-hydroxyhelichrysetin ($\text{IC}_{50} 14.8 \pm 2.1$) showed that the prenyl side chain at C-3' has an influence on the cytotoxicity against HeLa cells only for the dihydroxylated derivative. This offers interesting synthetic possibilities for the development of more potent compounds. The ORAC (Oxygen Radical Absorbance Capacity) fluorescein activity of the synthesized compounds was also investigated for their antioxidant activity evaluation and revealed the highest activity for the compounds helichrysetin '1-(2,4-dihydroxy-6-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one' (31), 4'-methyl xanthohumol, and desmethylxanthohumol, with 4.4 ± 0.6 , 3.8 ± 0.4 , and 3.8 ± 0.5 Trolox equivalents, respectively (Vogel et al., 2008).

Mammalian alpha-amylase inhibitory activity

Trans-chalcone (1), a biphenolic core structure of flavonoids precursor was tested for inhibitory activity toward alpha-amylase (1,4- α -D-glucan glucanohydrolase) using Bernfeld method. Porcine pancreatic alpha-amylase was observed to be effectively inhibited by this compound, which showed competitive behavior with a K_i of $48 \mu\text{M}$ and an IC_{50} of $96.44 \mu\text{M}$ as compared to flavonoids possessing IC_{50} values ranging typically from about 10 to about $30 \mu\text{M}$ for mammalian alpha-amylase. Soluble starch (the natural substrate of the enzyme) was used in this study in order to obtain more realistic results. The possible binding mode of the compound was assessed *in silico*, and the two residues Trp59, and Tyr62 were proposed as main interacting residues with transchalcone. In conclusion, this compound could be used to design effective inhibitors of alpha-amylase. The core chalcone structure that could be detected in the flavone structure (scutellarein) has been highlighted by circles in the figure (32) and putative mode of interaction between trans-chalcone (represented as sticks) within porcine pancreatic alpha-amylase structure. Elements of secondary structure of

the enzyme, as well as a transparent surface of the interaction site are also visible. Two π - π interactions of *trans*-chalcone with Trp59 and Tyr62 are highlighted with the use of circles in the center of aromatic components (Najafian et al., 2010).

Cyclooxygenase (COX) inhibitory activity

Chalones possessing a methanesulfonamido (MeSO_2NH) or an azido (N_3) pharmacophore at the *para*-position of the C-1 phenyl ring and evaluated their biological activity as cyclooxygenase-1/-2 inhibitors. *In vitro* COX-1/COX-2 structure-activity relationships were determined by varying the substituents on the C-3 phenyl ring (4-H, 4-Me, 4-F, and 4-OMe). Among the chalones possessing a C-1 *para*- MeSO_2NH COX-2 pharmacophore '1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one' (33) was identified as a selective COX-2 inhibitor (COX-2 IC_{50} = 1.0 μM ; selectivity index >100) that was less potent than the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM ; SI > 200). The corresponding chalcone analogue possessing a C-1 *para*- N_3 COX-2 pharmacophore '1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one' (34), exhibited potent and selective COX-2 inhibition (COX-1 IC_{50} = 22.2 μM ; COX-2 IC_{50} = 0.3 μM ; SI = 60). A molecular modeling study where these two chalones were docked in the binding site of COX-2 showed that the *p*- MeSO_2NH and N_3 substituents on the C-1 phenyl ring are oriented in the vicinity of the COX-2 secondary pocket (His90, Arg513, Phe518, and Val523). The data acquired indicated that the propenone moiety constitutes a suitable scaffold to design acyclic 1,3-diphenylprop-2-en-1-ones with selective COX-1 or COX-2 inhibitory activity (Zarghi et al., 2006).

Monoamine oxidases (MAOs) inhibitory activity

A large series of substituted chalchones tested *in vitro* for their ability to inhibit human monoamine oxidases A and B (hMAO-A and hMAO-B). The potential effects of the test drugs on hMAO activity were investigated by measuring their effects on the production of hydrogen peroxide (H_2O_2) from *pyramine* using the Amplex Red MAO assay kit and microsomal MAO isoforms prepared from insect cells infected with recombinant baculovirus containing cDNA inserts for hMAO-A or hMAO-B. While all the compounds showed hMAO-B selective activity in the micro- and nano-molar ranges, the best results were obtained in the presence of chlorine and hydroxyl or methoxyl substituents. The most active compounds, '3-(4-chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one' (35) and '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one' (36) (IC_{50} =0.0044 +0.00027 μM and 0.0051+0.00019 μM , respectively), are disubstituted in the 2- and 4-position of the B aromatic moiety with two hydroxyls or hydroxyl and methoxy groups and in 4'-position of the A aromatic moiety with a chlorine atom. To better understand the enzyme-inhibitor interaction and to explain the selectivity of the most

active compounds toward hMAO-B, molecular modeling studies were carried out on new, high resolution, hMAO-B crystallographic structures. For the only compound that also showed activity against hMAO-A as well as low selectivity, the molecular modeling study was also performed on the hMAO-A crystallographic structure. The docking technique provided new insight on the inhibition mechanism and the rational drug design of more potent/selective hMAO inhibitors based on the chalcone scaffold. In the reversibility and irreversibility tests, hMAO-B inhibition was found to be irreversible in presence of the compounds '3-(4-chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one' and '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one' (chosen for docking experiments) (Chimenti et al., 2009).

DISCUSSION

Chalchones are the principal precursors for the biosynthesis of flavonoids and isoflavonoids. A three carbon α,β -unsaturated carbonyl system constitutes chalchones. Chalchones are the condensation products of aromatic aldehyde with acetophenones in attendance of catalyst. They go through an assortment of chemical reactions and are found advantageous in synthesis of pyrazoline, isoxazole and a variety of heterocyclic compounds. In synthesizing a range of therapeutic compounds, chalchones impart key role. They have showed worth mentioning therapeutic efficacy for the treatment of various diseases.

Chalcone based derivatives have gained heed since they own simple structures, and diverse pharmacological actions. A lot of methods and schemes have been reported for the synthesis of these compounds. Amongst all, Aldol condensation and Claisen-Schmidt condensation still grasp high up position. Other distinguished techniques include Suzuki reaction, Witting reaction, Friedel-Crafts acylation with cinnamoyl chloride, Photo-Fries rearrangement of phenyl cinnamates etc. These inventive techniques utilize various catalysts and reagents including SOCl_2 natural phosphate, lithium nitrate, amino grafted zeolites, zinc oxide, water, sodium carbonate, PEG400, silica sulfuric acid, ZrCl_4 and ionic liquid etc. The development of better techniques for the synthesis of α,β -unsaturated carbonyl compounds is still in high demand. In brief, we have explained the methods and catalysts used in the synthesis of chalchones along with their biological activities to provide information for the development of new-fangled processes targeting better yield, less reaction time and least side effects with utmost pharmacological properties (Sahu et al., 2012; Bai et al., 2012; Kumar et al., 2012; Deb Majumdar et al., 2011; Orlikova et al., 2011; Ruan et al., 2011; Jin et al., 2013; Reddy et al., 2010; Dong et al., 2010; Dong et al., 2010). The review provided an overview of the recent scientific reports describing the affectation and study of new chalchones. The review emphasizes the rationale behind the natural sources, the discovery, the design, the synthesis, and the biological activities. Although a great number of chalchones

have been reported, the potential of this scaffold could be deeply studied in many different areas in which almost nothing has been described. A lot of work should be done to reach the potency and safety requirements needed to develop new chemical entities as new drugs (Karaman et al., 2010; Kong et al., 2010; Padhye et al., 2009; Corrêa et al., 2008; Lorenzo et al., 2008). From the above discussion, it can be concluded that chalcones and their derivatives display a wide range of pharmacological activities, such as antimalarial, anticancer, antiprotozoal (antileishmanial and antitrypanosomal), antiinflammatory, antibacterial, antifilarial, antifungal, antimicrobial, larvicidal, anticonvulsant and antioxidant activities (Ávila et al., 2008; Bandgar et al., 2009; Batovska and Todorova, 2010; Chiaradia et al., 2008; Climent et al., 2004; Sahu et al., 2012; Kalirajan et al., 2009; Lee et al., 2006; Nowakowska, 2007; Prasad et al., 2008; Rahman, 2011; Tran et al., 2012; Viana et al., 2003; Vogel et al., 2010). They also show inhibition of the enzymes, especially mammalian α -amylase, cyclooxygenase and monoamine oxidase and antimitotic activity too. Because of this, chalcones and their derivatives have attracted increasing attention of the scientists for the search of new potent pharmacological activity in it.

CONCLUSIONS

In this review, described an efficient protocol for the synthesis of chalcone in good yields from aromatic aldehyde and acetophenone using the catalytic system. There are several of strategies for the synthesis of chalcone, the synthesis of this system is based on the formation of carbon-carbon bond have been reported and among them Aldol Condensation and Claisen Schmidt reaction occupy the prominent position. Chalcones are found to be effective pharmacological agents.

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