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Chalcone: A Versatile Molecule

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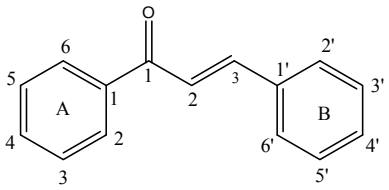
ABSTRACT:
Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system.These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids. The aim of this review to give summary of methods for synthesis of chalcones, its chemical modifications to flavonoids, flavanone, pyrazoles, oxazoles, pyrimidines. This article also highlights antioxidant potential of chalcone, mechanism of antioxidant activity of chalcones and structure activity relationship of chalcone derivatives for antioxidant ability and different methods to evaluate antioxidant activity of chalcone, anti-inflammatory, cytotoxic and antihyperglycemic activity of chalcones is also discussed in this review article.

KEYWORDS: Antioxidant, chalcone, Claisen-schimdt reaction, MOM (methoxymethyl)-protected benzaldehyde

INTRODUCTION [1]

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system as,



Chalcone

These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids.

Chalcones possess conjugated double bonds and a completely delocalized Π-electron system on both benzene rings. Molecules possessing such system have
relatively low redox potentials and have a greater probability of undergoing electron transfer reactions.

1. Methods for synthesis of chalcones:

Chalcones are synthesized by claisen-schmidt condensation of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield chalcones.

A. Base catalyzed reaction [2][3][4]

The main method for the synthesis of chalcones is the classical Claisen-Schmidt condensation in the presence of aqueous alkaline bases.

Procedure [2]

Place a solution of 22g of sodium hydroxide in 200ml of water and 100g (122.5ml) of rectified spirit in a 500ml bolt-head flask provided with a mechanical Stirrer. Immerse the flask in a bath of crushed ice, pour in 52g (0.43mol) of freshly distilled acetophenone, start the stirrer and then add 46g (44ml, 0.43mol) of pure benzaldehyde.

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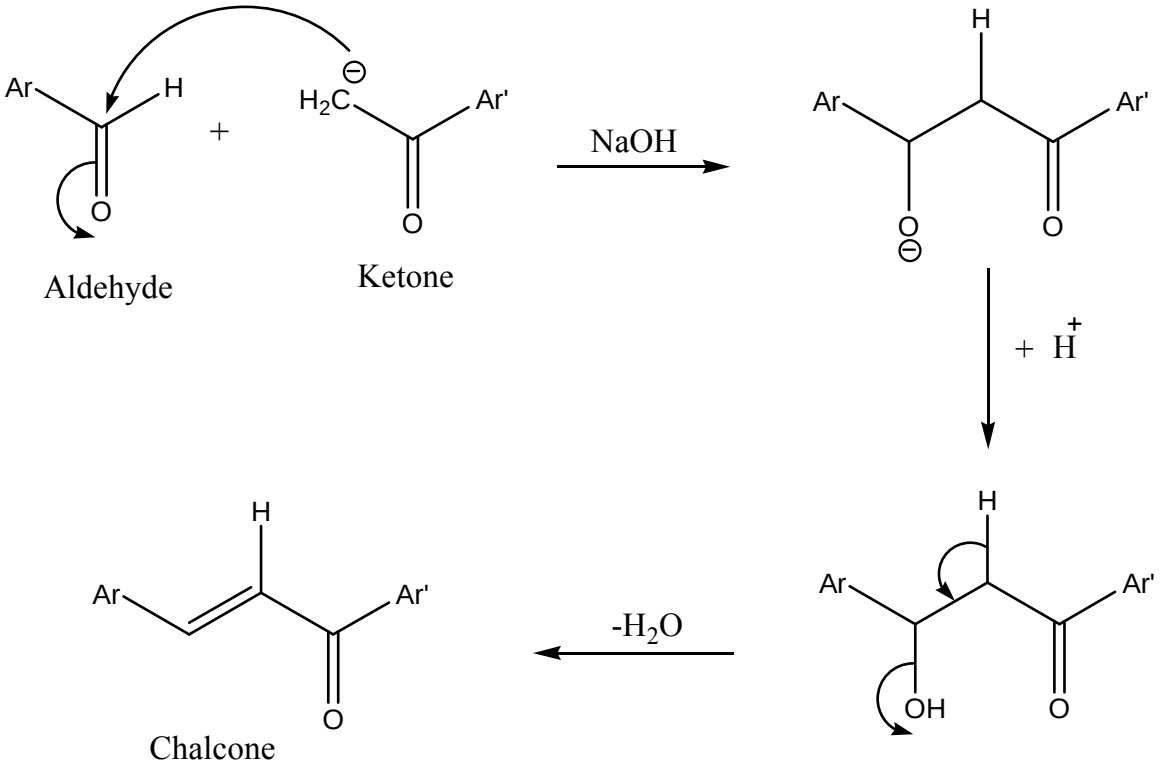
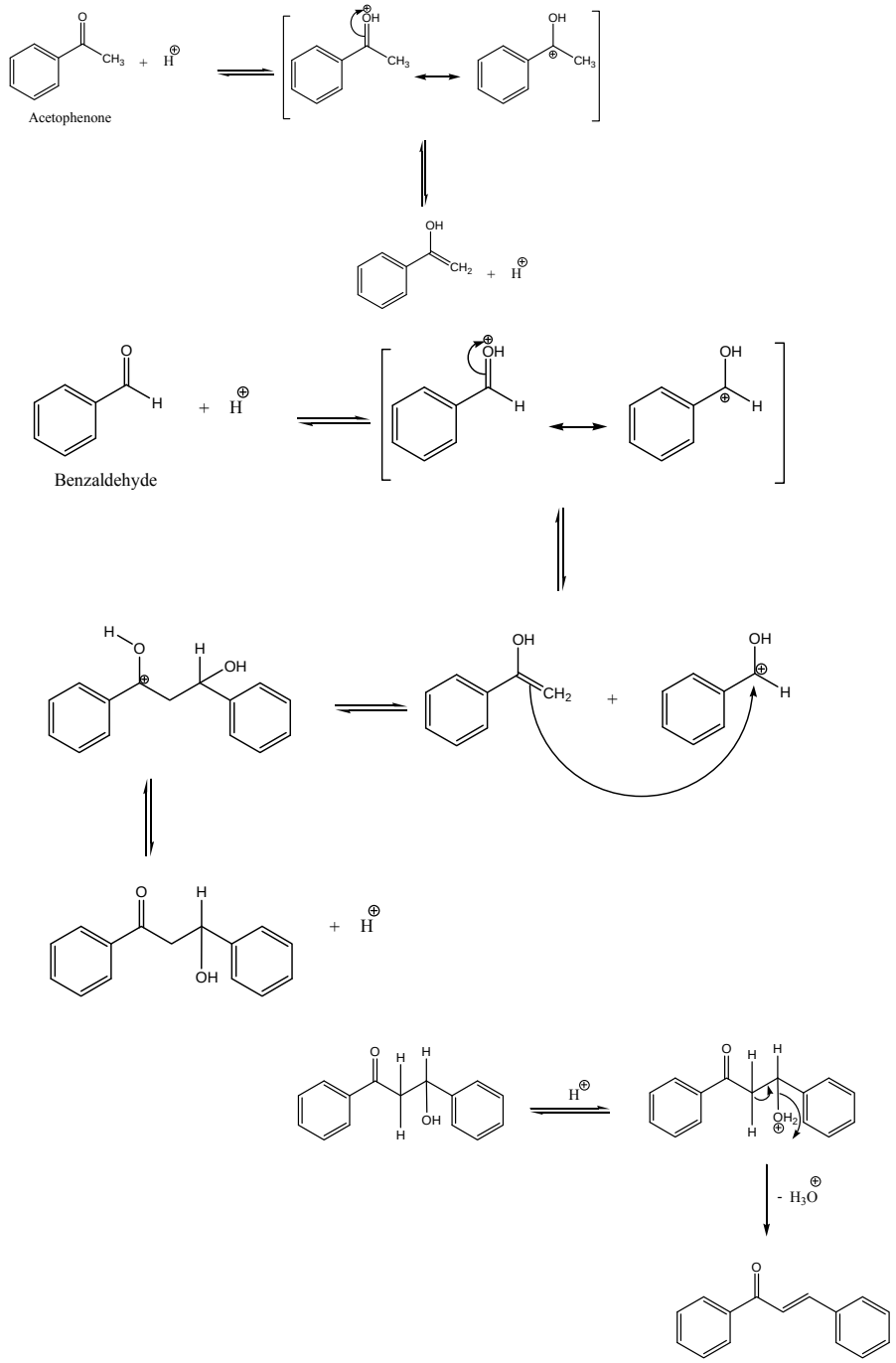
Mechanism[2]



Keep the temperature of the mixture at about 25^0C (the limits are 15-30^0C) and stir vigorously until the mixture is so thick that stirring is no longer effective (2-3 hr). Remove the stirrer and leave the reaction mixture in an ice chest or refrigerator overnight. Filter the product with suction on a buchner funnel or a sintered glass funnel, wash with cold water until the washings are neutral to litmus and then with 20ml of ice-cold rectified spirit. The crude chalcone after drying in the air weighs 88g and melts at 50-54^0C. Recrystallized from rectified spirit warmed to 50^0C (about 5ml per g). The yield of pure benzylideneacetophenone (a pale yellow solid) mp 56-57^0C, is 77g (85%).This substance should be handled with great care since it acts as a skin irritant.

B. Acid catalyzed reaction: Mechanism[5]



Chalcone

Procedure [6]

To a stirred mixture of acetophenone (0.01mol) and benzaldehyde (0.01mol) in absolute ethanol (5ml), add thionyl chloride (0.05ml) dropwise and continue stirring for two hour at room temperature. Allow to stand reaction mixture for 12hr. Precipitate the reaction mixture by addition of water. Filter the product, wash with cold ethanol. The yield of pure benzylideneacetophenone (a pale yellow solid) mp 56-57^{0}C, is 77.0g (85%).

In the presence of $SOCl_2$/EtOH as a catalyst various substituted chalcones are synthesized by aldol condensation. The HCl is generate in situ by the reaction of $SOCl_2$ with absolute ethanol.

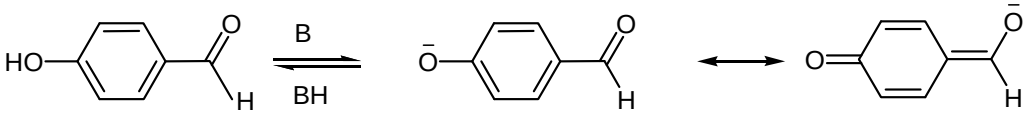
The aldol reaction is perform also under acidic medium, using HCl, BF_3, B_2O_3, p-toluene sulfonic acid, etc. The most common method applies ethanol saturated with HCl. The yields are low and vary between 10% - 40%. According to the literature data the presence of hydroxyl substituents in the aromatic aldehyde hinders the basic catalyze aldol reaction. The reason behind that is the fact that the basic catalysts decrease the activity of the aldehyde component because of delocalization of the anion, which is illustrated below,

It is necessary to use protective group for the preparation of the hydroxy chalcones under basic conditions. By using $SOCl_2$ as a convenient alternative to the gaseous HCl in the aldol condensation.

C. Methods for sy nthesis o f chalcones having hydroxy substituted aldehyde precursors[7]

The chalcone derivatives are prepare through base-catalyzed claisen-schimdt condensation of MOM-protected benzaldehydes with para- substituted acetophenones followed by acid catalyzed hydrolysis. In the reactions, the MOM- protected benzaldehydes are used instead of non-protected dihydroxylated ones, because the procedure with the free dihydroxylated benzaldehydes required long reaction time (more than one day) and relatively high temperature (above 60^{0}C) which resulted in poor yields with unknown degraded products.

The MOM group is proven to be the best choice. The MOM-protected benzaldehydes which are readily prepared by treating the corresponding benzaldehydes with MOMCl in basic condition (K_2CO_3/acetone), are successfully converted to the chalcone derivatives with diverse substitution patterns of two hydroxyl groups on benzaldehyde origin ring B. Now the hydroxyl protected chalcones are deprotect in situ by acid hydrolysis to provide the desired final chalcone derivatives in good yields (>70%) with some exception.



Anion delocalization of the aldehydic component

The relatively low yields for some products containing para- hydroxyl acetophenone are consider probably due to the phenoxide ion formation from the acetophenone in the presence of strong and excess amount of base. The double bond geometry of all chalcones is determine as E form the characteristic coupling constants between α and β protons.

I. Hydroxy benzaldehydes protected by MOM[7]

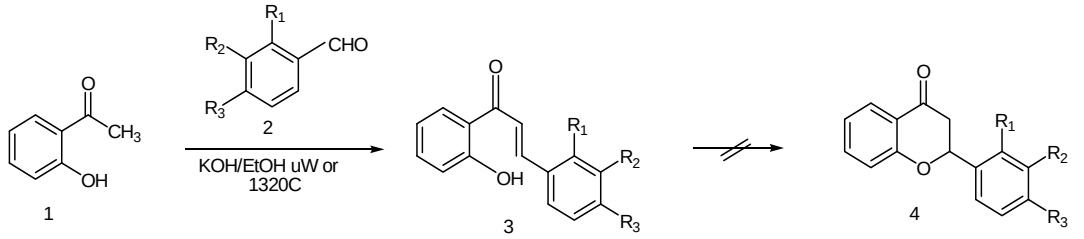
Cool the solution of hydroxy benzaldehyde (21.17 mmol) and K_2CO_3 (217.20 mmol) in acetone (100ml) to 0^0C under Argon atmosphere and add methoxymethylchloride (MOM-Cl, 93.65 mmol) dropwise. Stir the resulting mixture at room temperature for 6-10 hr. Dilute the reaction mixture with water (100ml) and extract with ethyl acetate (50ml x 3). Wash organic layer with water and brine, dry over anhydrous $MgSO_4$ and evaporate to dryness to yield crude MOM- protected benzaldehyde. Purify by silica gel column chromatography to give analytically pure compounds (90-99%).

II. General synthetic procedure for the preparation of dihydroxychalcones[7]

To a solution of MOM-protected benzaldehydes (0.9 mmol) and acetophenone (10mmol) in ethanol (10ml), add 5% aqueous NaOH (1.1mmol, 0.5ml). Stir the reaction mixture at room temperature for 1-2 hr. Moniter the reaction, add 10% HCl (1ml) and continue stirring for 30 min at 60^0C to deprotect the MOM groups. Dilute the mixture with water (20 ml) and adjust pH to 5 with 1N aqueous NaOH solution. Extract the aqueous solution with EtoAc (20 ml x 3). Wash the organic layer with water (20 ml x 2) and brine (20ml), dry over anhydrous $MgSO_4$ and evaporate to give a crude solid. Purify resulting product by column chromatography, elute with hexane-ethyl acetate co-solvent to afford a solid.

D. Microwave assisted synthesis[8]

The Claisen–Schmidt condensation stays the most common method in homogeneous phase or in interfacial solid-liquid conditions using barium hydroxide catalyst (C-200). Unfortunately 2'-hydroxychalcones always cyclized to flavanones. One synthetic pathway to avoid this undesirable reaction is using protective group or the Friedel–Crafts reaction of phenols with acyl halides. This method request long reaction time and anhydrous conditions which limits the scope of its application. Convenient reaction procedure for the synthesis of 2'-hydroxychalcones with very good yields without formation of by-products. By applying successful microwave irradiation for the preparation of target molecules . The reaction took place in well closed pressure tube for 2 min with high yields. It is noteworthy to mention that to carry out the reaction in an open vessel failed. A mixture of two products (3 and 4) and starting compounds was obtained in this case. Obviously, the well closed tube affords to reach temperatures much higher than boiling point of ethanol. The measured temperature in the reaction tube immediately after the irradiation was 132^0C.



2. Chemical modifications of chalcones:

I. Flavonoids[9]

Flavonoids or bioflavonoids are a ubiquitous group of polyphenolic substances which are present in most plants. Flavonoids have been shown to have antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic and vasodilatory activity. The potent antioxidant activity of flavonoids their ability to scavenge hydroxyl radicals, superoxide anions and lipid peroxy radicals may be the most important function of flavonoids.

The structural components common to these molecules include two benzene rings on either side of a 3-carbon ring. Multiple combinations of hydroxyl groups, sugars, oxygen, and methyl groups attached to these structures create the various classes of flavonoids; flavonols, flavanones, flavones, flavan-3-ols (catechins), anthocynins and isoflavones.

General procedure for the synthesis of flavanone[10]

Reflux a solution of the 2'-hydroxychalcone (1 equiv) in AcOH glacial (25.0 ml/mmol of 2'-hydroxychalcone) for 72 hr. Pour the mixture into water. Extract with EtOAC (3x25.0ml). Wash the organic layer with brine until neutrality and dry with $MgSO_4$ anhydrous. Evaporate the solvent in vaccuo.

Purify the residue by chromatographic column (SiO_2, petroleum ethermethylene dichloride (0-30%).

[II] Synthesis of 3, 5-diphenyl-4, 5-dihydro-1, 2-oxazole[11]

Dissolve anhydrous sodium acetate (0.02 mol) in hot acetic acid. Add hydroxylamine hydrochloride (0.01 mol) in absolute alcohol (10ml) to the solution of chalcone in ethanol. Transfer the solution of sodium acetate in acetic acid to this reaction mixture and reflux for 10 hr. Pour the reaction mixture into ice cold water, Filter the product and recrystallize with ethanol.

[III] Synthesis of 1, 3, 5 -triphenyl-4, 5- dihydro-1H-pyrazole[11]

To a mixture of chalcone and phenyl hydrazine (0.01 mol) in absolute alcohol, add catalytic amount of pyridine and reflux reaction mixture for 5-8 hr. Cool the reaction mixture, Pour slowly into crushed ice with stirring. Filter the solid product. Dry and recrystallize with ethanol.

3. Pharmacological profile:

I Antioxidants[9]

Free radicals, including the superoxide radical ($O_2^{\cdot-}$), hydroxyl radical ($^{\cdot}OH$), hydrogen peroxide (H_2O_2), and lipid peroxide radicals

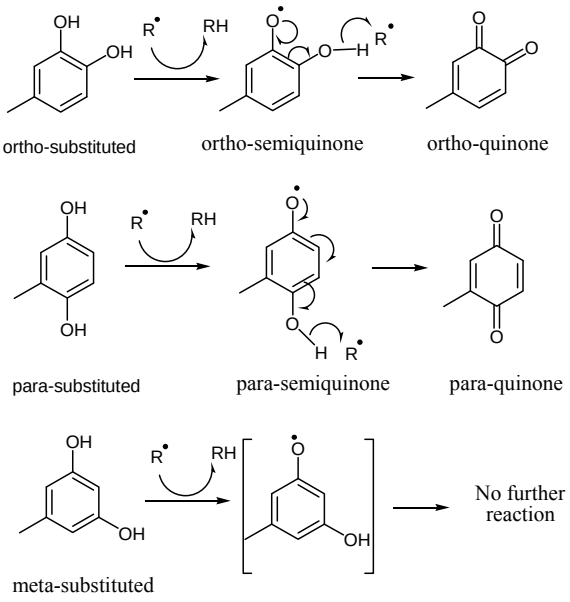
have been implicated in a number of disease processes, including asthma, cancer, cardiovascular disease, cataracts, diabetes, gastrointestinal inflammatory diseases, liver disease, macular degeneration, periodontal disease and other inflammatory processes. These radical oxygen species (ROS) are produced as a normal consequence of biochemical processes in the body and as a result of increased exposure to environmental and/or dietary xenobiotics.

Antioxidants are the agents, which can inhibit or delay the oxidation of an oxidisable substrate in a chain reaction.

Chalcones belongs to the largest class of plant secondary metabolites. Which, in many cases, serve in plant defense mechanisms to counteract reactive oxygen species (ROS) in order to survive and prevent molecular damage and damage by microorganisms, insects, and herbivores. They are known to possess antioxidant character at various extents. The antioxidant activity of natural compounds like chalconoids is related to a number of different mechanisms such as free radical scavenging, hydrogen donation singlet oxygen quenching, metal ion chelation and acting as a substrate for free radicals such as superoxide and hydroxide.

Mechanism of antioxidant activity of chalcones[7]

When the chalcone molecules react with the radicals, they are readily converted to the phenoxy radicals due to the high reactivity of hydroxyl groups of chalcones. The *ortho* (i.e. catechol structure) and para-dihydroxylated benzene ring system are generally known to delocalize electrons. As the phenoxy radicals occurring at the ortho- (i.e. catechol structure) or para-dihydroxylated benzene ring system are much more readily converted to a fairly stable semiquinone radicals while, meta dihydroxylated benzene ring system is comparatively less efficient to delocalize electrons as the phenoxy radicals occurring at the meta dihydroxylated ring system is converted to quinone structure which is not much stable.



Proposed rationale for strong activity of *ortho*- and *para* dihydroxylated chalcones *vs* *meta*-dihydroxylated ones.

Structure Activity Relationship[7]

It is proven as, the chalcone compounds with the *ortho*- (i.e. 2', 3'- and 3',4'-) and *para*- (i.e. .2,5'-)

substitution patterns show an excellent antioxidant activities (80-90% of control at the concentration of 50μM) which are comparable to those of ascorbic acid and α-tocopherol as positive reference materials.

On the contrary, the compounds with *meta*- (i.e. 2',4'-, 3',5'-) substitution pattern demonstrate very dramatic decrease in activities which are around 25% of the control even at the concentration of 200μM (IC50 > 200μM).

Thus, it indicate that the substitution patterns of two hydroxyl groups on ring B are very important structural factors for their radical scavenging activity enhancement.

The para substituted group exhibited better free radical scavenging activities than ortho substituted system.

The variation of the substituents at para position of ring A makes no distinctive differences in activities. This observation indicates that the electronic effects of para- subsistent of the phenyl ring-A does not affect the radical scavenging activity and therefore are unlikely to contribute to variation of antioxidant activities.

II Antiinflammatory[12]

Activated macrophages play a key role in inflammatory responses and release a variety of mediators, including nitric oxide (NO). NO is a potent vasodilator that facilitates leukocyte migration and formation of edema, as well as leukocyte activity and cytokine production.

NO can also react with superoxide anion to form peroxynitrite, a potent oxidizing molecule that contributes to tissue injury during inflammatory responses. Nitric oxide is generated from L-arginine by nitric oxide synthase (NOS).

Compounds that inhibit excess production of NO by macrophages might be of benefit for the prevention and treatment of autoimmune diseases, septic shock and different inflammatory pathologies.

Chalcones with substituents that increase the electronic density of the B-ring, such as methoxy, butoxy or dimethylamine groups, did not show significant activity in the inhibition of the nitrite production.

Trimethoxy chalcone derivatives with fluoro substitution at C_4' are better inhibitors of nitrite production. Trifluoromethyl group at C_2' in dimethoxy chalcones as well as trimethoxy chalcones possess very potent inhibition of nitrite accumulation.

Trifluoromethyl group at C_3' or C_4' in dimethoxy chalcone as well as trimethoxy chalcone possess less activity than when it is at C_2'.

III Cytotoxic activity[13]

Mannich bases of phenolic azobenzenes demonstrated cytotoxic activity, and various mannich bases analogs of chalcones exhibited potent cytotoxicity against murine P338 and L1210 leukemia cells as well as several human tumor cell lines. Mannich bases of heterocyclic chalcones are evaluated for cytotoxic activity against four human cancer

cell lines (PC-3, MCF-7, KB and KB-VIN). Mannich base of chalcone with morpholine substitution at C_3 or C_5 and pyridyl or phenyl at C_2 substitution are found to possess good cytotoxic activity.

IV Hypoglycemic activity[14]

Non-insulin dependent diabetes mellitus (NIDDM, type-II diabetes) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulinaemia. The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risks.

β_3-adrenergic receptors (β_3-AR) are found on the cell surface of both white adipose (WAT) and brown adipose tissue (BAT) where their stimulation promotes lipolysis and thermogenesis respectively. BAT also plays an important role in the maintenance of glucose homeostasis; hence β_3-AR agonists are useful for treating diabetes as well as obesity. The aryloxypropanolamines were first described as β_3-AR agonists.

Chalcones with proper substitution have recently been isolated from *Broussonetia papyrifera* known to selectively inhibit enzymes like protein tyrosine phosphatase 1B (PTP1B) and aldose reductase. Their antioxidant property attracted to explore hybrid structures as antihyperglycemic agents, because oxidative stress also plays an important role in diabetic patients leading to vascular complications.

3, 4-Dimethoxy compound displayed significant antihyperglycemic effect. Mono methoxy series showed blood glucose lowering activity. Compounds vicinally deoxygenated as dimethoxy and methylenedioxy substitution showed the best antihyperglycemic activity when compared to the corresponding monomethoxy compounds. Compounds containing propanolamine chain at *para* position showed significant activity as compared to *meta* and *ortho* substituted compounds.

V Antihepatotoxic activity[15]

Silymarin isolated from seeds of *silybum marianum* commonly known as *Milk Thistle* has been used as a potent Antihepatotoxic agent against a variety of toxicants. It is a mixture of three isomers namely, silybin (1), silydianin (2) and silychristin (3). Silybin is the most active component containing 1,4-dioxane ring system, whereas other isomers do not possess 1,4-dioxane ring, and thus do not display significant activity.

Chalcone derivatives possessing 1,4-dioxane ring system exhibiting antihepatotoxic activity. The potent compounds possess 2-hydroxy methyl group at position 2 of the dioxane ring of chalcone derivatives, which has also indicated that the presence of hydroxy methyl group at position 2 in dioxane ring possesses a significant role in exhibiting the antihepatotoxic activity. This is in accordance with the view that silybin too possess the same group at the same position.

The substitution in the aromatic ring of chalcones have no significant role in exhibiting antihepatotoxic activity.

VI Antimicrobial activity[16]

Compounds with electron releasing groups such as methoxy and hydroxyl showed better antibacterial activity than the others not having such groups. Compounds having pharmacophores such as chloro, dichloro and fluoro groups have exhibited more antifungal activity on all the three fungi than the others. Chalcone derivatives with these substituents showing greater antimicrobial activity.

VII Antimalerial activity[17][18][19]

Antimalarial property of some chalcone derivatives is derived from their ability to inhibit the parasitic enzyme, cysteine protease. The enzyme catabolizes globin into small peptides within the acidic food vacuole of the intra-erythrocytic malaria parasite. Without cysteine protease action osmotic swelling occurs, food vacuolar functions are impaired, and parasite death ensues. Malaria blood stage cysteine protease as the most likely target enzyme of chalcones. The chalcones are conjugates of α, ß-unsaturated ketones that assume linear or near planar structure. This structure is stable in acidic food vacuolar environment where malarial cysteine protease acts, and structural conformation may fit well into the long cleft of the active site of the enzyme.

The chloro-series compounds showed marked antiplasmodial activity. Compound , a triazole substituted chalcone was found to be the most effective against the parasites, and pyrrole and benzotriazole showed comparable activities. The morpholine substituents in chloroseries was found to be the least active. Compound , containing triazole and chloro substituents, was found to be the most potent antiplasmodial derivative evaluated, suggesting that small lipophilic groups containing single or multiple nitrogen can enhance antimalarial activity in vitro.

In vitro antiplasmodial results of 4-chloro, 4-methoxy and 3,4,5-trimethoxy series suggested that small or medium sized but highly lipophilic groups containing multiple nitrogen or amine in acetophenone moiety impart antiplasmodial potential. Such compounds may provide additional hydrogen bonding with histidine residue present at the active site of the enzyme, cysteine protease. This is the first report in which chalcones containing small highly polar, lipophilic cyclic amines are showing antimalarial potential.

VIII Antileishmanial activity[20]

Conventional structure activity relationships show that antileishmanial activity is favoured by chalcones with more hydrophilic character, with the most active members found among 40-hydroxychalcones. The good antileishmanial activities of the naphthalenyl and pyridinyl derivatives suggest that considerable tolerance for the size of ring A exists.

IX Tyrosinase inhibitors[21] [22]

Tyrosinase (monophenol monooxygenase, E: C: 1.14. 18.1), also known as polyphenol oxidase), is a copper-containing enzyme widely distributed in nature. It catalyzes two reactions involving molecular oxygen in the melanin biosynthesis pathway: the hydroxylation of monophenols to

o-phenols (monophenolase activity), and the oxidation of the o-phenols to o-quinones (diphenolase activity). These quinones are highly reactive and tend to polymerize spontaneously to form brown pigments of high molecular weight (melanins), which determine the color of mammalian skin and hair. Quinones can also react with amino acids and proteins and thus enhance the development of brown color. The inhibitory activity of a series of chalcones was set against their structure and their antioxidant potency (which can contribute to prevent pigmentation resulting from nonenzymatic oxidation). The position of the hydroxyl groups attached to the A and B aromatic rings is of major importance, while hydroxylation on ring B contributes markedly more to inhibition than when it is on ring A. Butein, an effective tyrosinase inhibitor, was also able to delay linoleic acid auto-oxidation, as shown by conjugated diene (CD) formation. The OH in position 4 (ring B) was the major factor affecting potency.

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