International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 5 Sep-Oct 2021, pp: 500-506 www.ijprajournal.com ISSN: 2249-7781

Chalcones: A review on synthesis and pharmacological activities

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Date of Submission: 15-09-2021 Date of Acceptance: 28-09-2021

ABSTRACT:

[Chalcones, pre-chain chain flavonoids and isoflavonoids are present in edible plants, and their release has attracted increasing attention due to the many existing applications of the drug. They have shown a lot of pharmaceutical activities. Changes in their design have yielded high diversity that has proven to be useful in the development of new therapeutic agents with improved strength and low toxicity. The current revision highlights the newly developed chalcones and their derivatives that have important medicinal functions.]

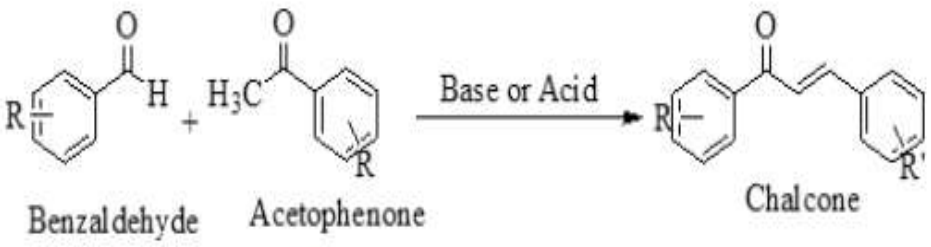
I. INTRODUCTION

Chalcones (trans-1,3-diaryl-2-propen-1-ones) belonging to the flavanoid family before the opening of the chains of flavonoids and isoflavonoids, are packed with edible plants. Chalcones are also important precursors in the synthesis of many highly important heterocycles such as benzothiazepine, pyrazolines, 1, 4-diketones, and flavones. Chalcone is an aromatic ketone with two phenyl rings, it's central core serves as a precursor for many biologically active therapeutic compounds. Chalcone possess variety of pharmacological activities such as antibacterial, antifungal, antimicrobial, antidiabetic and anticancer. Chalones are precursor for synthesis of flavonoids, changes in their structures offers variety of Pharmacologically.

II. METHODS OF SYNTHESIS OF CHALCONES

1.) Claisen–Schmidt's condensation

This method for the preparation of chalcones is the condensation [31-38] of ketone with aldehyde in the presence of aqueous alkaline bases or in the presence of alcoholic alkali. In the method, chalcones are synthesize by condensing substituted or unsubstituted benzaldehyde with substituted or unsubstituted acetophenone with the use of bases or acids as catalysts in an appropriate solvent at about 50°C–100°C for few hours . It is normally carried out in the liquid phase, but some syntheses occur in the solid phase, like resin was bound with acetophenone compounds and then reacted with benzaldehyde compounds or under solvent-free conditions such as catalytic condensation in the presence of triazabicyclodecene .



Scheme 1. The Claisen–Schmidt condensation.

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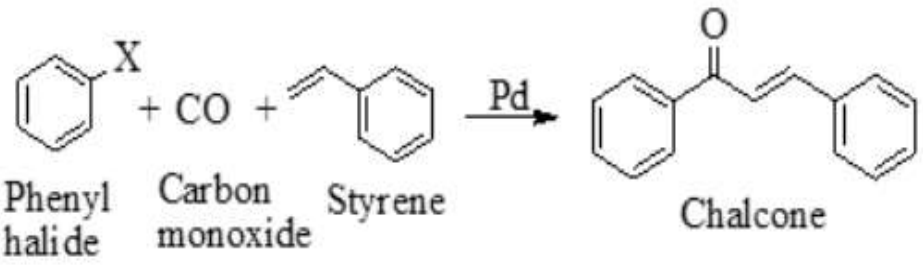
2.) Carbonylative Heck's coupling reaction

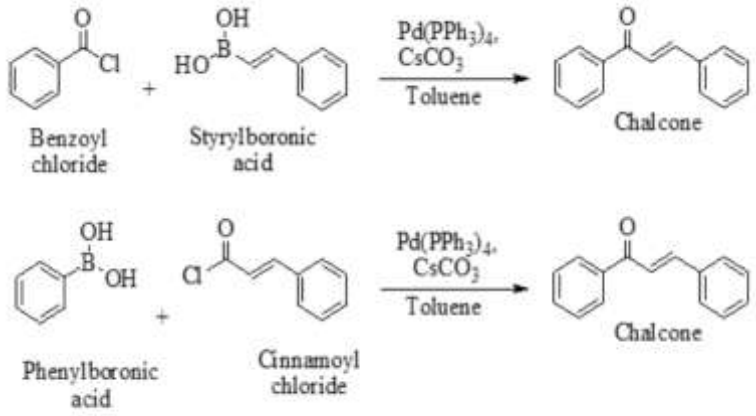
Chalcones have been synthesized by vinylation of aryl halide (such as phenyl halide) with styrene under carbon monoxide and the catalyst palladium can undergo carbonylative coupling.



Scheme 2. Carbonylative Heck coupling reaction.

3.) Suzuki–Miyaura's coupling reaction

Chalcones can be prepared by Suzuki through a reaction [39-45] between phenyl boronic acid and cinnamyl chloride or benzoyl chloride and phenyl vinyl boronic acid. This coupling reaction takes place by combining benzoyl chloride and styryl boronic acid using Pd(PPh3) 4 , CsCO3 , and anhydrous toluene or by combining phenyl boronic acid and cinnamoyl chloride using Pd(PPh3)4 , CsCO3 , and anhydrous toluene.



Scheme 3. Suzuki–Miyaura coupling reaction

4.) Sonogashira's isomerization coupling

This reaction involves the synthesis of chalcones by the microwave coupling of the electron-insufficient group, like phenyl halide, and prop-2-yn-1-ol and catalyst PdCl2 (PPh3)2 and solvent like tetrahydrofuran (THF).

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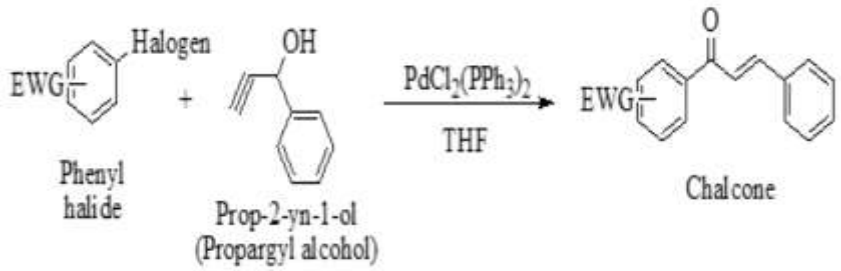
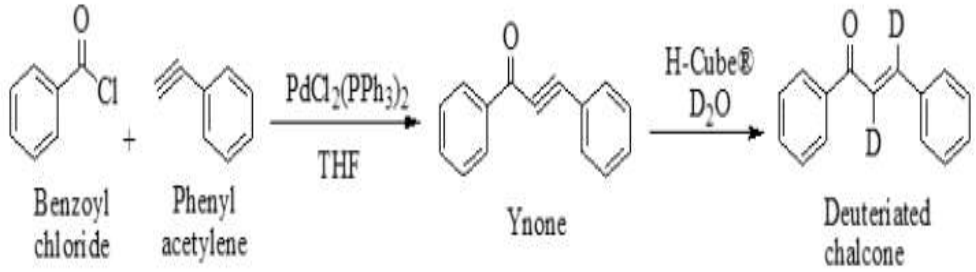


Scheme 4. Sonogashira isomerization coupling.

5.) Continuous-flow deuteration reaction

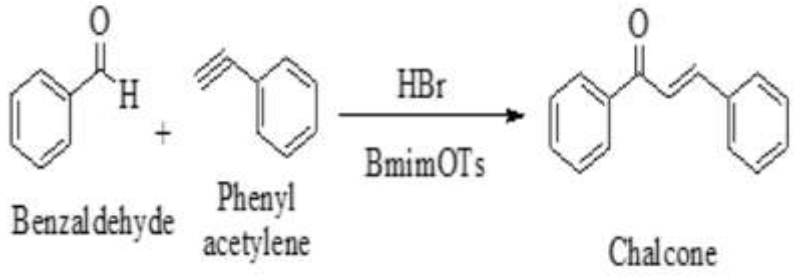
Ynones basically were synthesized by the process available in the literature by the reaction of benzoyl chloride and phenylacetylene under Sonogashira's conditions and then for deuteration, which was carried out in an H-Cube system caused by replacing H2 O with D2 O as the deuterated source.



Scheme 5. Continuous-flow deuteration reaction.

6.) Coupling reaction

Chalcones are prepared by coupling benzaldehyde with phenylacetylene in hydrogen bromide and ionic liquids like BmimOTs (1-butyl-3-methyl-1H-imidazolium 4-methylbenzenesulfonate) for about 12 hours at 100°C.



Scheme 7. Coupling reaction.

7.) Reaction of ketones and aromatic aldehyde (Aldole Reaction)

The prepared chalcones in basic medium by reaction of ketones with aromatic aldehyde in ethanol.

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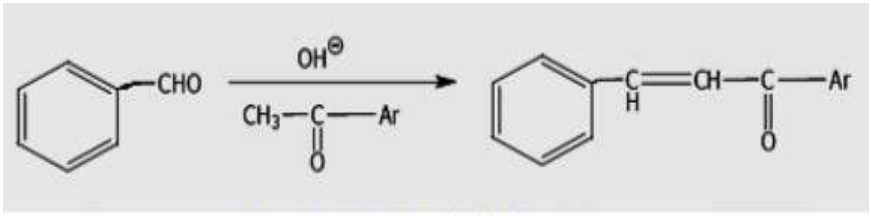

Fig. 4. Preparation of Aldole –Chalcone.

8.) By Fridel –Graft Reaction

By reaction with aluminium chloride AlCl3.

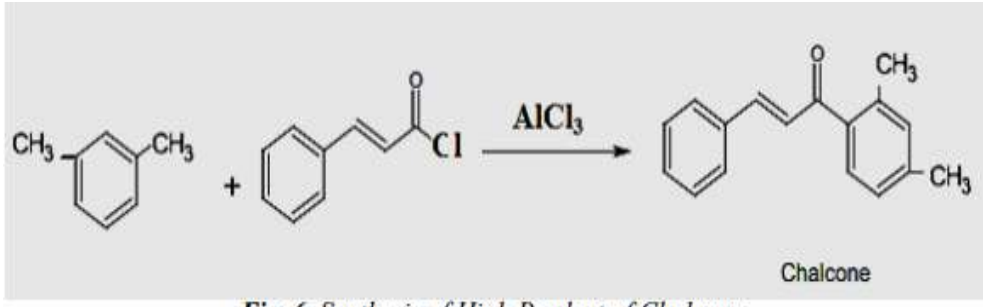

Fig. 6. Synthesis of High Product of Chalcone.

9.) Synthesis of chalcones using Schiff bases

Schiff bases result in aryl amino ketones, which in the presence of an acid lead to hydramine breakdown and produce products such as primary aromatic amine and chalcones .

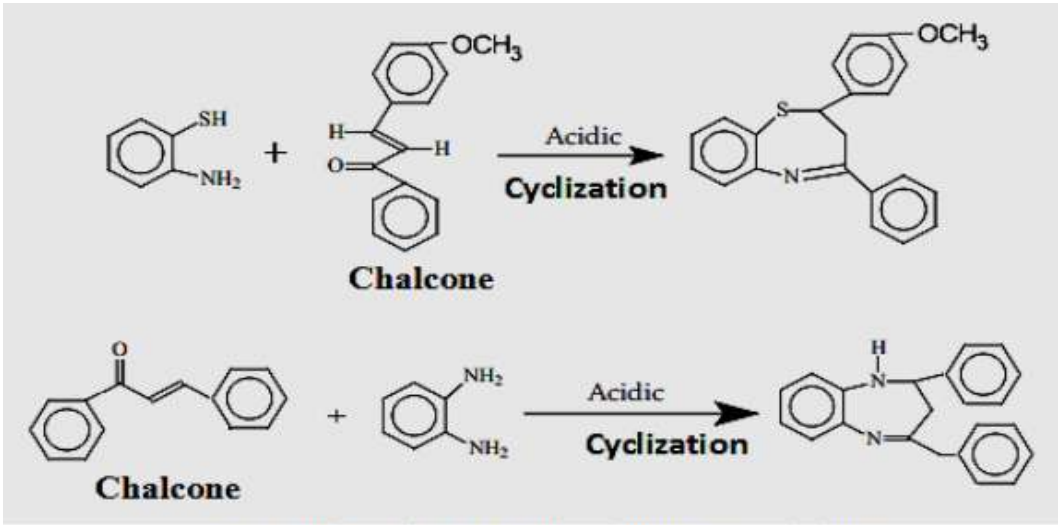

Fig. 7. Synthesis of Seven Membered Ring From Chalcone.

Pharmacological activity of Chalcones

1.) Antimalarial activity

Motta et al studied the composition of chalcone. He has developed many structural relationships for a series of substances derived from chalcone (1, 3-Diphenyl-2-propen-1-one).The study investigated the key factors in the preventive work of Pavan Kumar G. et al J. Chem. Drug. Res., 2016, 8 (1): 458-477 from chalcone to P. falciparum cysteine protease.The results showed that the performance on the W2 and D6 models was preferred if the A ring had a wide range of chemical properties. The main conclusions of the project were:

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(i) The double binding of C2-C3 is essential for performing a large preventive function. Not only is it a harmonious link between A and B fragrances, but it also increases cellular fusion.
(ii) The replacement of the chalcone series bridge bridge has resulted in a significant decrease in the blocking activity, possibly due to strong interactions;
(iii) Substituting chloro or fluoro in ring B and electron substitutes in ring A has increased anti-malarial activity;
(iv) The Quinolinyl group in ring B led to an increase in activity.

2.) Antifungal activity

Bag et al incorporated a series of chalcone-containing sulfur as part of a hetero-aromatic ring (thiophene) or as a side chain (thiomethyl group) and tested for its in vitro activity. Compounds have shown excellent anti-fluconazolesensitive and fluconazoleresistant and chalcone'3- (4- (methylthio) phenyl) -1- (thiophen-2-yl) prop-2-en-1-one showing the highest activity. Lahtchev et al reported compounding, antifungal testing and research on the adverse effects of several chalcones.. The antifungal effects of replacement chalcones were compared with those of parental chalcone. The following combinations have been detected:

(i) The introduction of EW substituents (Cl, CN and NO2 groups) in the p-position in ring A revealed chalcones less effective than parental chalcone.
(ii) Introduction of ED substitutes (OH, CH3 and OCH3 groups) in the p ring area Produced inactive chalcones.
(iii) The presence of a single hydroxyl group was effective in the m-ring area in ring A. The introduction of a single group of methoxy m-position in ring A led to a non-activation.
(iv) The introduction of the p-chloro atom in ring B assisted only chalcones with a single hydroxyl group in the m- and p-areas. The m-position was more attractive than the p-position. The presence of m- and p-hydroxyl groups together led to an inactive chalcone.
(v) The expansion of the integrated system with the introduction of one additional double bond between the ketovinyl organization and ring A did not produce a functional effect. Based on these observations, it was concluded that the chalcones were not significant in demonstrating antifungal activity.

3.) Cyclooxygenase (COX) Preventive Action

Zarghi et alsynthesized chalones containing methanesulfonamido (MeSO2NH) or azido (N3) pharmacophore instead of the para-ring C-1 phenyl also tested its activity of cyclooxygenase-1 / -2 inhibitors. The in vitro activity relationship of COX-1 / COX-2 was determined by replacing the C-3 phenyl ring substitutes (4-H, 4-Me, 4-F, and 4-OMe). Among chalones with C-1paraMeSO2NH COX-2 pharmacophore'1- (4- methanesulfonamidophenyl) -3- (4-methylphenyl) prop-2-en1-one identified as COX - selected 2 inhibitor (COX-2 IC50 = 1.0 µM; selection indicator> 100) with less potency than reference drug rofecoxib (COX-2 IC50 = 0.50 µM; SI> 200.

4.) Anti-inflammatory activity

Anti-inflammatory drugs are used to reduce pain and inflammation. In other words, these are painkillers. These drugs are particularly effective in blocking the enzymes cyclooxygenase, COX-1 and COX-2, which produce prostaglandins. Chalcone elements contain the α, β-unsaturated carbonyl moiety which is responsible for the antiinflammatory activity.Yadav et al compiled a series of five chalcone substances and performed anti-inflammatory tests using the carrageenaninded rat hind paw edema model. Chalcone findings at a dose of 25 mg / kg by oral route significantly inhibited the formation of edema compound 4-flouro / chloro chalcone showed high activity comparable to the common indomethacin drug due to the F / -Cl groups present in the compound. Therefore, the antiinflammatory activity of chalcone was increased when the electron emission group (EWG) was present in the chalcone group. compound '3- (4- chlorophenyl) - 1- (2,4 di hydroxy phenyl) prop-2-en-1-one exhibits inflammatory activity (68% inhibition) compared to or more potent than drug used ibuprofen (53%) .

5.) Antitubercular activity

Tuberculosis (TB), caused by the acid-fast gram-positive bacillus, Mycobacterium tuberculosis. M. tuberculosis develops infection through attacks of alveolar macrophages. Currently, TB treatment uses four first-line drugs, isoniazid, rifampin, pyrazinamide, and ethambutol, which should be given to the body daily for a period of two months. The emergence of multidrug-resistant (MDR) antibodies, described as

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resistant to isoniazid and rifampin, requires the use of ineffective and toxic TB drugs. Here we discuss some recent updates on the use of anti-tuberculosis chalcones: Sulfonamidecarrying chalcones are composed of Claisen-Schmidt condensation and are reported as excellent antituberculosis indicators of limited selectivity, equally preventing TB. Gomes et al. studied the antitubercular functions of chalcones .Babu et al. studied chalcones containing nitrophenyl moitions for antitubercular activity using MABA assay and antibacterial and antifungal activities in the form of a cup plate.

6.) Anticancer Activity

Anticancer or antineoplastic drugs are those drugs which are adequate in the treatment of malignant or cancerous diseases. Methoxylated and hydroxylated derivatives are synthesised by AhceneBoumendjel et al. (16) by using condensation of substituted aldehydes required acetophenone called Claisen Schmidt condensation. They prepared chalconein vitro antimiotic activities against K562 leukemia cell stained with propidium iodide at a concenteration of 10µM for 24 hrs. Chalcones were synthesized and graded for anticancer activities for human colorectal carcinoma cell line HCT116 by Dias et al. (26). Halogens at third position of the chalcones were found to increases the anticancer activity of the compound.

Chalcones in Clinical Trials

Current clinical trials have shown the main tittle role of two chalcones hesperidin methylchalcone and hesperidin trimethylchalcone in treating the chronic venous disorders (Boyle et al., 2003) . In a riffled open-label study, the therapeutic property of a mixture of hesperidin methyl chalcone, Ruscusaculeatus with vitamin C in contrast to rutozide in patients suffering from chronic venous insufficiency was explored (Beltramino et al., 2000). This clinical trial was happened for three months and contained eighty patients divided into two groups: the first group received the mixture with hesperidin methyl chalcone, and the second experienced only rutoside. The signs and symptoms of chronic venous insufficiency were calculated initially and then monthly. A significant and lasting reduction of the symptoms were seen in the patients from the first group treated with the mixture of chalcone and vitamin C compared to the othergroup,that was treated only with rutozide (Beltramino et al., 1999).

BIOAVAILABILITY OF CHALCONES

Studies shows that bio-accessibility of chalcones from sources of food are bordered, but experimentally manufactured chalcones have assumed to contain immense ranges of biological activities (Won et al., 2005). Chalcones have a crucial position in the bio-production of flavonoids (Shirley, 1996) and are recognizable in a number of foods and drinks, like rooibos tea or apples, but there is unavailability of data on their bio-accessibility in human beings.

The prenylatedchalconexanthohumol is the consequential chalcone produced in hop cones. Throughout beer preparation, a magnificent fraction of xanthohumol is changed to the related isomeric prenylflavanoneisoxanthohumol. Following administration of xanthohumol to rodents by force feeding at intensely elevated dosage (1 g/kg of body weight), linked metabolites were identified in plasma. The most crucial metabolite that is xanthohumol- 49-O- glucuronide, acquired its topmost concentration of 3.1 M/L after 4hrs of administration. The maximum concentration of xanthohumol which wasn't metabolized is 10 times lower with the similar Tmax of 4 h (Gerhäuser, 2005).

III. CONCLUSION

Chalcone derivatives have a great Pharmacological usage as anticancer agents, Antitubercular agents, Antimicrobial Agents, Anti inflammatory agents, Anticancer agents, Antioxidant activity and various other miscellaneous activities.

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