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A Review on the Synthesis and Pharmocological Activities of Novel Chalcones Derivatives

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ABSTRACT

Chalcones are organic chemical compounds with a simple chemical structure known as 1,3-diphenyl-2-one. The word "chalcone" is derived from the Greek "chalcos," meaning bronze, which results from the colors of the most natural plants. Chalcones are mostly found in flavonoids in their two isomers, trans and cis, and their structure is similar to that of open chain flavonoids. Chalcones, also known as 1,3-diphenyl-2-prope-1-one, are chemically 1,3-diphenyl-2-prope-1-one and are 3-carbon,ß unsaturated carbonyl compounds that act as precursors for many chemical compounds and flavonoids. Many researchers were impressed by the anti-tubercular, anti-bacterial, anti-fungal, anti-viral, antioxidant, anti-ulcer, anti-inflammatory, anti-ulcer, anti-cancer, and anti-diabetic activities of Chalcones, which were synthesized and determined with prediction of the structural activity relationship of Chalcones. This review article gives the maximum amount of information about different modes of synthesis and the various pharmaceutical activities of chalcone derivatives.

INTRODUCTION

Many organic and heterocyclic nuclei are available in the world of medicinal chemistry. Even though chalcones are very potent chemical compounds with a simple molecular framework, The first of all chlacones is primarily found in many natural plants of the angiosperm family, and they are known as chalconoids. Chalcones are 3-carbon chains that contain aromatic ß unsaturated carbonyl compounds (ketones). Chalcones undergo many chemical reactions, and they can be synthesized easily with a simple reaction procedure. Chalcone research is fueled by the most potent pharmacological activity with this simple nucleus. The investigation of chalcone derivative synthesis and pharmacological activity leads to the study of the structural activity and relationship of the chalcone nucleus. This Structural activity relationship study (SAR) will lead to the discovery of the most potent Chalcone's derivatives with the least toxicity.

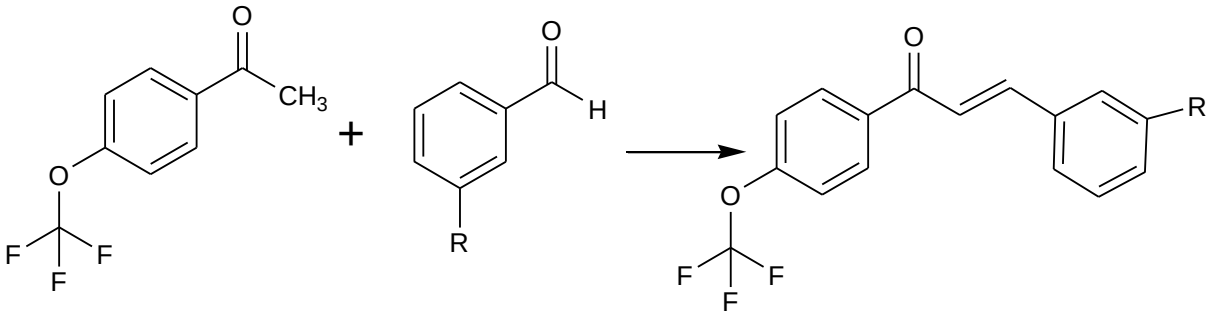
SYNTHESIS OF CHALCONES

Synthesis of trifluorochalcones

Surendra Babu Lagu *et al* were studied the synthesis of fluorinated chalcones [1].

Procedure:

4'-trifluoromethyl (-CF3) or 4'-trifluoromethoxybenzophenone is substituted for benzaldehyde in 40% aqueous NaOH by stirring continuously for 6-15 hours. After the reaction completed, the mixture was neutralized with HCl, and then the precipitated solids were filtered and recrystallized with ethanol.

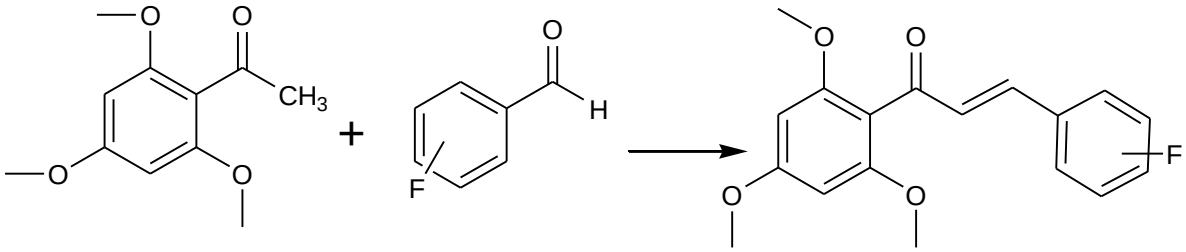


Synthesis of mono Fluorinated Chalcones

Serdar Burmaoglu *et al* were investigated synthesis of potent mono fluoro substituted chalcones [2].

Procedure:

Take an appropriate amount (4.75 mmol of 2, 4, 6 trimethoxyacetophenone in 20 ml of methanol) and add 4-fluorobenzaldehyde (7.6 mmol) to 50% potassium hydroxide. This mixture is allowed to stir for 15 hours at room temperature. Following the completion of the stirring, the mixture was neutralized with 2 M HCl and then poured into crushed ice cubes, with the resulting solid mass being filtered and washed with water. It was also recrystallized with methanol.

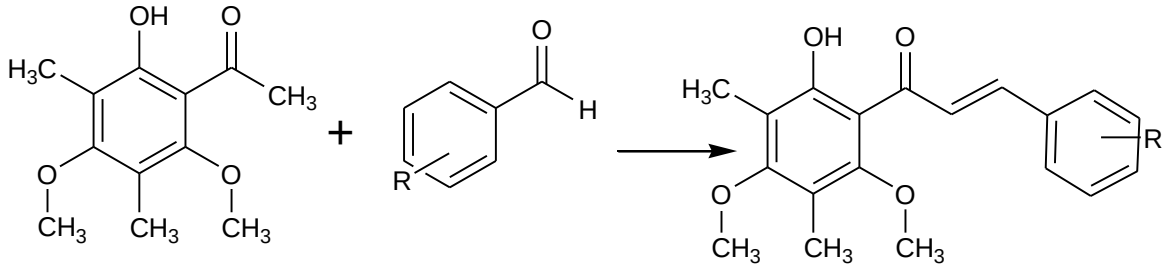


Synthesis of C-dimethylated Chalcones

Rambabu Anandam *et al* were studied the synthesis of novel C-dimethylated chalcones [3].

Procedure:

Prepare a solution by dissolving 0.002 mm of acotophenone and 0.0059 mol of substituted benzaldehyde in 100 ml of ethanol. To this solution, aq. KOH was added. The mixture is then stirred at room temperature for 24 hours. After completion of the reaction, the mixture was added to ice-cold water and acidified with dilute HCl. The obtained solid precipitate was filtered, washed with water, and recrystallized with MeOH.



Synthesis of triazine based chalcones

Pankit R. Shah (Gala) *et al* were synthesized the new triazine based Chalcone derivatives [4].

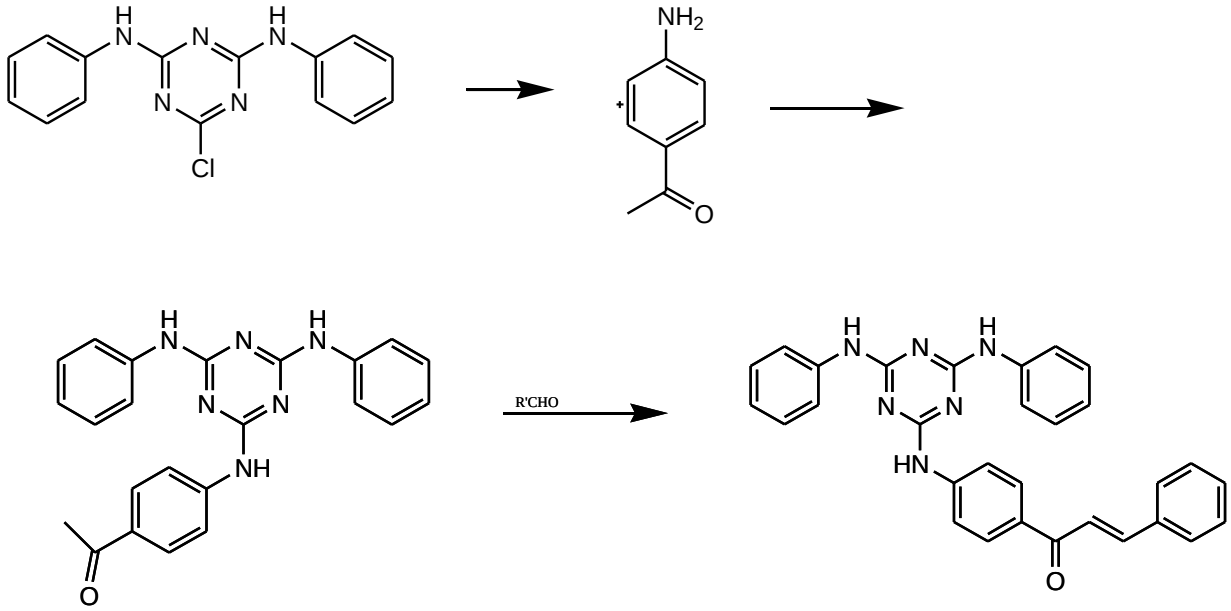
Procedure:

Stir for 3 hours an equal molecular mixture of cyanuric chloride (0.01 mmol) and aniline (0.01 mmol) in acetone (25 ml). 10% sodium carbonate was added to neutralize the HCl. Then it is poured into a crushed ice bath. The solid precipitate that was obtained was filtered, washed with water, and recrystallized from ethanol.

Then, an equal molecular mixture of compound I (from the first step) and 4-acetaminophene was added to acetone (40 ml), and it was refluxed for 6 hrs. After 6 hours, sodium carbonate (10%) was added to neutralize the HCl that evolved during the reaction. Finally, the mixture was poured onto crushed ice. To obtain compound II, the obtained solid was filtered, washed with water, dried, and recrystallized from ethanol.

A mixture of 4-aminoacetephenone (0.025 mmol) and active anhydride (4 ml) was taken. Then the mixture was refluxed for 45 minutes. The solution was poured into an ice bath, and the resulting solid was filtered, washed with water, and then recrystallized from ethanol to yield compound III.

The 10 ml of compound III and 5-methyl furfuraldehyde were dissolved in 4 mL of ethanol and 2 mmol of potassium hydroxide and sonicated for 15 to 30 minutes in an ultrasonic cleaning bath's water bath. Then the reaction mixture was poured into a crushed ice bath. The separated solid was filtered, dried, and recrystallized from ethanol to yield triazine-based chalcone derivatives.



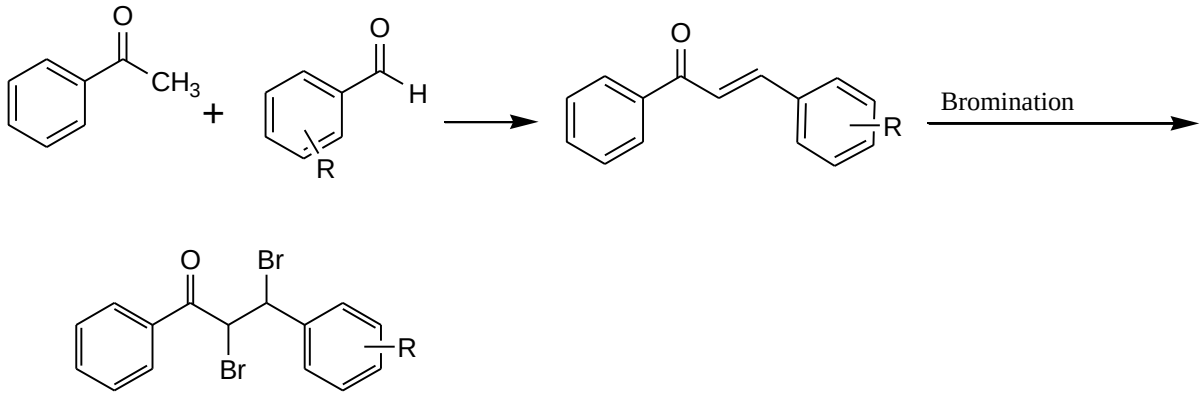
Synthesis of Dibromo Chalcones

Mohammed Sayed Alam *et al* were studied the synthesis of novel dibromochalcone derivatives [5].

Procedure:

Take 2 mmol of acetophenone and 2 mmol of benzaldehyde in potassium hydroxide (4 ml) and ethanol (20 ml), and then keep the mixture at ambient temperature for 72–96 hours. After stirring, the mixture was diluted with ice-cold water, acidified with HCl, and extracted with ether. Then the solvent was evaporated and subjected to column chromatography for purification.

Prepare a mixture of 2 mmol of bromine in chloroform (10 ml), and it is added to a solution of chalcones (1 mmol) in chloroform (20 ml). Then the mixture was subjected to stirring for 3–4 hours. After completion of the reaction, water was added, and the precipitate was collected by filtration. Then the product was extracted with ether. Then it is dried with sodium sulfate, and the solvent evaporates to afford the corresponding brominated chalcones.

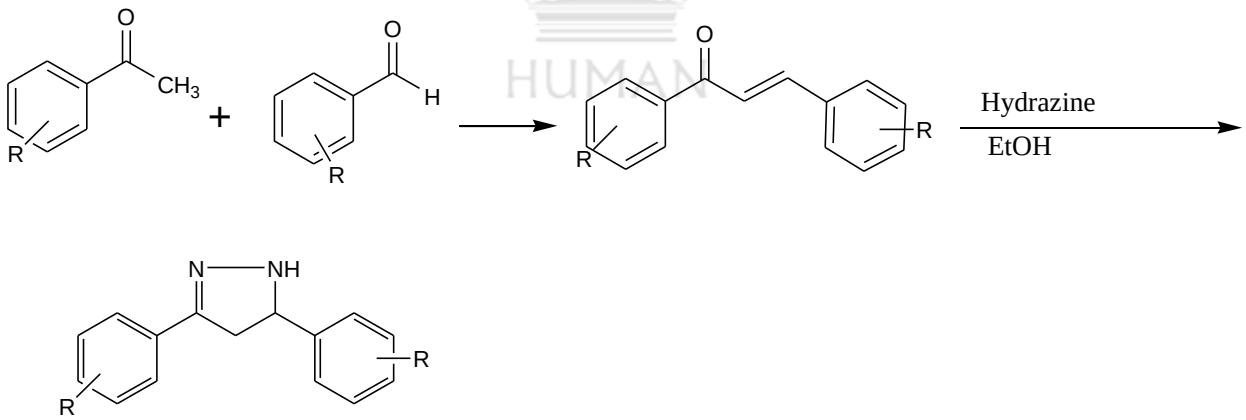


Synthesis of functionally substituted Chalcones

O. A. Nurkenov *et al* were investigated the synthesis of functionally substituted chalcones [6].

Procedure:

First of all, they synthesized the novel chalcones by the conventional method by keeping aromatic aldehydes and acetophenone at constant stirring in a basic condition for 6 hours. After synthesizing Chalcones, it was treated with hydrazine hydrate in ethanol by reflecting the mixture for 4-6 hours. This intermolecular cyclocondensation of chalcone and hydrazine yields pyrazole derivatives of chalcone.



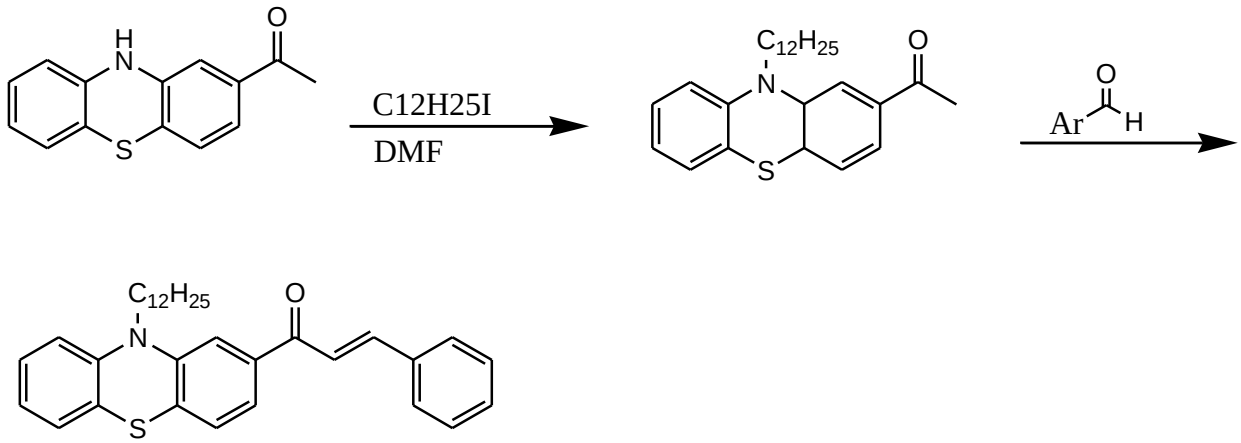
Synthesis of Phenothiazine based Chalcones

Nourah A. AlZahrani *et al* were developed the new Chalcone derivatives [9].

Procedure:

A mixture of 2-acetylphenothiazine (6 mmol), dodecyl iodide (1.8 mmol), KOH (20 ml), and tertiary butyl ammonium iodide (1.8 mmol) in 20 ml toluene was heated at 80˚C with continuous stirring for 1 hr. After stirring, cool the mixture and add 100 mL of water, followed by ethyl acetate extraction. Then brown oil for the product was obtained. At room

temperature, 1 mmol of compound I and 2 mmol of aldehyde were stirred overnight in 15 ml of 5% alcoholic NaOH. After completion of the reaction, water was added, and the precipitate was filtered often, washed with water, and purified by column chromatography.

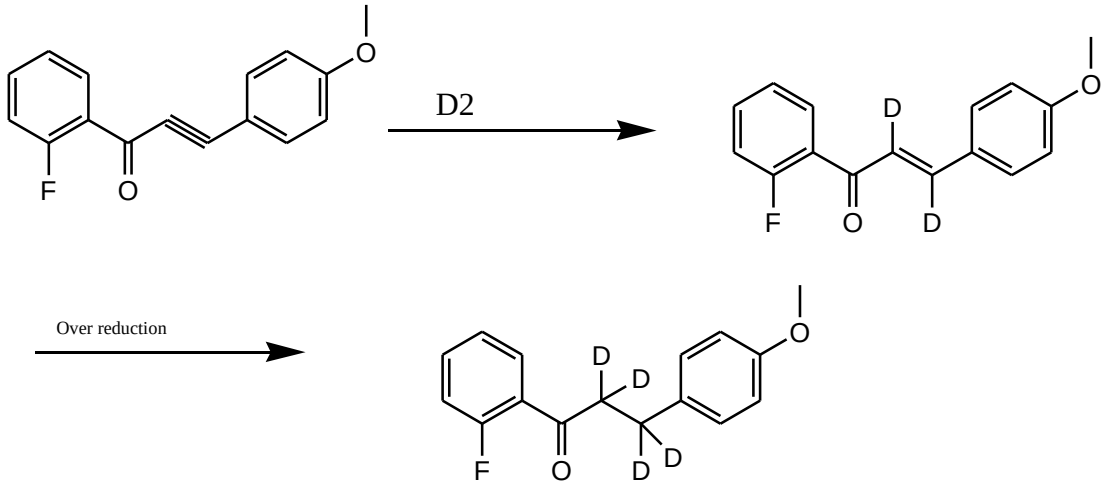


Synthesis of Deuterated Chalcones

Ötvös S *et al* were investigated the synthesized the Deuterated Chalcones [15].

Procedure:

Deuteration was carried out in an H-cube system with the replacement of water and hydrogen sources. The continuous stream of the reaction solution was provided by an HPLC pump [15].

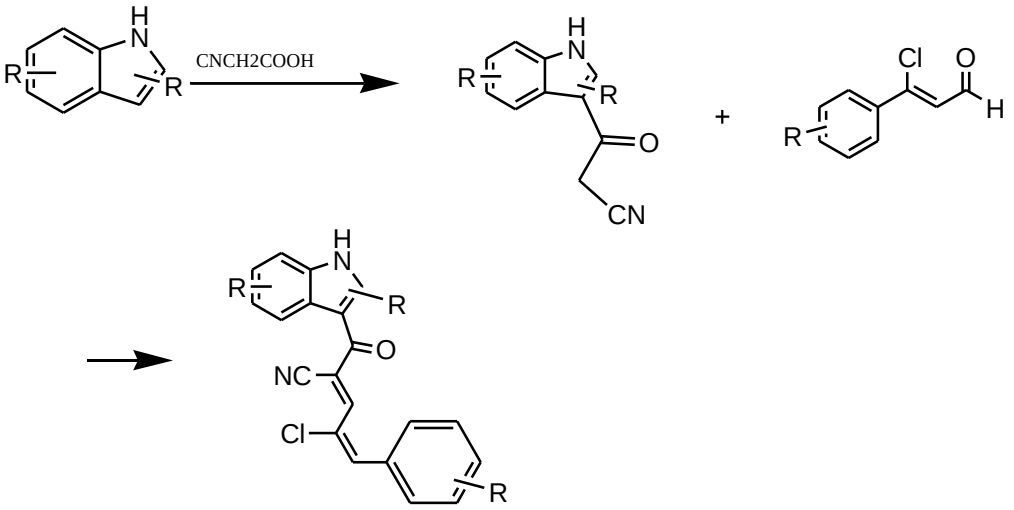


Synthesis of indole based Chalcone

Pravin S. Bhale *et al* were investigated the synthesis of conjugated indolyl chalcones by Knoevenagel condensation reaction [16].

Procedure:

For 8 hours, an equal molecular mixture of 3-Cyanoacetyl indoles and substituted 3-Chloco-3-phenyl propenals was kept at constant stirring in 20 ml of piperidine and ethanol.



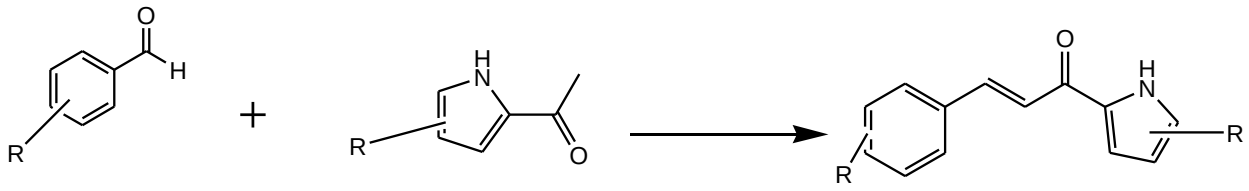
Synthesis of Pyrole based Chalcones

Ibidapo S. Williams *et al* were investigated the synthesis of some novel pyrrole based Chalcone derivatives [18].

Procedure:

An equimolecular mixture of aromatic aldehyde and 2-acetylpyrole (ketone) in alcoholic potassium hydroxide (20 ml) was kept at continuous stirring for 6–8 hours.

After stirring, the content was cooled and neutralized with HCl. The precipitated sludge was filtered, washed with water, dried, and recrystallized with ethanol.

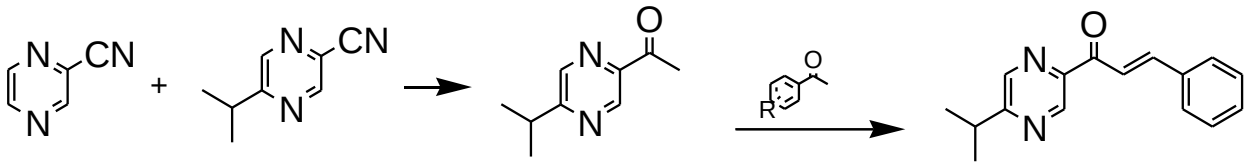


Synthesis of Pyrazine based Chalcone

Marta Kucerova-Chlupacora *et al* were studied the synthesis of pyrazine analogues of Chalcones [19].

Procedure:

0.1 mmol of 1-(5-isopropylpyrazin-2-yl)ethan-1 and 0.1 mmol of substituted aromatic aldehydes in ethanol (20 ml) and KOH (20 ml). The reaction mixture is then poured into the ice cubes and neutralized with HCl after being kept at this temperature for 6-10 hours. The precipitated solid was filtered and washed with water, and it was recrystallized from ethanol.

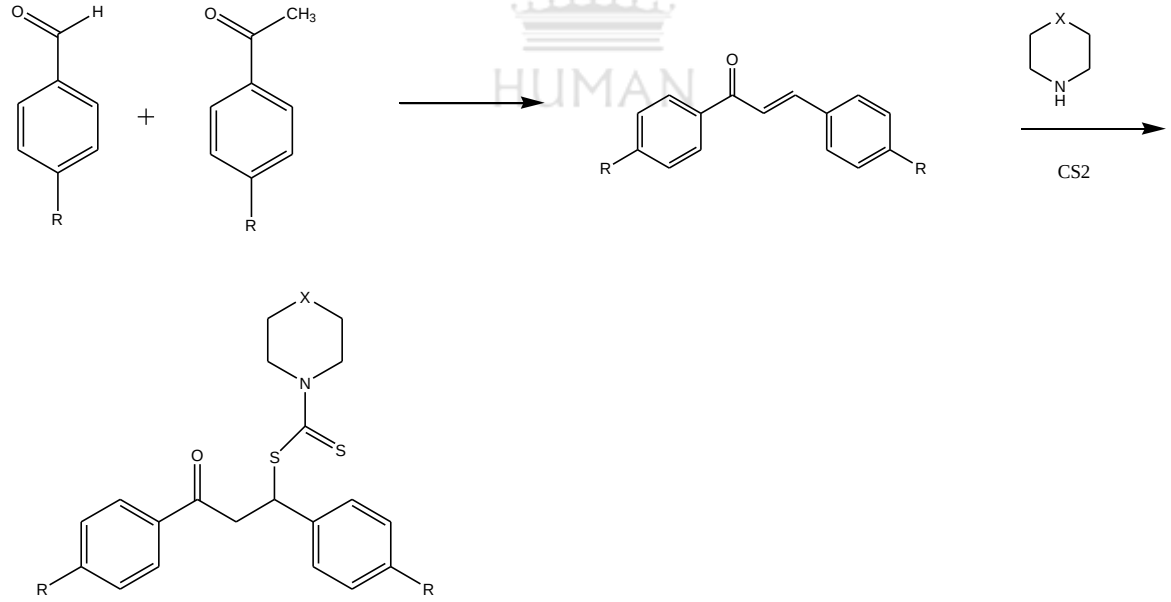


Synthesis of Dithiocarbamate based Chalcone

Marwa Ayman *et al* were screened the novel Dithiocarbamate based Chalcone derivatives [20].

Procedure:

Condensation of aromatic aldehydes and acetophenones yields chalcone, which, on further reaction with carbon disulfide (CCS2) in ethanol, yields an intermediate, which, on further reaction with morpholine, yields dithiocarbomate-based chalcone.

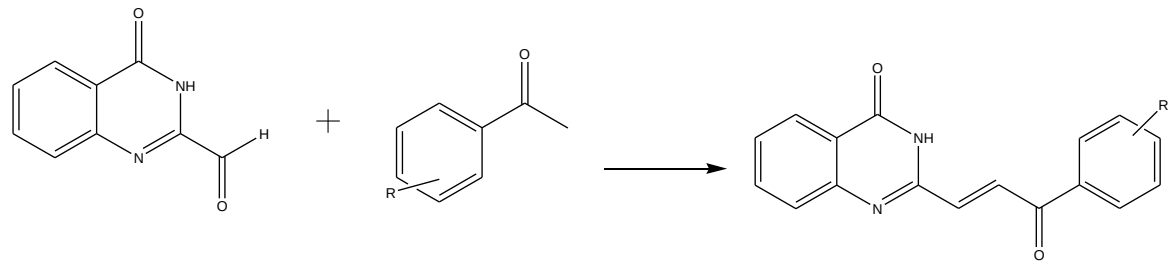


Synthesis of Quinazoline based Chalcone

Xue Han *et al* were investigated the synthesis of quinazoline based Chalcone [21].

Procedure:

2-methyl quinazoline (4(3H)-1) was oxidised to 2-formyl quinazoline (4(3H)-1) by an oxidising agent, selenium dioxide, which on further treatment with various substituted acetophenones, yields (4-oxoquinoline-2-yl chalcone), a quinazoline analogue of chalcones.

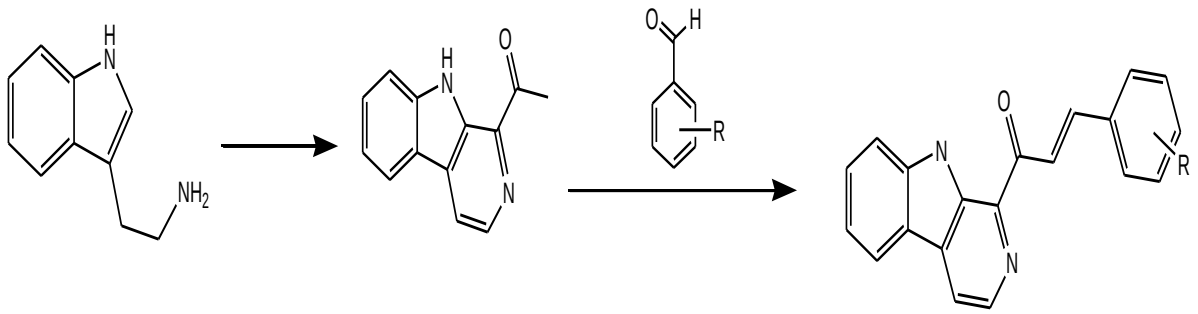


Synthesis of ß-carboline based Chalcones

Venkataramana Reddy P O *et al* were studied the synthesis of ß-carboline based Chalcones [22].

Procedure:

Tryptamine reacting with pyruvaldehyde yields 1-acetyl ß-carbolin, an acidic medium. This 1-acetyl ß-carbolin with substituted aromatic aldehydes yields ß-carbolinechalcone derivatives.



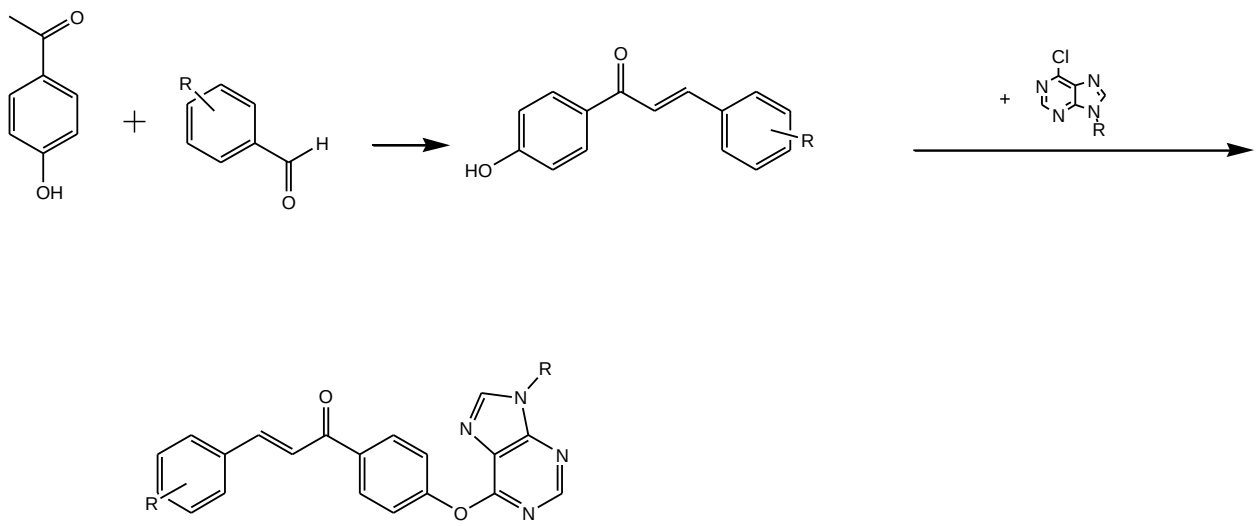
Synthesis of purine based Chalcones

Xiuhai Gan *et al* were synthesized the novel Chalcones containing purine moiety [23].

Procedure:

On stirring, an equal amount of aromatic aldehydes and acetophenone in an alcoholic basic condition yields chalcones. 0.2 gm of chalcones were mixed with 0.2 gm of 6-chloro-9-H-purine in Dimethyl formamide (4 ml), and the mixture was stirred for 1 hour. The precipitated solid was filtered and washed with water, and the mixture was then treated with

chloropurine for 6 hours while stirring. Then it was poured into a crushed ice bath. The solid mass obtained was filtered and washed with water. Finally, it was recrystallized from ethanol or ethlylene chloride to give pure crystals of purine-based chalcones.

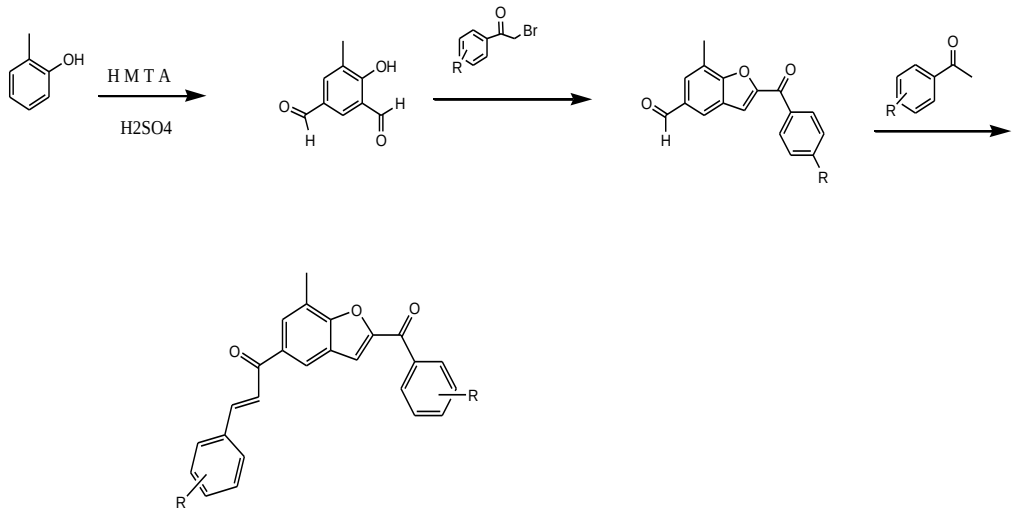


Synthesis of benzofuran based Chalcones

Malose Phahlele J M *et al* were investigated the synthesis of Benzofuran Chalcone derivatives [25].

Procedure:

Duff formylation of ortho cresol with hexa-methylene tetra acetic acid at 120˚C resulted in aromatic dicarbaldehyde. This aromatic dicarbaldehyde, which, on further condensation with phenacyl bromide in the presence of potassium carbonate, yields chalcone-based benzofurancarbaldehyde derivatives.

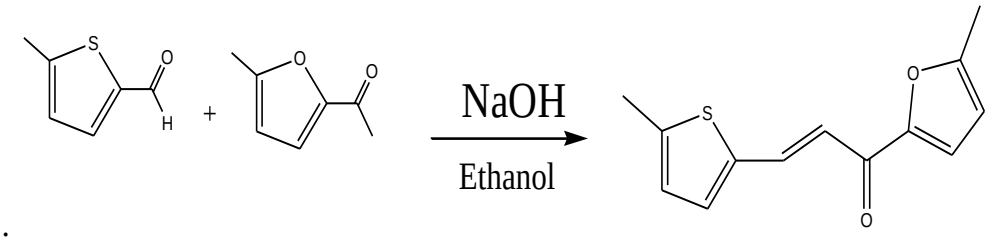


Synthesis of thiophene based Chalcones

Liew Suk Ming *et al* were investigated the synthesis of thiophene based Chalcone derivatives [27].

Procedure:

Take 0.6 gm of 3-methyl-2-thiophene carboxaldehyde and 0.62 gm of 2-acetyl-5-methyl furan in ethanol (5 ml) and add 4 ml of sodium hydroxide. The mixture was kept on constant stirring for 8 hours until it became cloudy. Then it was filtered and washed with ice-cold water. It was then recrystallized from ethanol to yield thiophene-based Chalcone.

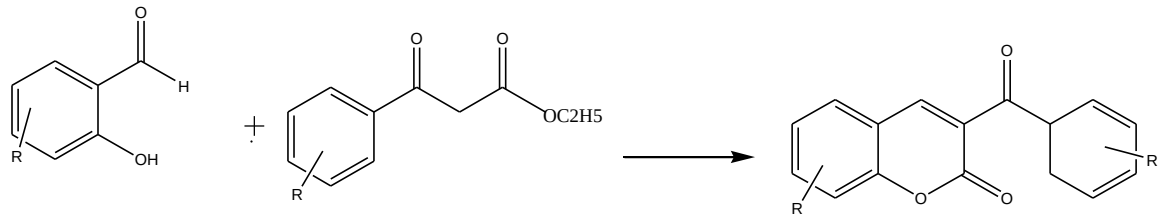


Synthesis of coumarin based Chalcones

Saleta Vazquez-Rodriguez *et al* were synthesized the novel coumarin chalcone derivatives.

Procedure:

Take equal molecular mixture of salicylaldehyde and corresponding ethyl substituted benzoyl acetate with piperidine in ethanol at reflux for 2-5 hours [26].



PHARMACOLOGICAL ACTIVITES OF CHALCONES

Antianxiety Activity

Josefina Higgs *et al* investigated the anti-anxiety activity of Chalcone derivatives in two *in vivo* studies, the elevated plus maze test and the tail suspension test. They also investigated the analgesic activity of chalk using hot plate and writhing tests [7].

Anti oxidant Activity

Alka N. Choudhary *et al.* investigated the study of anti-inflammatory activity by using a carrageenan-induced rat paw edoema assay. They also tested the Chalcone-induced inhibition of lipid peroxidation using rat liver as a polyunsaturated fatty acid source. The sample mixture was prepared by mixing rat liver suspension with synthesized Chalcones. Chalcone's lipid peroxidation activity can be determined by comparing the absorbance of the sample and control mixtures [8].

Nourah A. Al Zhahrani *et al* investigated the antioxidant activity of synthesized chalcones using the indicator DPPH (2,2-diphenyl-1,4,6-trinitrophenyl hydrazyl). The antioxidant activity is based on the compound's ability to transfer a hydrogen atom or single electron to DPPH [9].

Jiabing Wang *et al* studied the antioxidant activity of synthesized chalcones by DPPH assay, which determines the hydrogen atom's (one electron's) donating capacity [14].

Antiulcer Activity

Alka N. Choudhary *et al.* investigated the antiulcer activity of all synthesized novel Chalcone derivatives in rats with indomethacin-induced ulcers in the stomach [8].

Anticancer Activity

Nourah A. Al Zhahrani *et al* investigated anticancer activity against several carcinoma cell lines, including MCF-7 human breast cancer cells and HepG-2 human hepatocellular carcinoma cells [9].

Malose Phahlele, J. M., *et al.* studied the anticancer activity of benzofuran by SRB viability assay. The anticancer activity of Chalcones was evaluated using the Sulphoramide B assay. The viability cells were calculated by taking an absorbance reading at 564 nm with a spectrophotometer [25].

Pravin *et al*. investigated the cytotoxic properties of indolylchalcone in human breast cancer cells *in vitro*. The majority of the compounds inhibited growth in human breast cancer cells at a high percentage, which was calculated as the GI50 (growth inhibitory) value [16].

Antiviral Activity

Yun Fu, Dan Liu, *et al.* estimated the antiviral activity of synthesized chalcones against the tobacco mosaic virus. The curative effect of synthesized Chalcones was 47–48.8%, which was better than that of ribavirin [10].

Xiuhai Gan *et al*. screened the antiviral activity of synthesized purine-based chalcones against purification of Tobacco Mosaic Virus (TMV) and Cyto Megalo Virus by the Gooding method. After purification, the concentration of virus was determined using a UV spectrophotometer at 26 nm [23].

Anti-Alzheimer activity

Benzofuran Chalcone derivatives were tested for anti-Alzheimer activity by Koneni V. Sashidharan *et al.* and they also estimated the acetylcholine level and anticholinesterase activity in control and test compound-treated worms, along with positive and negative controls. By inhibiting the Acetylcholinesterase enzyme, which degrades Acetylcholine, some compounds significantly increased Acetylcholine levels in worms [24].

Anti-diabetic Activity

Samere Welday Kahssay *et al.* studied the anti-diabetic activity of some synthesized chalcones in streptozotocin- induced diabetes in Swiss mice. The anti-diabetic activity was determined by analyzing the blood glucose level of each group's animals [11].

Chi Ting Hsich *et al* [67] used glucose uptake activity induced by different chalcones to assess the anti-diabetic activity of all synthesized compounds.

Immunomodulatory activity

Priyanka Bhoj *et al.* investigated the immunomodulatory activity of novel sulfornamide chalcone derivatives in filarial parasite-infected mice [12].

Xanthine Oxidase inhibition activity

Trung Huu Bui *et al.* assayed the xanthine oxidase (XO) inhibitory activity by a spectrophotometric method in an aerobic condition. By comparing the absorption of a xanthine oxidase enzyme mixture and a Chalcone-containing enzyme mixture at 290 nm, the inhibitory activity of synthesized Chalcones was determined [13].

Anti-inflammatory Activity

Pravin S. Bhale *et al.* investigated the anti-inflammable effect of synthesized Chalcones on egg albumin denaturation [16].

Topoisomerase II inhibitory Activity

Peng-Hui Li *et al.* investigated the topoisomerase-II inhibitory activity of carbagle-containing chalcones using Topo II assay hits from Topo GEN and using bromophenol blue as an indicator, the reaction products were analyzed and stored in electrophoresis and transillumination under UV height [17].

Peng-Hui Li et al assessed the apoptosis efficiency of synthesized Chalcones in HL60 cells, and the cells were flow cytometrically analyzed after incubation staining [17].

Anti-fungal Activity

Marta Kucerova Chlupacova *et al*. screened the antifungal activity of pyrazine based chalcone derivatives by *in vitro* susceptibility testing on eight fungal strains [19].

Anti-tubercular Activity

Marta Kucerova Chlupacova *et al.* evaluated the anti-mycobacterial efficiency of the synthesized chalcones [19].

CONCLUSION:

Currently there are more and more marketed drugs with novel chemical nuclei are available in the market. The chalcones are also one of the plant product derivatives because of this reason they are not too harmful to human being. In this study reveals the many synthetic procedures for novel Chalcones derivatives with very simple procedure and so and so pharmacological activities such as anticancer, antiulcer, anti-inflammatory, anti-tubercular, anti-diabetic, anti-oxidant and anti-anxiety activities of Chalcones. From the above review study it concluded that the novel potent Chalcones are very easy to synthesize and it shows different pharmacological activities with minimum toxicities.

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