

Comprehensive Study of Chalcone Derivatives

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ABSTRACT

Chalcones are flavonoid molecules that exist naturally and are essentially plant substances. These are the chemical compounds that have demonstrated a variety of intriguing biological actions with therapeutic potential against a variety of ailments. Anthranilic acid and orthophenylene diamine combine to produce benzimidazole. Additionally, the benzimidazole acetylated product goes via Claisen-Schmidt condensation with aryl aldehyde to create the respective chalcones. Due to phenolic groups and the existence of α , β unsaturated carbonyl groups, naturally occurring chalcones are polyhydroxylated in the aryl ring and exhibit a variety of biological activities, including antioxidant, antibacterial, anti-inflammatory, and anticancer properties. Being natural precursors, chalcones are intermediates that are crucial for the synthesis of flavones. This review article emphasizes on the informative aspects, methods of synthesis, biological activities and applications of Chalcones.

Keywords: Chalcones, Synthesis, Activity, Phenolic, Flavones.

INTRODUCTION

Chalcones are widely present in fruits, vegetables, teas, and other plants and are a simple chemical framework of numerous naturally occurring chemicals. Chalcones are a type of naturally occurring flavonoid compounds that are essentially plant chemicals. Chalcones are primarily composed of 1,3-diphenyl-2-propen-1-one, which comprises two aromatic rings linked together by an unsaturated ketonic molecule. As a result of the colors of the majority of naturally occurring chalcones, the word "chalcone" is derived from the Greek word "chalcos," which means "bronze."^[1]

Anthranilic acid and orthophenylene diamine combine to produce benzimidazole. Additionally, the benzimidazole acetylated product goes via Claisen-Schmidt condensation with aryl aldehyde to create the respective chalcones. In nature,

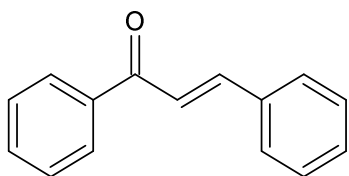
chalcone are abundantly found alongside foods like fruits, vegetables, tea, and spices. Due to phenolic groups and the existence of α , β unsaturated carbonyl groups, naturally occurring chalcones are polyhydroxylated in the aryl ring and exhibit a variety of biological activities, including antioxidant, antibacterial, anti-inflammatory, and anticancer properties. Being natural precursors, chalcones are intermediates that are crucial for the synthesis of flavones.^[2]

Chemical Structure (Backbone) of Chalcone Ring System/ Chalcone Derivatives:

Chalcones are, -unsaturated ketones (trans-1,3-diaryl-2-propen-1-ones) composed of two aromatic rings (A and B) connected by a, -unsaturated carbonyl system including a variety of substituents.

The general structural backbone of Chalcones is as follows:

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(2E)-1,3-diphenylprop-2-en-1-one

Chalcones from Natural Sources:

Chalcones are the building blocks of numerous biologically fascinating chemicals derived from natural sources, and they have sparked significant academic interest for decades. The isolation and structural elucidation of such natural chalcones depends upon the width of the net cast.

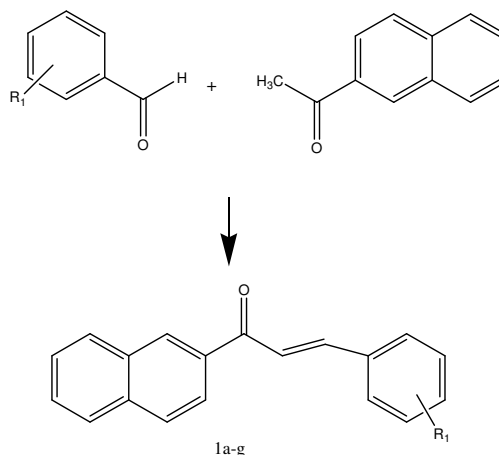
Some of the representative chalcones along with their respective biological properties are discussed as follows:

Names	Structure	Activities shown	Natural Source
Isoliquiritigenin ^[3-4]		Anticancer Antioxidant Anti-inflammation	Nepalese propolis
Butein ^[5]		Anticancer Anti-inflammation	Rhus verniciflua
Cardamonin ^[1]		Schistosoma mansoni ATP diphosphohydrolase	Piper aduncum L.
Sappanchalcone ^[6]		Anti-inflammation	Sappan Lignum
Isobavachalcone ^[7]		Anti-oxidant α -Glucosidase inhibitory activity Cancer chemopreventive Anti-cancer Anti-bacterial Anti-fungal	Psoralea corylifolia (Leguminosae) Kadsura ananosma

Synthesis of Chalcone derivatives:^[8]

Synthesis of Chalcone Derivatives of 2-Acetyl Naphthalene

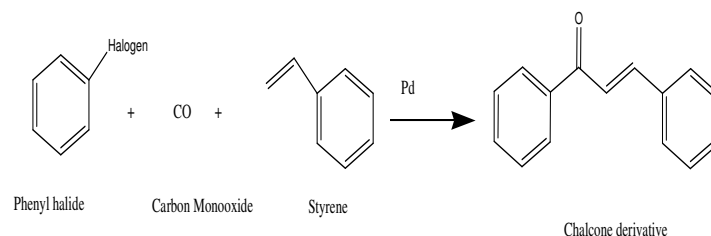
By reacting 2-acetyl naphthalene with benzaldehyde or modified benzaldehyde in methanol and potassium hydroxide, chalcones were created.



- 1a, R₁=H
 b, R₁=4-Cl
 c, R₁=4-Br
 d, R₁=4-F
 e, R₁=4-CH₃
 f, R₁=4-OCH₃
 g, R₁=4-NO₂

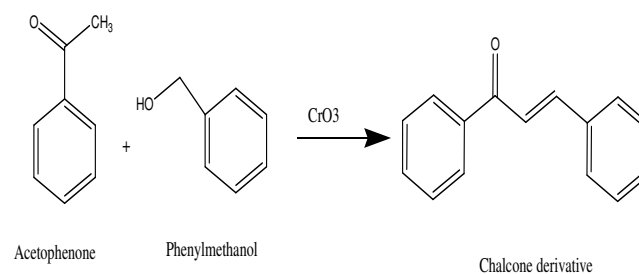
Synthesis of Chalcone from Phenyl Halide

Phenyl bromide and styrene were combined to create chalcone 100 using carbon monoxide and a Pd catalyst.



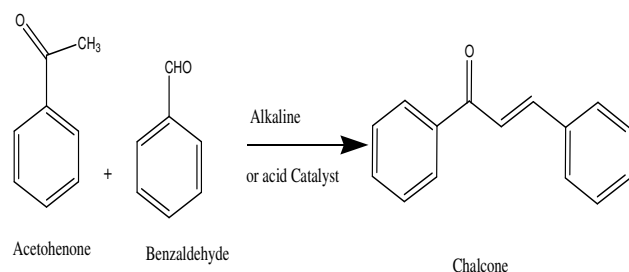
Synthesis of Chalcone via One-Pot Synthesis

Chalcone derivative 100 was produced by treating phenyl methanol 105 and acetophenone with CrO₃ as the oxidizing agent.



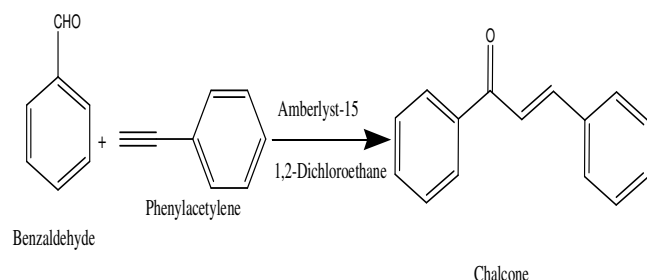
Claisen–Schmidt Condensation

In the presence of a liquid fluid, treatment of benzaldehyde and acetophenone derivatives in an acid catalyst or an alkaline environment at 50–100 °C produced 100.



Synthesis of Chalcone Using Solid Acid Catalyst

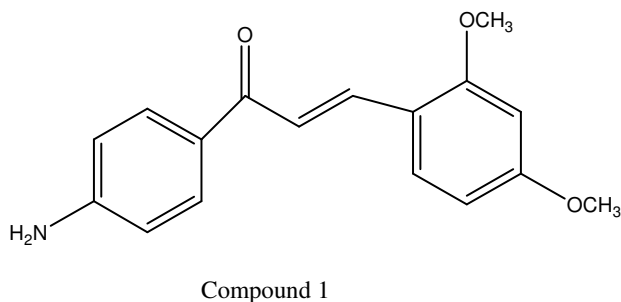
The corresponding chalcone 100 was produced by treating benzaldehyde and phenylacetylene with heterogeneous acid in a catalytic quantity in 1,2-dichloroethane as the solvent.



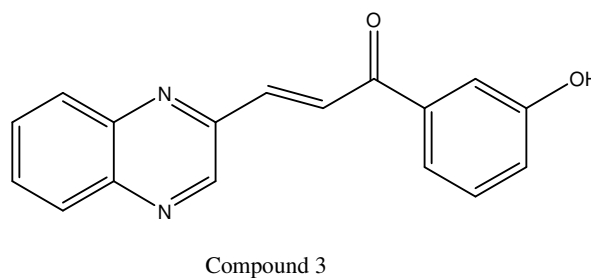
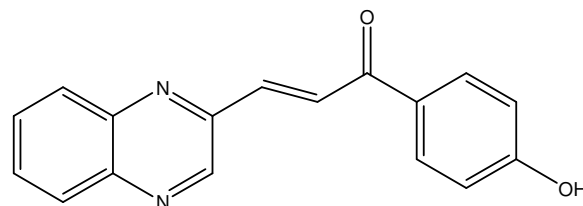
Biological activities ^[9-10]

Antimicrobial Activity:

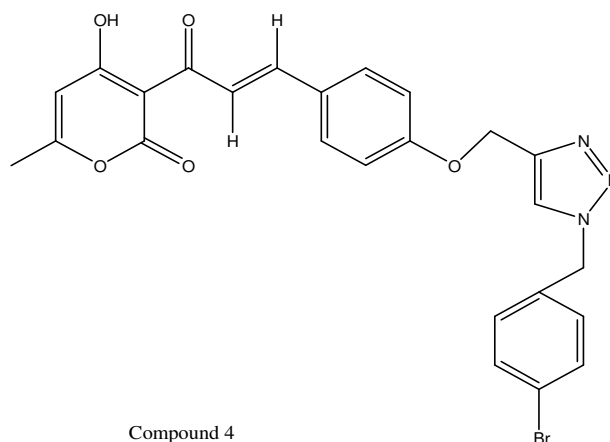
Methoxy-4'-amino chalcones demonstrated effective in vitro antibacterial activity against *Candida albicans*, *Staphylococcus aureus*, and *Escherichia coli*. ^[11]



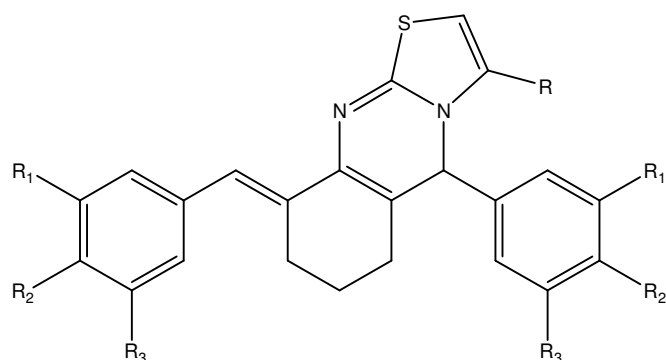
Vidya Desai et al^[12] synthesized the quinoxaliny chalcones derivatives using Claisen-Schmidt condensation were found to be good antimicrobial agents. By using the common serial dilution approach, some fluorinated chalcone-triazole hybrids were tested for their antibacterial effects against the bacterial strains *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* using disc diffusion procedure. Synthesized derivative also exhibited antitubercular and anticancer activity.



Dehydroacetic acid chalcone-1,2,3-triazole hybrids were synthesized by Kashmiri Lal et al^[13] and found to have effective in vitro antibacterial activity (*Staphylococcus epidermidis*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*) and two fungal strains (*Aspergillus niger* and *Candida albicans*).

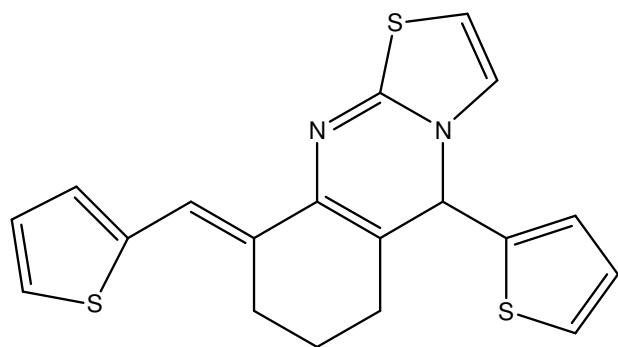


When screened against both gram-positive and gram-negative bacteria using thiazole-based chalcones such as thiazolo[2,3-b] quinazoline and pyrido[4,3-d] thiazolo[3,2-a]pyrimidine analogues, reported by Waad D. Alrohily et al.^[14] it was discovered that the tilted compounds had minimum inhibitory concentration (MIC) values in the range of 1-4.0 g/ml against *S. aureus*, *B. The* outcomes were determined to be comparable to the norms for ampicillin and ciprofloxacin. The synthesized derivative exert their effect by inhibiting DHFR.



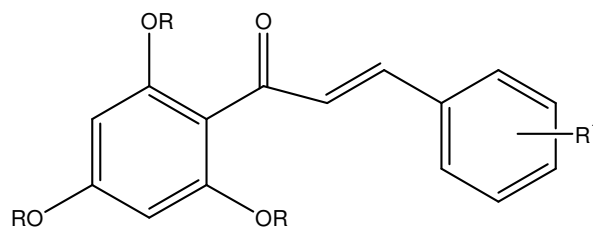
R= H, CH₃, OCH₃ R₁, R₂, R₃= H, OCH₃

Compound 5



Compound 6

Antimicrobial activity of fluoro-substituted chalcones against *S. aureus*, *S. pyogenes*, *E. faecalis*, *E. coli*, and *P. aeruginosa* bacteria and *C. albicans*, *C. glabrata*, and *C. parapsilosis* fungal strains.^[15]

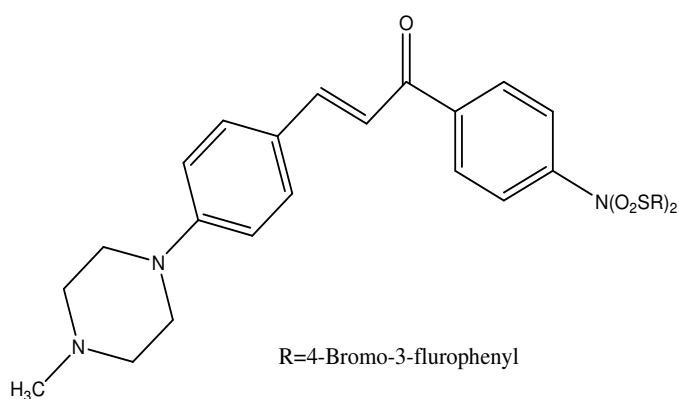


R= H, Me

R¹= H, 2-F, 3-F, 4-F, 2,5-diF

Compound 7

Piperazine substituted chalcone sulphonamides derivative were synthesized by Yan-Ling Tang et al^[16] and showed promising antibacterial action against *Escherichia coli*, *Aspergillus niger*, *Salmonella typhi*, *Penicillium chrysogenum*, and *Staphylococcus aureus* bacterial strains as well as *Aspergillus flavus*, *Bacillus subtilis*, and *Candida albicans* fungi.

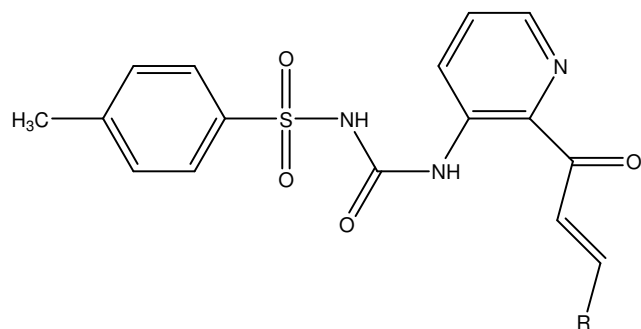


R=4-Bromo-3-fluorophenyl

Compound 8

The in vitro antibacterial and antifungal activities of oxyazolidinones combined with chalcone hybrids were assessed using the stepwise dilution method.

Novel diarylsulfonylurea-chalcone hybrids were assessed by M. Akkulu Naidu et al^[17] using the agar well diffusion technique against a variety of bacterial and fungal strains, including *Bacillus subtilis*, *Escherichia coli*, *Bacillus pumilus*, *Staphylococcus aureus*, *Micrococcus luteus*, *Candida albicans*, and *Penicillium chrysogenum*.



R = 2-NO₂C₆H₄, 5-OH,2-NO₂C₆H₃, 3-FC₆H₄, 3-NO₂C₆H₄

Compound 9

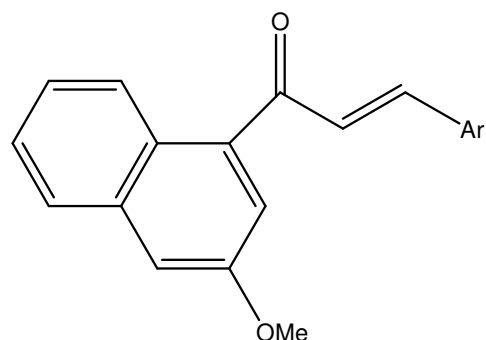
By condensation of vanillin with various acetophenone compounds, vanillin moiety-containing chalcones were created, and their antimicrobial properties were investigated.^[18]

Anti-cancer activity:

Anticancer drugs are agents that demonstrate activity against malignant disease. Alternative or synergistic anticancer medications with low side effects are always needed. Chalcones have the ability to target important molecular processes that could lead to the origin and development of cancer. Through the stimulation of tumour cell death, microtubule polymerization, anti-inflammatory properties, antiangiogenesis, and MDR inhabitation, chalcones may have an anticancer effect. Chalcones are extremely desirable as fundamental building blocks for the production of cancer molecule-targeting therapies because of this characteristic. Hybridization of the chalcone moiety with other anticancer pharmacophores produces hybrids that have the potential to overcome drug resistance and improve therapeutic specificity, rendering it a promising strategy for developing novel anticancer agents.

By using the aldol condensation, sulfonylpiperazines coupled with [1,3]dioxolo[4,5-g]chromenones were created by Rahul V Patel *et al*^[19], and their effectiveness as antioxidants against DPPH and ABTS as well as antiproliferative agents against non-cancer MDCK cell lines was assessed.

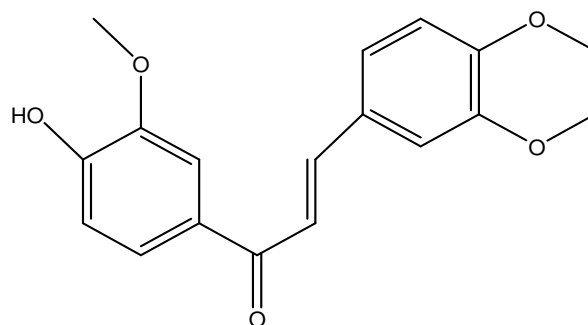
Guangcheng Wang *et al*^[20] reported Napthalene Chalcone derivatives and tested against human breast cancer MCF-7 cells in a concentration-dependent manner. In addition to make significant cell cycle arrest at the G2/M phase and cell apoptosis. The synthesized derivatives showed activity by inhibiting polymerization of tubulin protein with an IC₅₀ value of 8.4 μM, it was found to be more active than standard drug colchicine (IC₅₀ = 10.6 μM). Molecular docking analysis suggested that it also bind to same site where colchicine bind to the tubulin.



Ar = 3-Hydroxy-4-methoxyphenyl

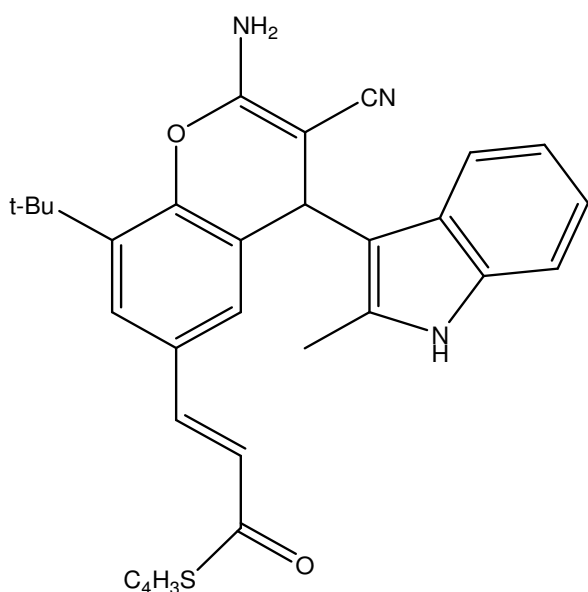
Compound 10

Human hepatic and lung cancer cells underwent an apoptotic induction and their migration and invasion was reduced by the chalcones. The *in vitro* growth inhibitory efficacy of the bis-chalcone derivatives against the human cancer cell lines MCF-7 and caco-2 was investigated.^[21]



Compound 11

It was discovered that the bis-chalcone with a fluoro group at the second or second-to-fifth position of the B-ring was a powerful inhibitor of the enzyme, with IC₅₀ values in the low micromolar range. The compounds' activities were discovered to be almost seven times greater than those of allopurinol in its most common form. Cancer is primarily caused by DNA ligases. On cancer cells, Gupta et al^[22] discovered that benzopyran chalcones based on indole-chalcone inhibited DNA ligases, leading to DNA nick-sealing activity and then antiproliferative activity.



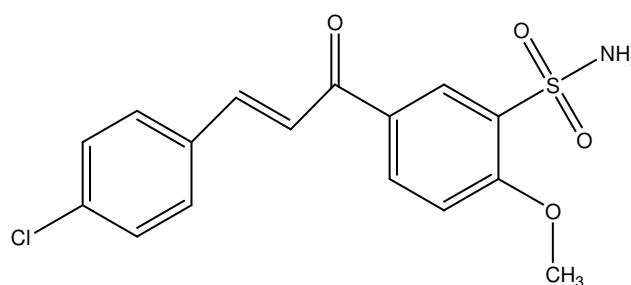
Compound 12

Antitubercular Activity:

The most common bacterial infectious illness is still tuberculosis (TB), which is brought on by the acid-fast gram-positive bacillus *Mycobacterium tuberculosis*. Alveolar macrophage invasion is how *M. tuberculosis* develops an infection. More than 60 adenylating enzymes, primarily tRNA synthetases, acyl-AMP ligases, etc., are encoded by the *Mycobacterium TB*. Four first-line medications are currently used to treat TB: isoniazid, rifampin, pyrazinamide, and ethambutol. These medications must be ingested daily for a 2-month intensive period. However, this treatment is 95% successful against susceptible TB strains. The rise of multidrug-resistant (MDR) strains, which

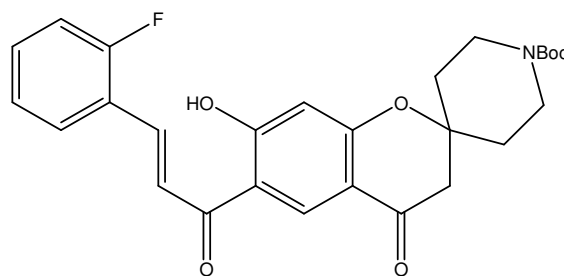
are toxic and less effective than first-line TB medications because they are resistant to isoniazid and rifampin, necessitates their use. Here, we discuss some new developments in the use of chalcones as a tuberculosis treatment:

By using the Claisen-Schmidt condensation, new chalcones bearing sulfonamides were created by Lina Fernanda Castaño et al^[23]. They were described as superb antituberculosis hits with low selectivity that was equally inhibitory to *M. tuberculosis* and mammalian T3T cells.



Compound 13

The antitubercular activity of spirochromone annulated chalcone conjugates against the *Mycobacterium tuberculosis* H37Rv strain has been reported. Based on the strong binding-affinity scores obtained during molecular docking experiments against the receptors, MTB phosphotyrosinephosphatase B protein was identified as the most likely target.^[24]



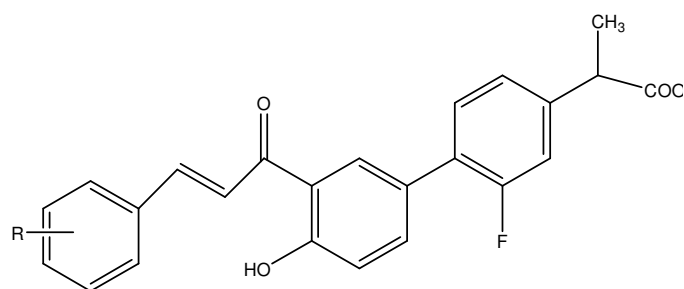
Compound 14

Babu et al^[25] investigated the antitubercular activity of chalcones containing nitrophenyl moieties using the MABA assay as well as the antibacterial and antifungal activities using the cup plate technique. A molecular docking study anticipated that *Mycobacterium tuberculosis* thymidine kinase would be inhibited.

Antioxidation activity:

Antioxidants prevent the decomposition process. These substances have the ability to stop or delay the harm that free radicals do to cells. Oxidation is a chemical process that produces free radicals, which can damage organisms' cells and cause oxidative stress, which in turn causes chronic diseases like Parkinson's disease, heart disease, cancer, arthritis, and other inflammatory conditions.

A number of 4'-OH-flurbiprofen-chalcone hybrids have been described and evaluated by Cao et al. as possible multifunctional treatments for Alzheimer's disease. Additionally, the substances were noted to have strong anti-oxidant, MAO inhibition, biometal chelating, and in vitro anti-neuroinflammatory actions.^[26]



4'-OH-Flurbiprofen-Chalcone Hybrid

Compound 15

Selenoenzymes and phase II enzymes that are regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) are the primary elements of cellular redox and antioxidant systems that provide information about numerous interrelations involved in the oxidation processes. It has been demonstrated that Chalcones prevent the production of Nrf2-regulated selenoenzymes.

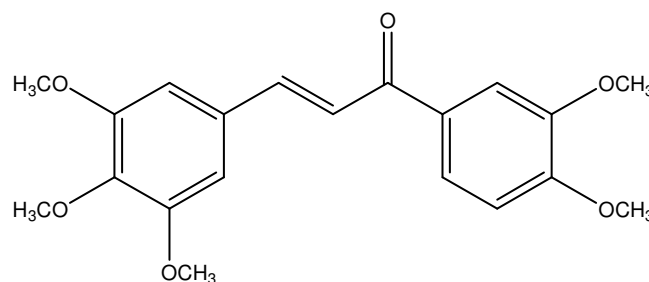
Anti-inflammatory:

Anti-inflammatory medications are the ones that are used to lessen inflammation and discomfort. In other words, these medicines act as painkillers. These medications primarily function by inhibiting

the COX-1 and COX-2 cyclooxygenase enzymes, which create prostaglandins.

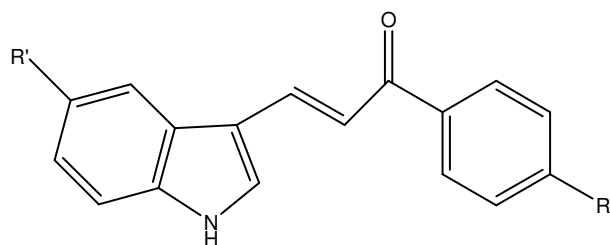
1-[3-Methoxy -4-(5-nitro-furan-2-ylmethoxy)-phenyl] -3-(substituted phenyl) (substituted phenyl) Propenones created by condensation of furfural and apocynin were tested for their ability to reduce inflammation.

Methoxy chalcones have been identified by Zhang et al^[26] as a potential treatment for acute inflammatory diseases.



Compound 16

Indole-based chalcones were synthesized and evaluated for in vitro COX-1 and COX-2 inhibitory activity

R' = OCH₃, Br R'' = SO₂CH₃, CN

Compound 17

Antibacterial Activity:

Chalcones are a type of naturally occurring flavonoids that are present in a variety of plant species and have powerful antibacterial, antiviral, and antifungal properties. A study was done so as to emphasize on the antibacterial activity of newly synthesized chalcone derivatives against some clinical isolates of MSRA (methicillin-resistant *Staphylococcus aureus*). The study found that three newly synthesized chalcones have considerable anti-MRSA activity and synergism

with non-lactam antibiotics. 1,3-Bis-(2-hydroxy-phenyl)-propanone was found to be the most effective.^[10]

CONCLUSION

Chalcone was discovered to be an effective antibacterial agent. Its derivatives have been found to suppress methicillin-resistant *Staphylococcus aureus* (MRSA). Chalcone derivatives demonstrated antifungal activity, particularly against *Microsporum gypsum*. The chalcone moiety is combined with other anticancer pharmacophores to form hybrids that have the ability to overcome drug resistance and improve therapeutic selectivity, making it a viable strategy for developing new anticancer drugs. Chalcone derivatives are used to alleviate pain and inflammation by suppressing the cyclooxygenase enzymes COX-1 and COX-2, which create prostaglandins. Licochalcone A and isoliquiritigenin compounds are utilized in acne therapy and skin whitening in the beauty business. For decades, chalcone and its derivatives have demonstrated antimalarial potential in order to develop new, safe, less toxic, and highly active antimalarials. It is utilized in sunscreen as a photoprotective agent. Licochalcone UVB-induced oxidative damage and inflammation are reduced. Chalcones, whether natural or synthetic, have considerable action in blocking cellular tyrosinase and lowering cellular melanin production, and are thus utilized in the treatment of melasma. Chalcone derivatives operate as hyper pigmenting agents in vitiligo by activating the tyrosinase enzyme and increasing melanin synthesis while melanocytes degenerate. For the treatment of atopic dermatitis, chalcone-containing formulations have been created and evaluated. It is prescribed for the treatment of psoriasis.

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