Chalcone Derivatives for Biological Potentials: A Strategy of Molecular Hybridization for Drug Design

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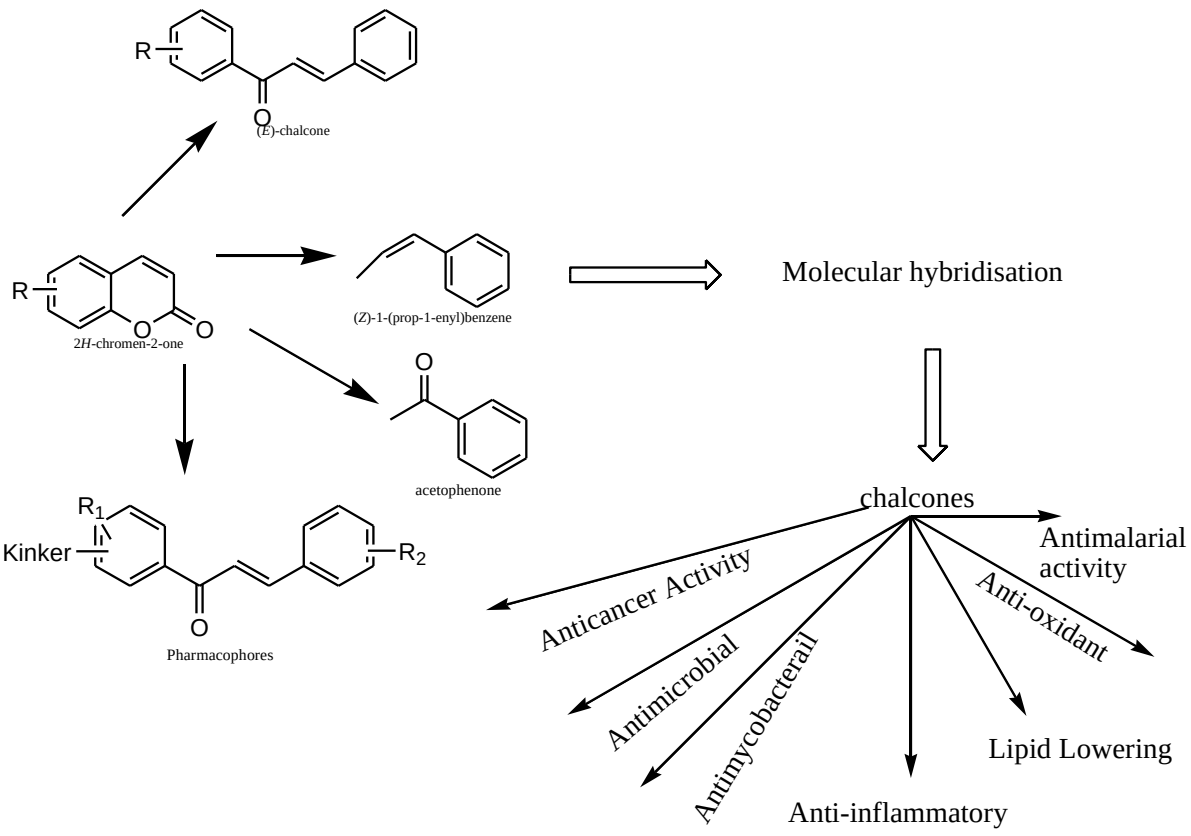
Abstract:

Naturally and synthetically derived hybrid molecules are promising sources for new drug development due to their multiple modes of action and other advantages. Chalcone, two important classes of synthetic chemistry affording diverse pharmacological activities, make themselves ideal blocks for building a chalcone hybrid scaffold as a bioactive agent. Provoked by the promising medicinal applications of such hybrids, the scientific community has reported dozens of chalcone hybrids with a wide spectrum of biological properties including anticancer, antimicrobial, antimalarial, antioxidant, antianxiety and so on, through synthetic hybridization strategy. It is expected to assist medicinal chemists in the effective and successful development of chalcone hybrids. In view of these observations, we herein report the literature review of Chalcone hybrids which possessing antimicrobial antioxidant and antianxiety potential.

Key words: Chalcone, Molecular hybridization, Biological potentials.

Graphical Abstract



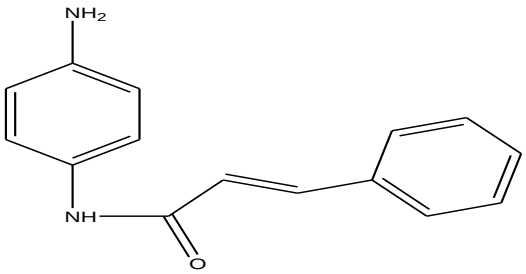
Intrduction

Chalcone is one of the privileged medicinal pharmacophores, which appears is an important structural component in natural compounds and has generated great attention because of its interesting biological activity including antimicrobial action. Chromene constitutes the basic backbone of various types of polyphenols and is widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins. It is known that certain natural and synthetic chalcone derivatives possess important biological activities [13-18]. Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. Chalcones can be prepared by an aldol condensation between benzaldehyde and acetophenone in the presence of sodium hydroxide as a catalyst. Chalcones are active lead molecules in medicinal chemistry for the discovery of new drugs. Chalcones have been reported to possess many useful biological properties including antimicrobial, anti-inflammatory, and anticancer and antioxidant activities [18-22]. In view of these biological significances of coumarin and chalcones, a strategy of synthetic molecular hybridization between coumarins with chalcones is used to design number of coumarin-chalcone hybrids for therapeutic potentials.

Literature Review

Chalcone hybrids

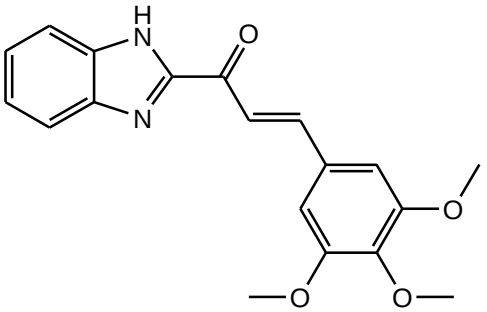
Elavarasan M et al., (2018) reported synthesize of the new chalcones by claisen Schmidt condensation of the substituted benzaldehydes with 4-aminoacetanilide in the presence of base catalyst. These are responsible for the antimicrobial activity and compared with the standard drugs



N-(4-aminophenyl)cinnamamide

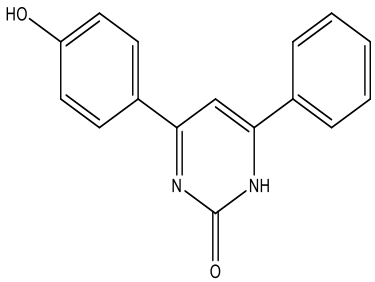
Jaiswal P et al., (2018) reported c synthesis of chalcone and their heterocyclic analogue. Various structural modifications of the heterocyclic analogies chalcones synthesized have been made to the explore its promising biological potential in the recent years. The various pharmacological activates of antihypertensive, antifungal, anticancer, anti-filarial, anti-

protozoal, anti-HIV, antimalarial, antioxidant, antiviral, antifungal, anticonvulsant, antibacterial.



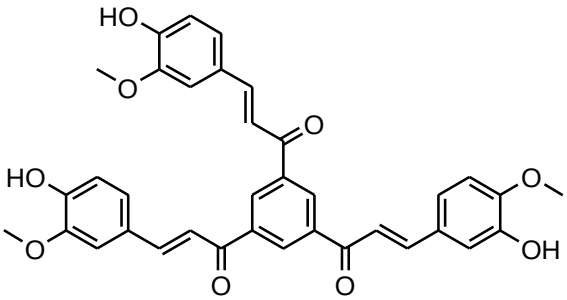
(2E)-1-(1H-benzimidazol-2-yl)-3-(3,4, 5-trimethoxyphenyl) prop-2-en-1-one

Sahoo B et al., (2017) reported synthesis of pyrimidines derivatives through Chalcones and its evaluation of their anthelmintic activity. In the present study, we focused in the environment-friendly processes used for the preparation of pyrimidine derivatives with pharmacological properties of antimicrobial.



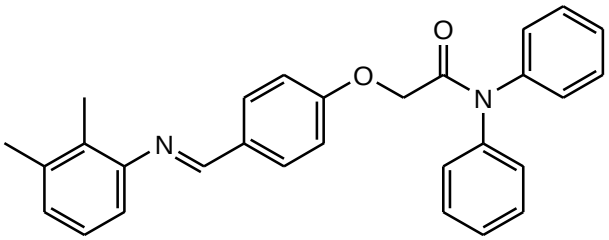
4-(4-hydroxy-phenyl)-6-phenyl-pyrimidin-2(1H)-one (4e)

Jung J et al., (2017) reported synthesis of chalcone derivatives and their biological activities. of molecular modelling studies to investigate of the chemical structural it characteristics for the biological activities of antibacterial , antimicrobial, and anti-neurotoxicity



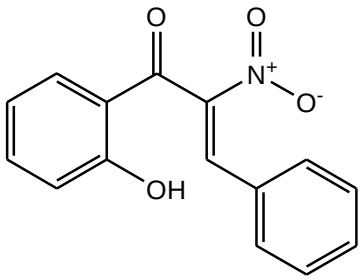
(2E,2'E)-1,1'-(5-((E)-3-(3-hydroxy-4-methoxyphenyl)acryloyl)-1,3-phenylene)bis(3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one)

Kumar et al., (2017) reported synthesis of some new schiff bases of pharmaceutical interest. a series of schiff bases of diphenylamine derivatives have been synthesized and evaluated for the antibacterial activity.



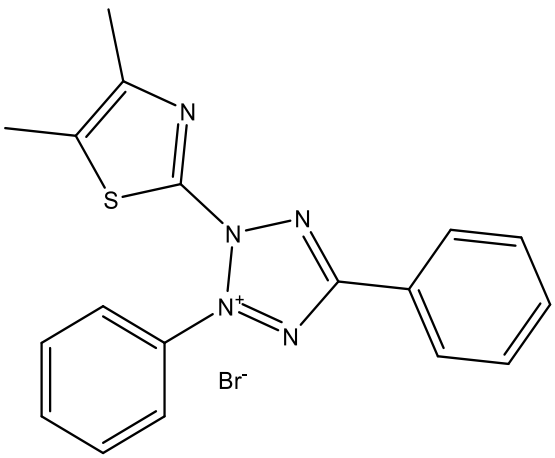
2-(4-(1-(2, 3-Dimethylphenylimino) methyl) phenoxy)N,N diphenylacetamide

Gaonkar S et al., (2017) reported synthesis and pharmacological properties of some chalcones. These chalcone derivatives is important for the antimicrobial, antifungal, anti mycobacterium, ant malarial, antiviral, anti-inflammatory, antioxidant, antileishmanial anti-tumour, and anticancer properties.



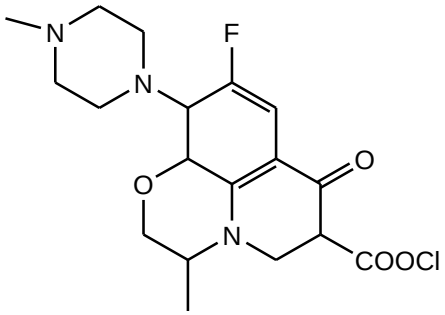
hydroxy-nitrochalcone

Chavan B et al., (2016) reported synthesis in the medicinal significance of chalcones derivatives. These compounds they have backbone of the chalcones it has been reported in to the possess of various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulators, and function of the chalcones is responsible for the antimicrobial activity.

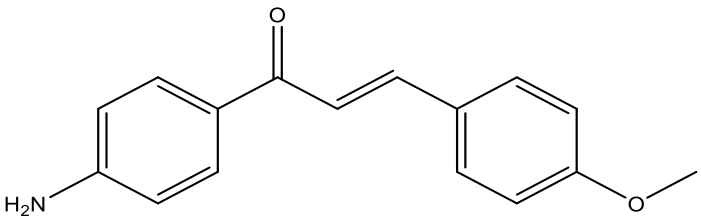


3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Ahmed K et al., (2016) reported Synthesis and anti-bacterial evaluation of new chalcone derivatives conjugates as possible mutual prodrug.

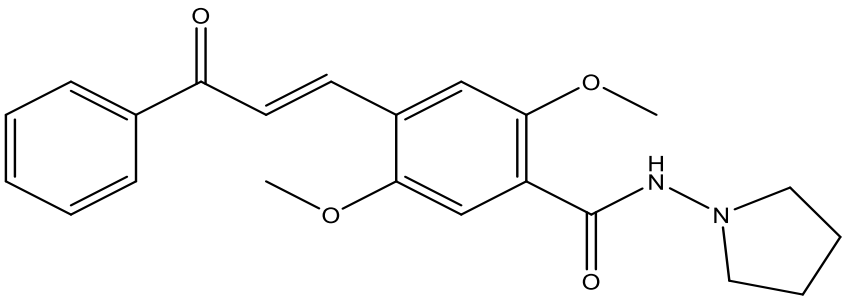


Suwito H et al., (2014) reported a review on (E)-1-(4-aminophenyl)-3-(4-methoxyphenyl) prop-2-en-1-one, (E)-1-(4-aminophenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one, and (E)-1-(4-aminophenyl)-3-(2,3-dimethoxyphenyl)prop-2-en-1-one, these are produce the antimicrobial activity.



(E)-1-(4-aminophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one

Chandrabose P et al., (2014) reported synthesis of the some new chalcones derivative Chalcones are naturally occurring compounds exhibiting broad spectrum biological activities including anticancer activity through multiple mechanisms.

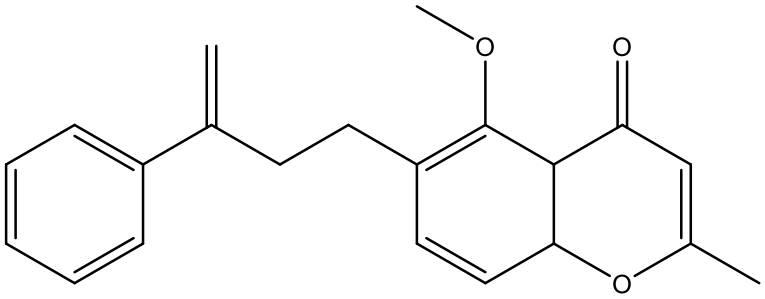


(4-tetrahydropyrrolylcarbamoyl-2..,5..-dimethoxychalcone)

This name appears to be ambiguous

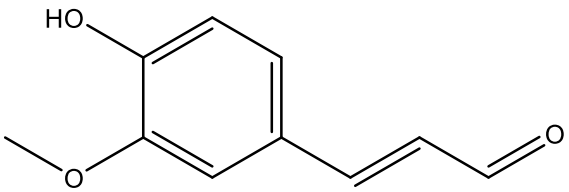
Yerragunta V et al., (2013) reported a review on chalcones and its importance and they can also be synthesized in the laboratory these .chalcones possess of a broad spectrum of biological

activity including ant oxidative, antibacterial, anthelmintic, amoebicidal, antiulcer ,antiviral, insecticidal, antiprotozoal, anticancer, cytotoxicity and immunosuppressive.



5-methoxy-2-methyl-6-(3-phenylbut-3-en-1-yl)-4a,8a-dihydro-4H-chromen-4-one

Ertan et al., (2011) reported synthesis and Structural Properties of Chalcones. Therefore, many researchers have synthesized these compounds and evaluated their biological activities. In this review, we aimed to provide a comprehensive presentation of chemical and structural properties of chalcone derivatives, to the researchers.

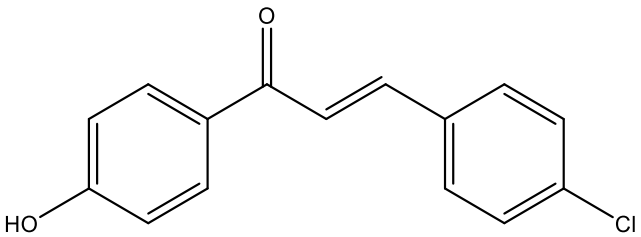


4-hydroxy-3-methoxy cinnamaldehyde

Aksoz et al., (2011) provided a comprehensive presentation of chemical and structural properties of chalcone derivatives to the researchers. Various methods are described for the synthesis of chalcones e.g. . Chalcone synthesis with aromatic aldehydes and acetophenones- Chalcone synthesis with the reaction of aromatic aldehyde and acetophenone in the presence of NaOH in EtOH, Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones with clay minerals, Chalcone Synthesis with the reaction of aldehyde and acetophenone in the presence of potassium carbonate and dimethyl formamide, Chalcone synthesis with the aromatic aldehydes and acetophenones by ultrasound, chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using Fly-ash:H_2SO_4 Reagent, Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using Silica-Sulphuric Acid, Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones

using Ba $(OH)_2$, Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using dimethylammonium dimethylcarbamate, Chalcone synthesis with the reaction of aromatic aldehydes and acetophenones using KF/NP as catalyst, Conformational Properties of Chalcones-Chalcones are flexible molecules capable of existing in various conformations and their properties depend on a suitable ring substitution and the presence of α,β-unsaturated ketone moiety .Chalcones exhibit very interesting stereochemical characteristics such as the existence of the conformational equilibrium illustrated in . The hydrogen atoms of the double Cα = Cβbond of chalcones present a cis or trans configuration, while the C = O bond can present a s-cis or trans conformation with respect to the vinylenic double bond due to free rotation along the single bond between C-carbonylic and C-α. Activity of compounds is affected by steric interactions between chalcones. So, stabilisation of suitable conformations and introduction of suitable substituents could result in a therapeutically useful agent.

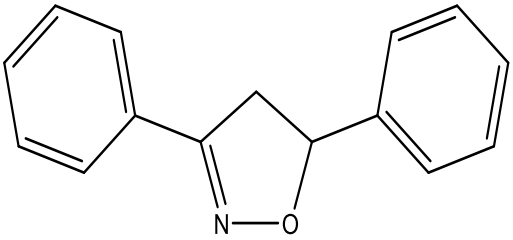
Jasinski et al., (2011) carried out the synthesis of 3-(4-Chlorophenyl)-1-(4- hydroxyphenyl) prop-2-en-1-one containing a heterocyclic.



3-(4-Chlorophenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one

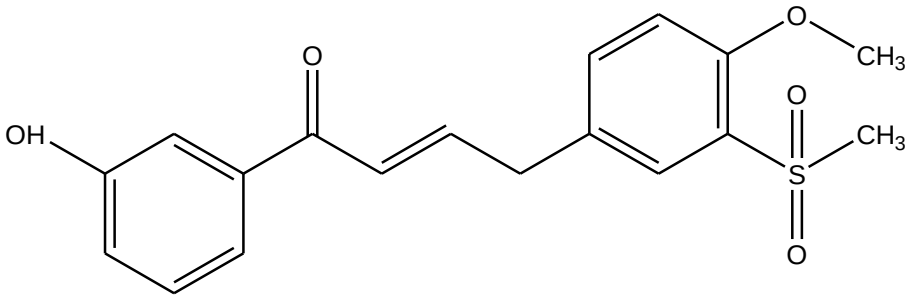
Tiwari et al., (2010) synthesized a series of chalcones by Claisen-Schmidt condensation of appropriate acetophenones with appropriate aromatic aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. The synthesized compounds were characterized by means of their IR, 1H-NMR spectral data. All the compounds were tested for their antibacterial and antifungal activities by the cup plate method. The present work reports the reaction of various substituted acetophenone with different substituted aromatic aldehyde to form chalcones . The structures of the various synthesized compounds were assigned on the basis of IR, 1H-NMR spectral data. These compounds were screened for their antimicrobial activity.

Patil et al., (2009) reported Chalcone a versatile molecule, synthesis of chalcones, its chemical modifications to flavonoids, flavanone, pyrazoles, ox azoles, 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, cytotoxicity and ant hyperglycemic activity of chalcones is also discussed in this review article.



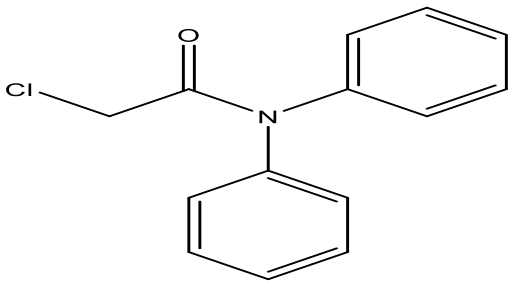
3, 5-diphenyl-4, 5-dihydro-1, 2-oxazole

Carla et al.,(2009) reported on a synthesis of sulfonamide 4 methoxy chalcone derivatives with antileshmanial activity against leshmania braziliensis,.



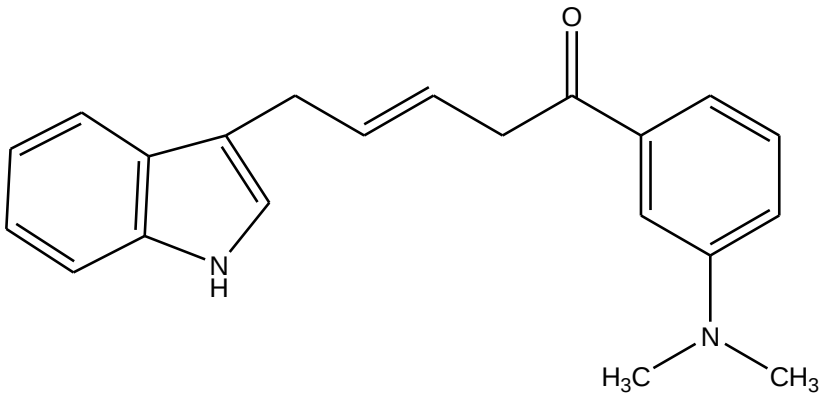
(*E*)-1-(3-hydroxyphenyl)-4-(4-methoxy-3-(methylsulfonyl)phenyl)but-2-en-1-one

Jie et al., (2009) reported synthesis 2-Chloro-N, N-diphenylacetamide.



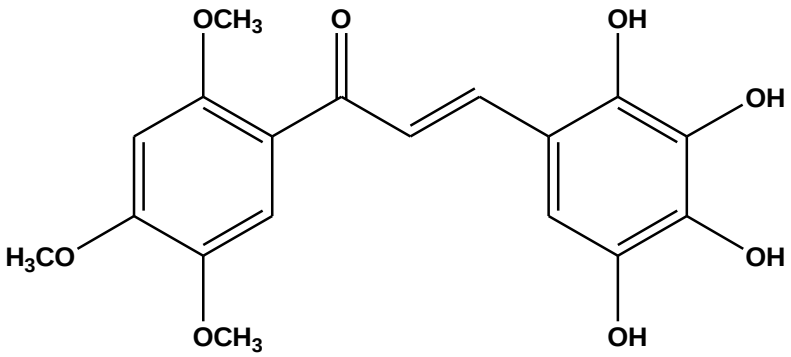
2-Chloro-N,N-diphenylacetamide

Romagnoli et al.,(2009) Synthesized novel series of α-bromo acrylolylamido chalcones which had the highest activity towards the five cell lines, .



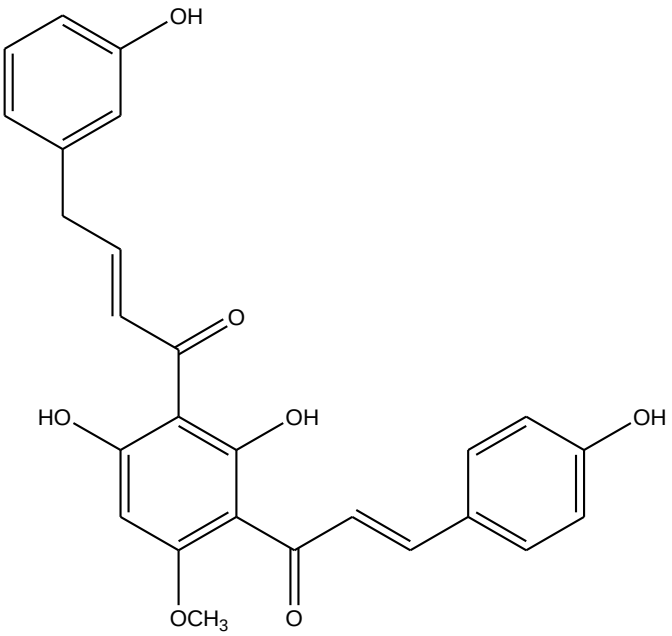
(*E*)-1-(3-(dimethylamino)phenyl)-5-(1*H*-indol-3-yl)pent-3-en-1-one

Rao et al.,(2009) reported a series of twenty three 3', 4', 5' – trimethoxy chalcones analogues as inhibitors of nitric oxide production in LPS treated macrophages and tumor cell proliferation, .



(*E*)-3-(2,3,4,5-tetrahydroxyphenyl)-1-(2,4,5-trimethoxyphenyl)prop-2-en-1-one

Susanne et al.,(2009) synthesized a series of 2'-hydroxy chalcones and their oxidative cyclization products for their antioxidant and lipoxygenase inhibitory activity.

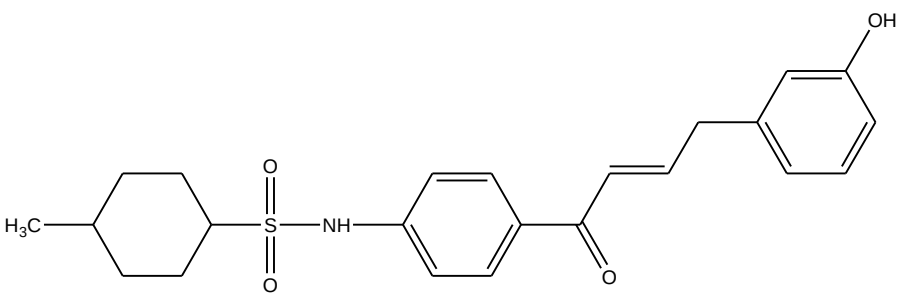


(*E*)-1-(2,6-dihydroxy-3-((*E*)-3-(4-hydroxyphenyl)acryloyl)-4-methoxyphenyl)-4-(3-hydroxyphenyl)but-2-en-1-one

Prasad et al., (2007) synthesized 3-[1-oxo-3-(2, 4, 5-trimethoxyphenyl)-2-propenyl]-2H-1-benzopyran-2-ones (2) that showed significant antimicrobial activity against *B.subtilis, B.pumilis and E.coli* when tested at a concentration of 1000 µg/ml. The study revealed the importance of electron releasing groups such as hydroxyl and methoxyl groups in enhancing the activity. Chalcones with halogen substituents like bromine and chlorine contributed favorably to the antifungal activity.

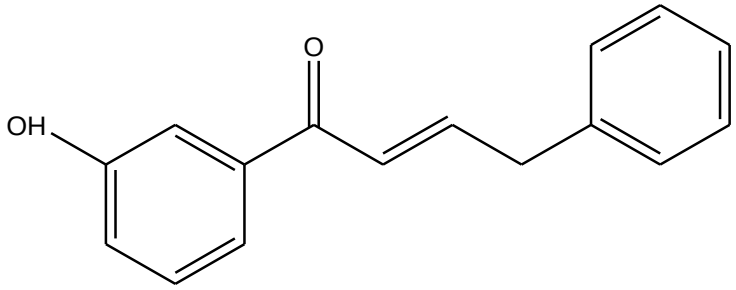
Karthikeyan et al., (2007) synthesized 3-aryl-1-(2,4-dichloro-5-fluorophenyl)-2-propen-1-ones (4) showing antimicrobial activity, again consistent with the observations that the halogens possess favorable lipophilic character required for antimicrobial activity.

Seo et al.,(2005) synthesized the chalcones a new clss of glycoside inhibitors. Non amino chalcones had no inhibitory activity. However amino chalcones had strong glycosidase (α,glucosidase, α, amylase and β, amylase) inhibitory activities,



(*E*)-*N*-(4-(4-(3-hydroxyphenyl)but-2-enoyl)phenyl)-4-methylcyclohexane-1-sulfonamide

Nielsen et al., (2004) described the bioisosteric replacement of the essential 4'-hydroxy group in the hydroxychalcones with bioisosters of varied degrees of acidity which resulted in both more potent and more soluble compounds. Exchanging the hydroxyl group, particularly with a carboxy group resulted in a potent compound with a high aqueous solubility. Further optimization and SAR analysis resulted in soluble and potent carboxychalcones having dibromo or trifluoromethyl substitution on B-ring (3). The MIC values for these compounds were found to be 2 µM and 40 µM respectively when tested against the Gram-positive bacterium Staphylococcus aureus. A dibromo or trifluromethyl substitution on B-ring was found to enhance the lipophilic character, while the carboxy group on A-ring contributed to the required aqueous solubility.



(*E*)-1-(3-hydroxyphenyl)-4-phenylbut-2-en-1-one

Acknowledgement

The authors would like to acknowledge the head of Department of Pharmaceutical Chemistry, Faculty of Pharmacy, School of Pharmaceutical Sciences, IFTM University, Lodhipur Rajput, Moradabad-244102, Uttar Pradesh, India for providing facility to conduct the research work.

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