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BRIEF REVIEW ON PHYSIOCHEMICAL PROPERTIES OF CHALCONE, SYNTHETIC PATHWAY AND ANALOGOUS WITH APPLICATION

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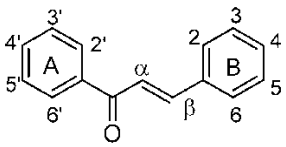
ABSTRACT

Chalcones are group of plant derived bioactive polyphenolic compounds belonging to flavonoids family. Human being had been using natural chalcones as traditional herbal medicine from many centuries. Chalcone, a colored organic compound contains three carbons α, β-unsaturated carbonyl system linked to two aryl rings. *Trans* form is thermally more stable than *cis* form. The various pharmacological activities include antioxidant, antifungal, antihypertensive, antiviral, anticancer, anti-protozoal, anti-HIV, antibacterial, antimalarial, antifungal, anticonvulsant. Chalcone had an object of interest for both academic and industry. The industrial application includes liquid crystals, fluorescent chemicals, metal sensors, corrosion inhibitor and plant hormones. This article briefly reviewed chalcone and their analogous reported for different applications and synthetic methods.

KEYWORDS: Chalcone, flavonoids, α, β-unsaturated, anticancer, physiochemical, analogous.

1. INTRODUCTION

Entire plant kingdom contains chalcone as leading category of flavonoids[1-2] for example Angiosperm families such as Moraceae, Leguminosae and Asteraceae are natural source of chalcones. Chalcones are abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes) and various plants and spices (e.g., licorice). Natural existing chalcones were not separated till the year 1910, though human beings had been using number of chalcones for centuries as a traditional herbal medicine.[3] Example, Licorice.[4] Scientists Stanislaw Kostanecki, a polish organic chemist – professor along with Josef Tambor, isolated first ever chalcone in laboratory.[5] The colour compound was coined as chalcone. The term chalcone is originated from the Greek language *chalkos* which means bronze. Structurally chalcones include two aromatic ring connected by three carbon as α, β-unsaturated carbonyl system.[6-7] γ-oxo-α, γ-diphenyl-α-propylene, Benzalacetophenone, phenyl styryl ketone, α-phenyl-β- benzoylethylene, β-phenylacrylophenone, benzylideneacetophenone are some of other names for chalcones.[8-10] Due to α, β-unsaturation, chalcones exhibit as *cis* chalcone and *trans* chalcone. *Trans* chalcone is thermally more stable, therefore trans form is more predominant among chalcone.[11] IUPAC nomenclature of chalcone is (E)-1,3-diaryl-prop-2-en-1-one. The chalcones had diversified pharmacological activities like anticancer[12], antiviral[13], anti-inflammatory[14], antileishmanial, antimalarial[15], antiulcer, antioxidant[16], analgesic[17], antigout as xanthine oxidase inhibitors[18], antidiabetic[19], antimicrobial.[21] Industrial application[22-23] of chalcone and their derivatives areliduid crystals, fluorescent chemicals, metal sensor, corrosion inhibitor, plant harmons, artificial sweeteners, scintillators, polymerization catalysts, fluorescent whitening agents, organic brightening agents, stabilizers against heat, visible light, ultraviolet light and aging.



(*E*)-1, 3-diaryl-prop-2-en-1-one

1.1 Classifications of chalcones: Chalcones are open-chain flavonoids, containing a three-carbon α, β-unsaturated carbonyl system linked to two aryl rings as ring A and ring B. Due to the structural diversity of these compounds; several authors divided them into different categories as follows.[24]

i) Classical chalcones

ii) Hybrid chalcones: These contain the 1, 3-diaryl-prop-2-en-1-one cores linked to another relevant chemical structure, sometimes known as pharmacophores.

iii) Fused chalcones: Chalcones of these type are a specific that contain a chalcone moiety connected to another chemical structure, like indole or oxathiole, through ring fusion

***iv) Bis*-chalcones:** *Bis*-chalcones contain two chalcone moieties in a single structure.

v) Dihydro chalcones: Chalcones compounds with a reduced α, β-unsaturated double bond.

vi) Chalcone mimics or analogues that contain a structure similar to an, β-unsaturated ketone system that mimics chalcones.

2. PROPERTIES OF CHALCONES

2.1) Physical and chemical properties: Natural occurring chalcones are generally crystalline solid and poses different color as brown, yellow, orange. Chalcones are more stable than relative flavonoids and isoflavonoids. Chalcones are not only soluble in organic solvent but also in aqueous acidic & alkaline condition. A deep red or orange red color is formed in aqueous alkaline medium. When chalcones treated with concentrated sulfuric acid, pink colour occur, i.e. positive Wilson test. Chalcones containing free phenolic hydroxyl groups when treated with alcoholic ferric chloride solution shades of colour i.e. Blue wine red, blue black, violet or green shades are produced.[25]

Chalcones undergo isomerization reactions to give flavonoids.[26] Chalcones on heating with traces of iodine in dimethyl sulfoxide for 120 minute give the corresponding flavones. Flavanones can be easily achieved through cyclization of chalcones treated with hydro bromic acid in glacial acetic acid. In this isomerization reaction, partial demethylation and debenzylation may occur. Chalcones were converted into flavones by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution. Another important isomerization reaction is known to be the formation of *aurones* from the chalcone precursors in the presence of aureusidin synthase.[27] The initial transformation of the *o*-dihydroxy groups of B- ring to an *o*-diquinone is a significant conversion because with one or without hydroxyl groups in ring B are anonymous at present.

2.2) Fluorescent properties: Fluorescence is physical property of an object that absorbs light at one wavelength and reemit at different wavelength, where the molecule is called fluorophore. Fluorescent materials have much attention because of their promising applications like fluorescent dyes, additive in dye sensitized solar cells, chemical probes,

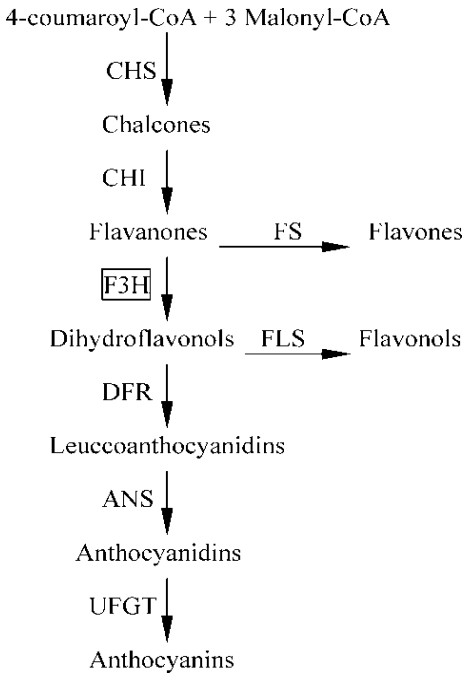
sensors, electro chromic materials and more significantly in diagnosis for the development of new drugs and to studied the interaction of bovine serum albumin with naphthyl chalcone derivatives.[28] Two aromatic rings of chalcones are connected α, β-unsaturated carbonyl system. Chalcones with suitable electron pull push arrangements of functional groups were reported to exhibits bright fluoresce.[29-31] Extinction coefficient (ε), Absorption (Abs λ *nm*) & emission (Emi λ *nm*) wavelengths and quantum yield (ϕ) are the key parameters that depend on electron density across the molecule. For an excellent fluorescent, chalcone it must be.[25] i) Molecule must be planner ii) Weak electron donating group in ring A result in promising quantum yields where electron-withdrawing groups result less quantum yields iii) In ring B, presence of disubstituted amino group is of great significance for the higher extinction coefficient, greater quantum yields and fluorescence with lower ionization potential iv) extension of α, β-unsaturated conjugated system with additional bonds, will cause red shift of maximum, emission fluorescence will be decreased.

2.3) Spectral properties: Chalcone consist of two absorption band in UV region as major band I and minor band II. Trans chalcone yields major band at 340-390 nm while cis chalcone gives minor band at about 200-270 nm.[32-35] The electronic transmission of n to π * and π to π * result of these band.[34] In general, the band I absorption originated from ring B cinnamoyl system and band II absorption maxima originated from the ring A benzoyl system.[36] If we increase free hydroxyl group in chalcone, increase in barthochromic shift for band I & band II occurs, but more in band I.[37] IR spectrum of chalcone shows two weak absorption band at 3110 & 3020 cm^{-1} for sp^2 C-H stretching. For Carbonyl C=O stretch at ~ 1690 cm^{-1} aromatic (C=C) at ~ 1600 cm^{-1} and alkenes C=C stretch observed at ~ 1500 cm^{-1}. In H NMR of chalcone displays two characteristic signals as H_α and H_β spectrum within range δ 6.7–7.4 and 7.3–7.7 as doublets (J = 15–17 Hz). The large J value (17 Hz) clearly reveals the *trans* geometry at the double bond.[36] However there are three characteristic signals for a chalcone in carbon nuclear magnetic resonance (^{13}C NMR) spectrum. For carbonyl carbon, one signal at δ188.6–194.4 ppm and two another prominent signals for C_α, and C_β in the range 116.1–128.1 and 136.9–145.4 ppm, respectively.[38] Carbonyl carbon shift downfield by the presence of 2'-hydroxy group relative to corresponding acetoxy and methoxy compounds, probably due to hydrogen bonding. The β- hydroxyl group of chalcones sometimes as the enol-tautomer's of dibenzoylmethane derivatives. The extent of keto-enol tautomerism is largely solvent dependent. Nuclear magnetic resonance spectroscopy (NMR) can determine the ratio of the tautomer's present. In the 1H NMR spectra recorded in $CDCl^3$,

the exchangeable proton of the β-OH of the enol tautomer appears as a 1H singlet at δ 16.0, whereas the α-CH_2 protons of the keto tautomer appear as a 2H singlet at δ 4.50. Another diagnostic resonance is the 1H methine singlet of the enol tautomer (α-CH), which is found at δ 6.5, with its corresponding C- α resonance at δ 90 to 92 in the ^{13}C NMR spectra.[39-40]

3. SYNTHETIC APPROACH

3.1 Biological approach: Zhiping jin et al reported chalcones are the important constituents of natural products possess varied biological and pharmacological activity. In higher plants, chalcones are synthesized by the enzyme *Chalcone synthase (CHS)* from one molecule of *p*-coumaril-CoA and three molecules of malonyl-CoA.

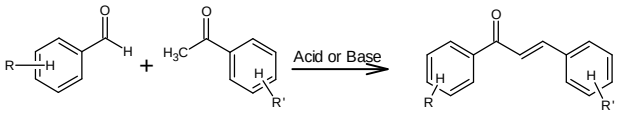


3.2 Synthesis approach

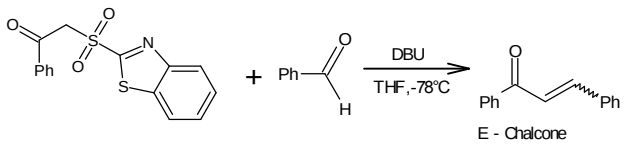
Naturally occurring chalcones have been reported to possess various medical properties. The chalcone family had demonstrated potential for *in vitro* and *in vivo* activity against cancers via multiple mechanisms, including cell cycle disruption, autophagy regulation, apoptosis induction, and immunomodulatory and inflammatory mediators.[41] Plant kingdom is vast source of number of chalcone source that had numerous biological effect. Some examples but not limited are Caesalpinia sappan (Sappanwood) used as cardiovascular[42], *Piper methysticum (kava)*used as intoxicating, Humulus lupulus (Hops) is used for anxiety, Alpinia rafflesiana exerted promising anti-inflammatory result.[43] Activity of any synthons depends upon their binding ability with enzyme. Though the chalcones possess numerous

applications, their broad bioactivity spectrum shows a causal target profile, which offer a challenging task for their clinical application. Thus it requires a pure chalcone. Secondly, availability of particular chalcone source in a desired plant is limited to that regional area only. This has given rise to the need for discovery and synthesis of new synthetically chalcones with different constituents as pharmaceutically important molecules. Chalcones can be prepared by various reactions. These include Aldol condensation, Claisen- Schmidt reaction, Julia Kocienski, Heck reaction, Friedel Craft reaction, Sonogashira coupling, Suzuki Miyaura coupling, Wittig reaction.

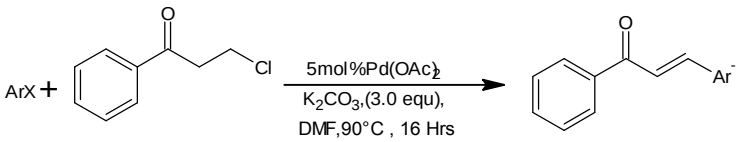
3.2.1 Claisen–Schmidt's condensation: It is a commonly employed and easy method. Substituted or unsubstituted benzaldehyde condenses with substituted or unsubstituted acetophenone in presence of base or acid as catalysts in an appropriate solvent for few hours at elevated temperature.[44] Chalcones have numerous biological activities as Anticancer, Antimicrobial, Antioxidant and Anti-inflammatory.



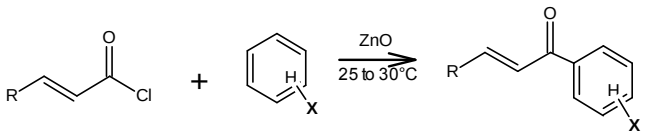
3.2.2 Julia Kocienski: The chalcones synthesized by Julia Kocienski method are exclusively as (E)-isomers. For the first time, an application of JuliaeKocienski olefination reaction leading to the synthesis of chalcones and flavanones in high yields. The reaction conditions are optimized with respect to the aryl sulfonyl group, the base, temperature and the solvent affording high yield.[45]



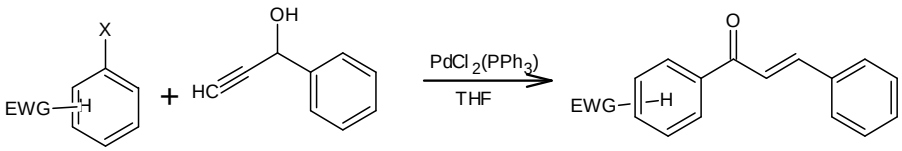
3.2.3 Heck reaction: Cross-coupling of aryl halides with β-chloroalkyl aryl ketones and their ester and amide analogs has been developed involving a domino dehydro-chlorination/Pd $(OAc)_2$-catalyzed Heck reaction with in-situ generated enones acting as the reaction intermediates.[46] In another method 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.[47-48]



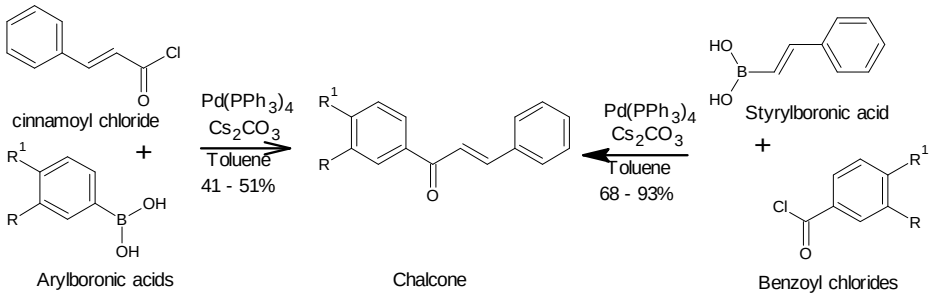
3.2.4 Friedel–Crafts: In Parmeshwar More et al, Activated as well as inactivated aromatics undergo Friedel–Crafts acylation with α, β-unsaturated acid chlorides resulting corresponding chalcone with excellent yields using zinc oxide as catalyzed under solvent-free conditions at room temperature.[49] C.B. Vagish et al developed an efficient, easy and one pot synthesis for the Friedel-Craft acetylation reaction of quinolones.[50]



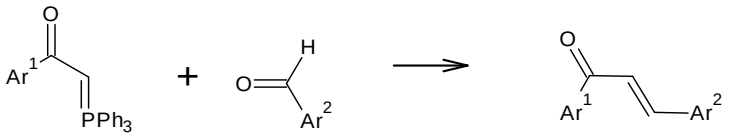
3.2.5 Sonogashira's isomerization coupling: The Sonogashira reaction is carbon – carbon cross-coupling reaction using palladium catalyst as well as copper co-catalyst to form a carbon–carbon bond between a *terminal alkyne* and an aryl or vinyl halide. In Sonogashira coupling, electron-withdrawing group (EWG) like phenyl halide and prop-2-yn-1-ol using catalyst $PdCl_2$ $(PPh3)_2$ with solvent like tetrahydrofuran gives corresponding chalcones.[51-52]



3.2.6 Suzuki–Miyaura's coupling reaction: A metal catalyzed coupling typically with Pd, between an alkenyl (vinyl), aryl, or alkynyl organ borane (boronic acid or boronic ester, or special cases with aryl trifluoroborane) and halide or triflate under basic conditions. Mild reaction conditions with different functional groups are main advantage of this reaction and thus allow the synthesis of flavonoids containing a number of sensitive substituent.[53] Eddarir and co-workers synthesized chalcones by the Suzuki-Miyaura reaction by two ways. In first way, coupling of arylboronic acids with cinnamoyl chloride afford moderate yields (41–51%) of chalcones, whereas the second pathway involved coupling of styrylboronic acid with benzoyl chlorides using Haddach and McCarthy's conditions [anhydrous toluene, $Pd(PPh_3)_4$, Cs_2CO_3]. These conditions gave the chalcones in good to excellent yields (68–93%).[54]

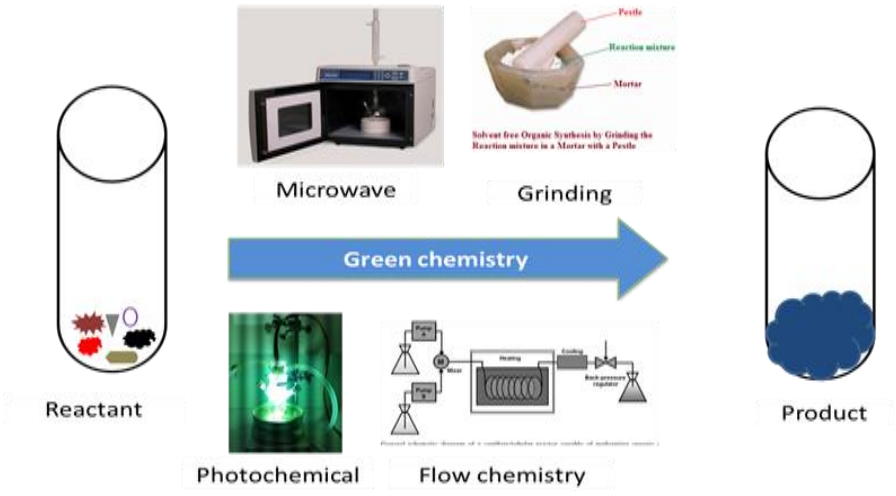


3.2.7 Witting reaction: Wittig reaction is preparation of an alkenes by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. Aldehyde or ketone reacts with stable ylide giving corresponding trans chalcone under mild reaction condition and good yield 82 – 96%.[55-56]

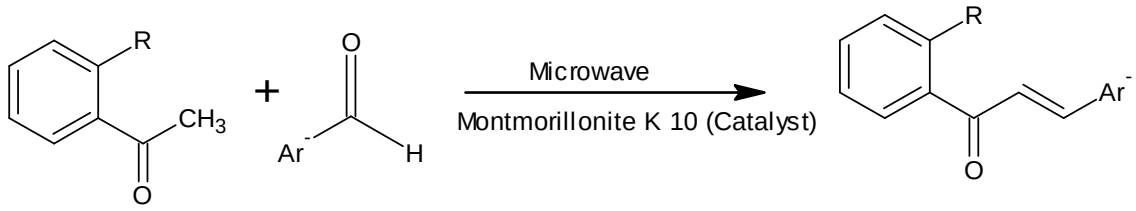


3.3 Conventional way: Increase in inflammation has adverse effect on price cutting. In conventional synthetic methods generally reactions are heated to high temperature, maintained over hours which may result in side reaction i.e. generating impurities that are hard to separate during purification; ultimately yield loss. Conventional batch mode synthesis uses precious solvent and catalyst in multiple volumes which were unable to recover completely. Also for recovery of these requires additional time and utility.

To overcome these problems modern technique required green route that allows mild reaction condition, shorter reaction time, use of less catalyst & solvent or eliminating both, avoiding purification resulting higher yield. These methods are brief below.

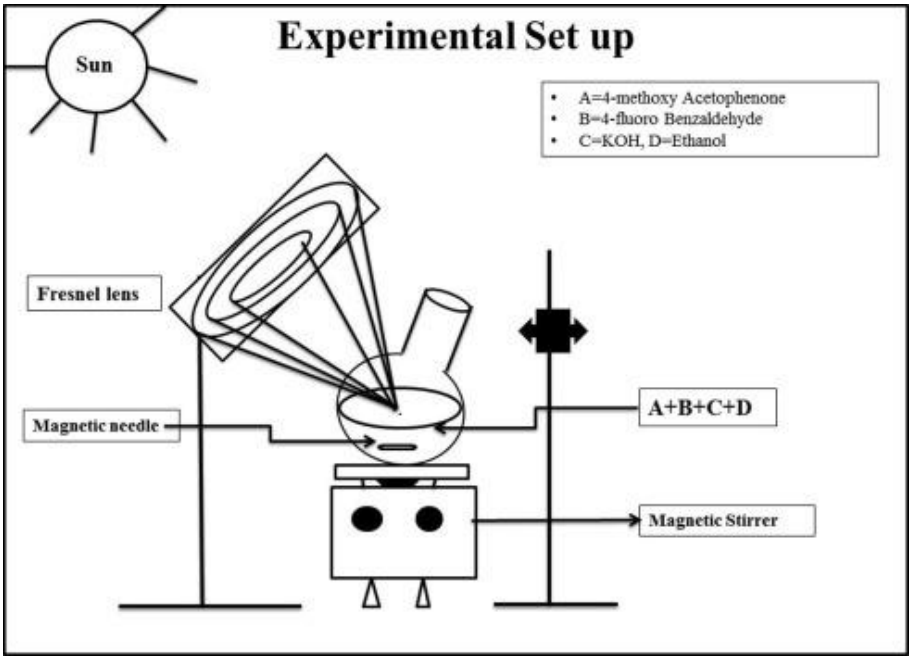


3.3.1 Microwave method: Microwaves can accelerate the reaction rate, provide better yields and uniform and selective heating, achieve greater reproducibility of reactions and help in developing cleaner synthetic routes.[57] Microwave assisted synthesis demonstrated convenience and green route with higher yield and shorter time, solvent free than the conventional method.[58-59]



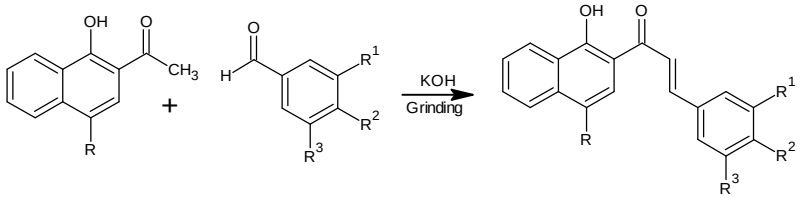
3.3.2 Photochemistry Method: In photochemical reaction, photon is used as reagent to generate radical ion. Photon is either absorbed (and the reaction is activated) or not (and moves out of the vessel). So photon is considered as greenest source since no residues are left at the end of the reaction. Due to high reactivity of radical ion, formation of undesired mixtures of products and the unpredictable course of the reactions together even with the expensive devices. Thus photochemical method are used less both in academia and industries as compared to other method.[60]

Jadhav and colleagues tested this new method by reacting 4-methoxyacetophenone with 4-fluorobenzaldehyde in the presence of potassium hydroxide. CSR (concentrated solar radiation) can be obtained through the Fresnel lens and allows rapid organic synthesis, eventually reaching high temperatures and gaining final compounds in high yields. The advantage of using CSR instead of a classical reaction method is a short-term reaction with a higher yield. The solar radiations include infrared waves that allow the molecules to vibrate and rotate faster. Interestingly, Jadhav group proposed a possible explanation based on the bombardment radiations, giving an increment of energy, which speeds up the reaction itself.[61]

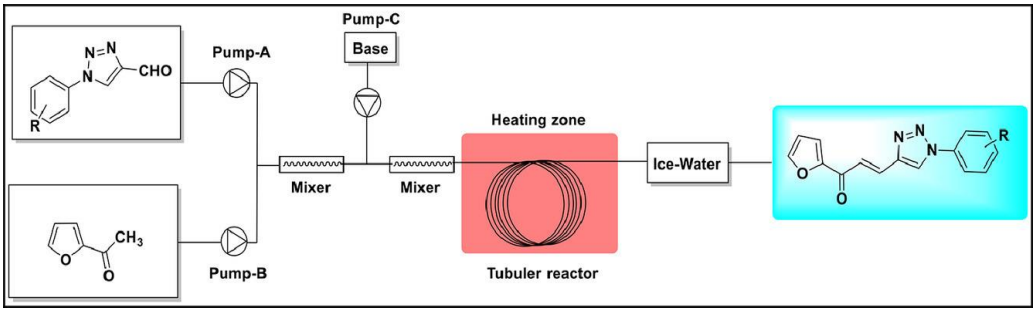


Green approach for the synthesis of chalcone using concentrated solar radiation.

3.3.3 Grinding Method: Mechanochemical activation by griding appears as fast, highly efficient, convenient, versatile, sustainable and eco friendly solvent free method. Mild reaction condition, no need of catalyst, non-hazardous and environmentally safer, giving excellent yield in short reaction time are notable advantages of this method.[62,59]

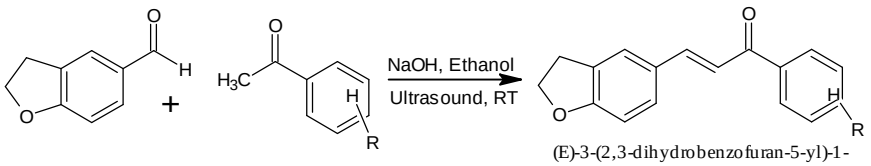


3.3.4 Flow reactor method: Flow chemistry equipment generally consists of pumps that transport reactants, reagents, and solvent into reaction loops that introduce small volumes of reagents. These feed into a mixing junction where reagent streams are combined and passed into a coil reactor to provide reaction residence time. The reaction mixture may be fed into a column reactor that contains solid reagents, catalysts, or scavengers. An inline back pressure regulator controls the system, pressure and inline analytics are often used to provide information about reaction performance. Flow protocol technique offers unique advantages to accelerate, integrate, simplify, scale-up and automatism chemical reactions, in combination with an inherently safer and 'greener' nature over traditional batch-based syntheses.[63]



Continuous-flow synthesis of novel hybrid chalcone derivatives.

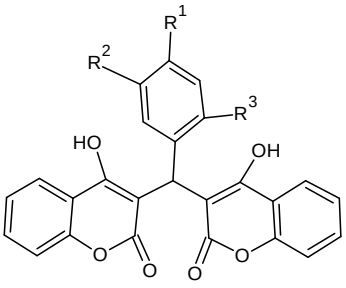
3.3.5 Ultra sound Method: The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic *cavitation*. Cavitation is a process in which mechanical activation destroys the attractive forces of molecules in the liquid phase. Applying ultrasound, compression of the liquid is followed by rarefaction (expansion), in which a sudden pressure drop forms small, oscillating bubbles of gaseous substances. These bubbles expand with each cycle of the applied ultrasonic energy until they reach an unstable size; they can then collide and/or violently collapse. (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives under ultrasound irradiation.[64] In another example, synthesized 2-(5-substituted-furan-2-yl)-4H-chromen-4-ones from furan-substituted chalcones, in dimethyl sulfoxide in the presence of a catalytic amount of iodine under ultrasound irradiation at room temperature conditions resulting higher yields, lower reaction time and simplicity compared to conventional methods.[65]



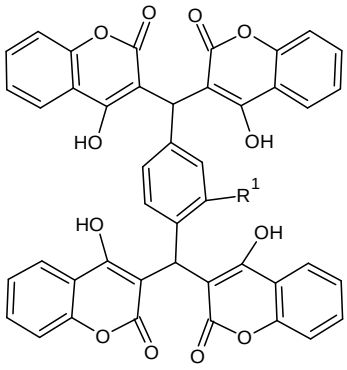
(E)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives

3.4 Chalcone Derivative: The approach involves combining two or more pharmacophoric units to obtain novel compounds with enhanced therapeutic properties and is finding increasing applications in the fields of drug discovery and medicinal chemistry.[66] The synthesis of these hybrids or conjugations typically uses the classical condensation or the synthesis methods discussed above. In addition to the biological activities, hybrid molecules are also selected for as improving the solubility and oral bioavailability.[67] Hybrid molecules have the potential not only to overcome drug resistance but also to exhibit increased activity and enhanced specificity.[68-69] Therefore, hybridization of the chalcone moiety with other pharmacophores is a promising method for developing novel agents.[70]

3.4.1 Chalcone–Coumarin: Coumarins are phenolic substances composed of fused benzene and α-pyrone rings. Kurt B Z et al. (2017) reported novel series of Coumarins chalcone derivatives containing urea moiety was synthesized and screened for their in vitro antiproliferative activities against the cancer cell lines (H4IIE and HepG2).[71] Vazquez-Rodriguez S et al[72] [2015] reported the antibacterial activity of coumarin-chalcone hybrids for the treatment of tenacibaculosis through disk diffusion assay.[72] Zavrsnik D et al.[73] [2008] reported 4-hydroxycoumarin derivatives of dimer and tetramer with good antibacterial and antimycotic activities.

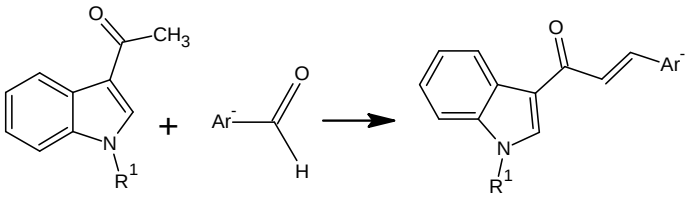


Dimer



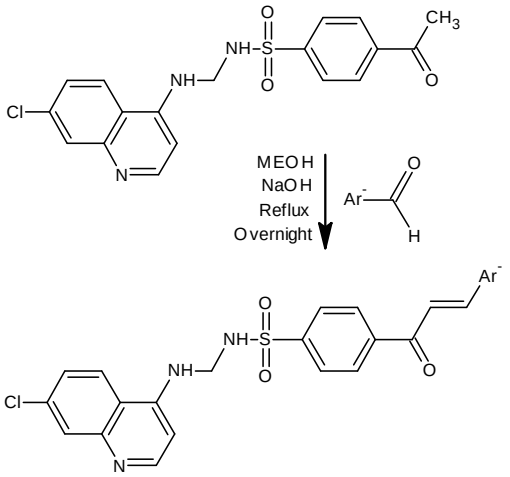
Tetramers

3.4.2 Chalcone–Indole Hybrid: A series of isatin-linked chalcones were successfully synthesized and evaluated for anti-breast cancer.[74] Novel series of chalcones indole hydride as anticancer and antioxidant Activity is described in Zuzana Kudličková et al.[75] New series of N-substituted indole -3-carbaldehyde and their indonyl chalcones as promising antitumor was synthesized by M.A. Zahran and A MIbrahim.[76]

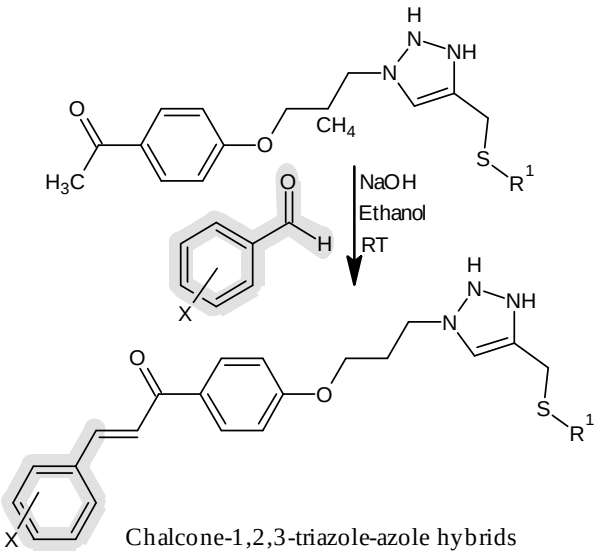


Aryl indolyl propenones

3.4.3 Quinoline–Chalcone Hybrids: Quinoline–Chalcone hybrids were successfully synthesized in good to excellent yields with good antiplasmodial activity.[77] A series of quinoline-chalcone hybrids was synthesized as potential anti-cancer agents.[78]



3.4.4 Chalcone–Azole Hybrids: Azoles are a class of five-member heterocyclic compounds containing a nitrogen atom and at least one other non-carbon atom (i.e. nitrogen, sulfur, or oxygen) as part of the ring.[79] The novel synthesized chalcone-1,2,3-triazole-azole hybrids showed the excellent anticancer activity.[80] Gao F et al mentions the various biological application of Chalcone- Azole hydrides.[81]



Chalcone-1,2,3-triazole-azole hybrids

3.4.5 Chalcones- Schiff base hybrids: The aldehyde/ketone condensed with amines through azomethine linkages to give Schiff base. Among the various types of Schiff bases, the chalcone-based Schiff bases play a vital role in the treatment of various ailments and various applications, which can be synthesized by using different types of chalcones as the starting materials. The various synthetic strategies and biological applications are summarized in Praveen et al[82] 2023. Umit M et al., synthesized Schiff base chalcone derivative for the treatment of epilepsy and Alzheimer's disease.[83]

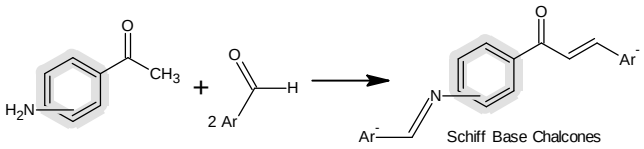


Figure: Chalcone Hydrides.

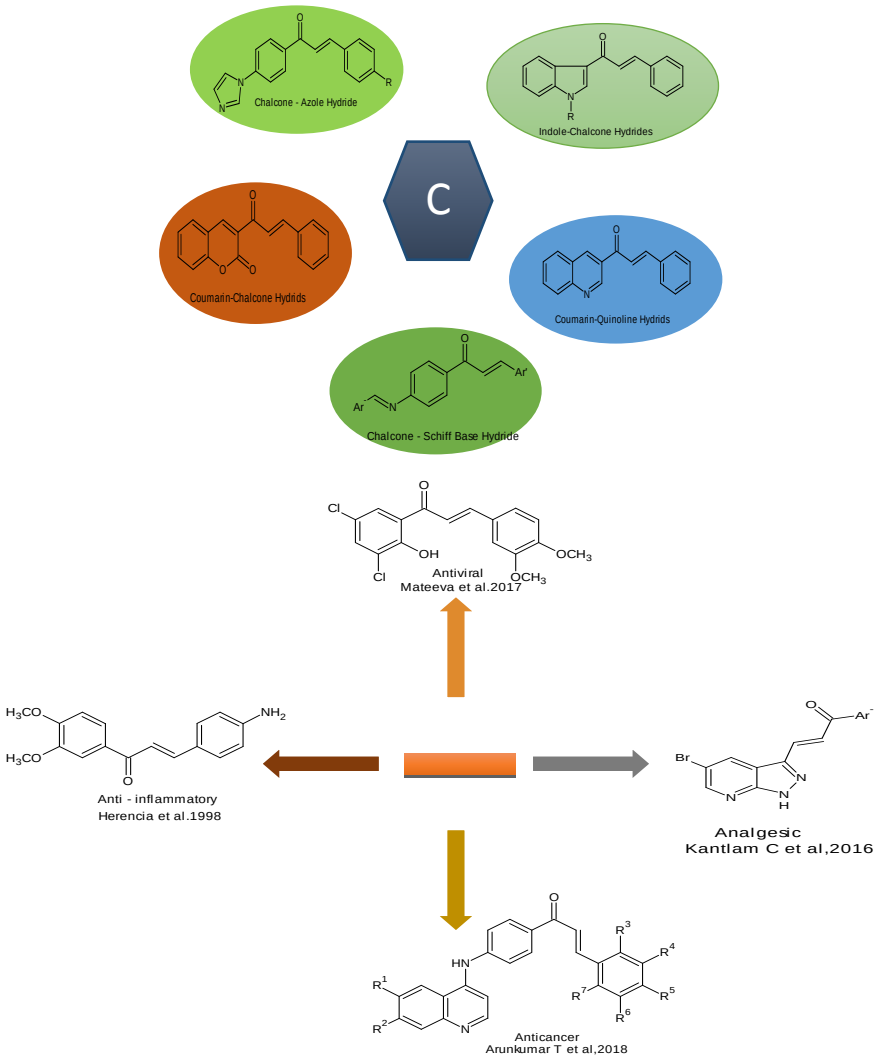


Figure: Biological application of chalcone.

CONCLUSION

Chalcone contain three carbons α, β-unsaturated carbonyl system linked to two aryl rings. Due to his structural blessing chalcones with chalcone analogous had numerous biological applications as well as industrial applications. Conventional synthetic methods such as Microwave, Grinding, Ultrasound, Flow chemistry, photochemistry are beneficial over traditional methods in ways of mild reaction condition, short time, solvent free and higher yield through green chemistry aspect.

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