Int. J. Chem. Sci.: 13(1), 2015, 459-500
ISSN 0972-768X
www.sadgurupublications.com

SYNTHESES AND PHARMACOLOGICAL APPLICATIONS OF CHALCONES : A REVIEW

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ABSTRACT

Chalcones are pharmacologically active compounds, chemically known as derivatives of 1,3-diphenylprop-2-en-1-one. They have found applications as anticancer, anti-diabetics, anti-HIV, antioxidants, antimalarial, anti-tubercular, antiviral, anti-inflammatory and antidiuretic agents. Some chalcones have been reported as inhibitors of lipoxygenase, β-secretase (BACE1), acylcholinesterase (AChE), butyrylcholinesterase (BChE), cyclooxygenase, peroxisome proliferator-activated receptor gamma and Yersinia enterocolitica tyrosine phosphate. The syntheses of various classes of chalcones and their mode of pharmacological applications have been reviewed. The broad pharmacological applications of chalcones, the ease of synthesis and the increased resistance of available chemotherapeutic agent informed this review.

Key words: Alzheimer, Chalcones, Cyclooxygenases, Grinding technology, Lipoxygenase inhibitors, Yersinia.

INTRODUCTION

Chalcone is a generic term given to compounds bearing 1,3-diphenylprop-2-en-1-one framework. Chalcones are also known as phenyl styryl ketones, benzal-acetonephenones, benzylidine acetophenones or alternatively called β-phenyl acrylophenone. They contain reactive keto-ethylinic group (COCH=CH). Chalcones are widely distributed in nature and originally isolated from natural sources e.g. licochalcone A **(1)**, licochalcone D **(2)**,

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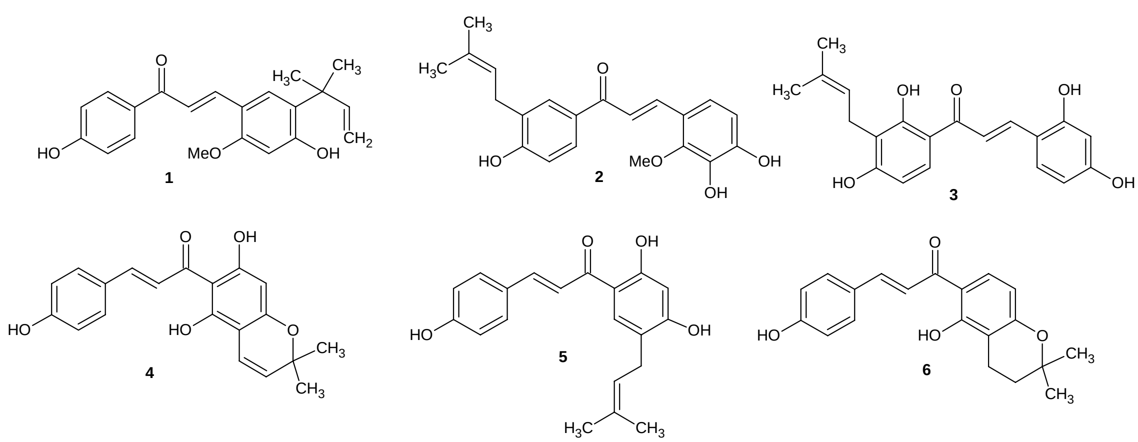
morachalcone A **(3)**. They are naturally occurring bioactive compounds with a 1,3-diarylpropane skeleton belonging to the flavonoid family.

Many chalcones are found to have medicinal and pharmaceutical applications ranging from antitumor[1,2], antispasmodic[3], antiulcer[4,5], antihelmintics[6,7], antibacterial[8,9], cardiovascular[10], antiallergic[11], anticancer[12,13], anti-inflammatory[14,15], antimalarial[16,17], antitubercular[18,19], antiviral[20], fungicidal[21-23], germicidal[24], herbicidal[25] and insecticidal[26-28]. Flavonoids, a group of polyphenolic secondary metabolites have been reported to display a large panel of biochemical properties including antioxidant activity, inhibition of tyrosine kinases, cAMP phosphodiesterases, and induction of phase II metabolizing enzyme both *in vitro* and *in vivo*[29]. Flavonoids like 4-hydroxyonchocarpin **(4)** have been reported to be a good chemopreventive molecule against ovarian cancer cell growth[30]. Isobavachalcone **(5)** and dorsmannin **(6)** isolated from *D. barten* Bureau[31] and *D. mannii*[32] exhibited inhibitiory effect on skin carcinogenesis test[33]. In addition to the medicinal and pharmaceutical applications of chalcones, they have also found application as light stabilizing agent[34], sweetening agent[35], analytical reagent for amperometric estimation of copper[36], spectrophotometric study of germanium[37], and as synthetic reagent for the synthesis of heterocyclic compounds of biodynamic behaviors[38-40].

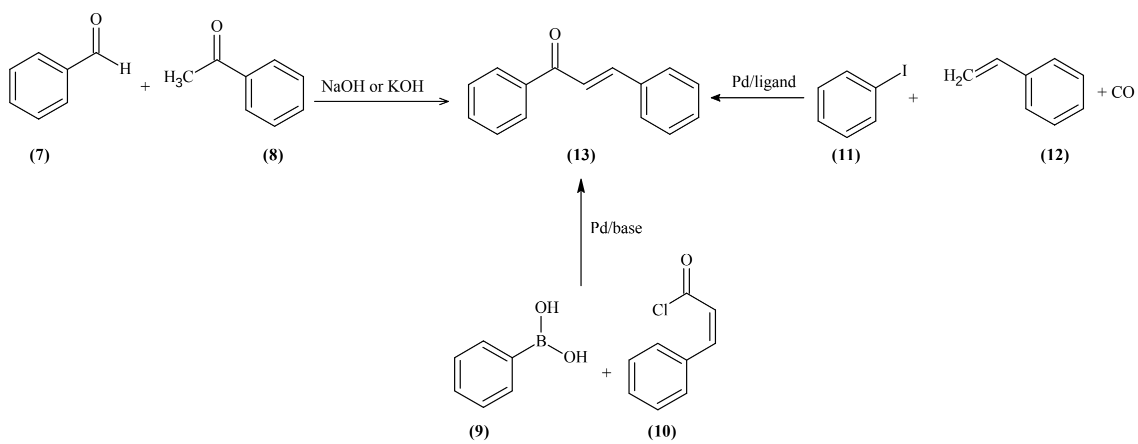


Scheme 1

Chalcones are conventionally synthesized by Claisen-Schmidt (Aldol) condensation reaction in which aldehyde reacted with acetophenone in the presence of aqueous alkaline bases[41], $Ba(OH)_2/LiOH$[42]. Chalcones have also been synthesized using microwave irradiation, ultrasonic irradiation[43] and by Suzuki reaction[44]. Recently, various modified methods for the synthesis of chalcones have been reported using different catalyst such as $SOCl_2$[45], natural phosphate lithium nitrate[46], KF/natural phosphate[47], acyclic acidic ionic liquid[48], Na_2CO_3[49], high temperature water[50], boron trifluoride-etherate $BF_3.Et_2O$[51] and solvent free synthesis[52]. The wide pharmacological application of chalcones, the ease of synthesis, the ever emerging resistance of existing drugs and the need to increase the arsenal of chemotherapeutic agents necessitated this review.

General synthesis of chalcone

Conventionally, chalcones are prepared by simple condensation of simple or substituted aromatic aldehyde **(7)** with simple or substituted acetophenone **(8)** in the presence of alkali. More exotic synthetic protocol involves palladium-mediated Suzuki coupling between cinnamoyl chloride and phenyl boronic acids or the carbonylative Heck coupling between aryl halides and styrenes in the presence of carbon monoxide **(Scheme 2)**.



Scheme 2

Synthesis of anticancer chalcones

Cancer is one the most dangerous, fast propagating with quite high mortality rate disease of present century. It is the leading cause of deaths in economically developed countries and second leading cause of deaths in developing countries[53]. It is considered to be one of the intractable diseases because of the innate characteristics of cancer cells to proliferate uncontrollably, avoid apoptosis, and invade and metastasizes[54]. The importance of tubulin and microtubules in chromosome segregation during cell division makes them attractive targets for anticancer drug designs[55]. The interference of tubulin/microtubule polymerization dynamic has two pivotal anticancer effects: **(i)** inhibition of cancer cell proliferation through interruption of mitotic spindle formation, which leads to apoptosis, and **(ii)** disruption of cell signaling pathways involved in regulating and maintaining the cytoskeleton of endothelial cells in tumor vasculature[56]. Antimitotic agents that interfere with tubulin dynamics act by targeting three different sites on the β-tubulin subunit: the colchicine, the vinca alkaloid and the paclitaxel binding sites[55]. Agents that bind to the colchicine binding site or the vinca alkaloid domain induce depolymerization of tubulin and are therefore defined as inhibitors of tubulin assembly. In contrast, agents that target the paclitaxel binding site are known to stabilize the microtubule cytoskeleton against depolymerisation thereby promoting tubulin assembly (Fig. 1)

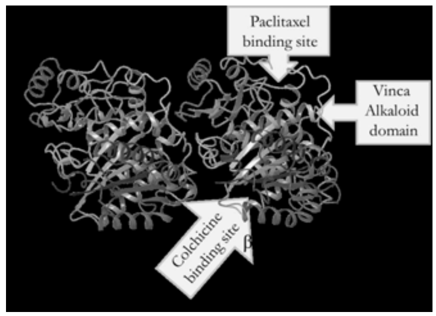
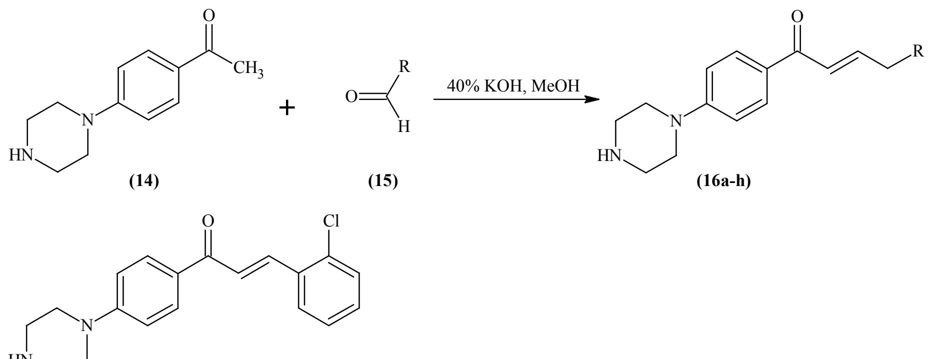


Fig. 1: Tubulin assembly pathway

Most anticancer chalcones acts as cytotoxic or microtubule destabilizing agents, preventing tubulin from polymerizing into microtubules[57-60]. Chalcones bind to the colchicine binding site on β-tubulin, thus inducing depolymerisation of tubulin assembly[60-63]. Besides the interference tubulin assembly, the cytotoxicity of chalcones can originate from other mechanisms involving inhibition of the suppressor protein P53 (leading to dysregulation of the cell cycle in various tumor cell lines), blockage of nitric oxide production (important in macrophage-induced cytotoxicity) and inhibition of cytochrome P450 enzymes that are associated with the activation of procarcinogens[64,65].

Synthesis of 41-piperazino aromatic nucleus containing chalcones

Experimental works supported that chemical compounds with nitrogen containing heterocyclics and chalcones showed anticancer activities against various cell line[66]. Natural and synthetic chalcones have been reported to have strong antiproliferative effects in both primary and established ovarian cancer cells[67] and in gastric cancer HGC-27 cell[68]. Piperazine containing chalcones have been shown to exhibit wide range of pharmacological activities including antihistamine[69], antioxidant, anti-inflammatory[70], antimicrobial[71] and anticancer properties[72]. This reported biological activities prompted Rahaman et al.[73] to synthesize piperazine nucleus containing novel chalcones and studied their *in vitro* anticancer activity. They achieved the synthesis by stirring a mixture of 4^1-piperazino-acetophenone **(14)** (0.001 M) and aryl aldehydes **(15)** (0.001 M) in methanol (10 mL) and adding to it 5 mM of 40% KOH. The mixture was kept for 24 hr and then acidified with 1:1 HCl and water. The product was filtered and washed with water and then recrystallized from ethyl acetate-methanol (8:2) to afford the target compound **(16a-h) (Scheme 3)**.



(14) **(15)** **(16a-h)**

(16g)

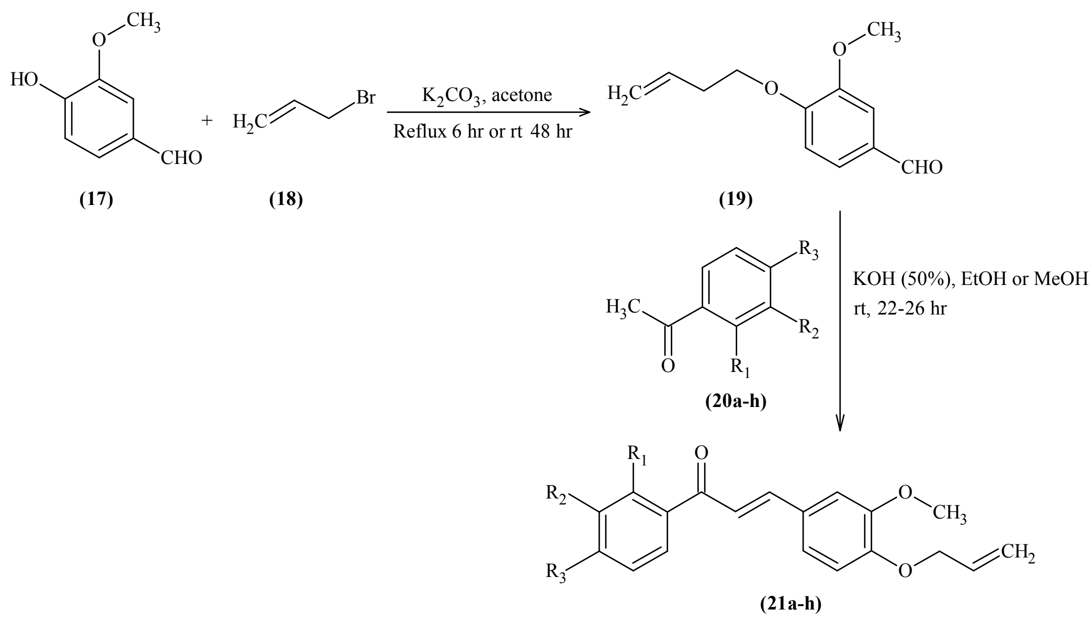
Scheme 3

Only compound **16g** showed significant growth inhibition against brine shrimp after 24 hr incubation. They further studied the growth inhibition action of **16g** against MCF-7 (breast), HepG2 (liver carcinoma), HeLa cells (carcinoma of cervix), carcinoma of brain and carcinoma of colon using MTT assay. The lead compound **16g** was active against the five human cancer cells tested but did not show improvement in activity when compared with tamoxifen.

Synthesis of O-allylchalcones

Chalcones holding allylic substitutions were recently reported as potent antimicrobial and antioxidant agents[74,75]. It has also been reported that substitution in ring B with methoxy or hydroxy groups improved the antiproliferative activity against human colon HT-29 cancer cell line[76]. These revealed activities of allyl chalcones in addition to the general broad biological applications of chalcones prompted Ngameni et al.[77] to synthesize novel *O*-allyl chalcones. They synthesized the allyl chalcones **(21a-h)** by adding to a solution of acetophenones **(20a-h)** in methanol, *O*-allyl vanillin **(19)** and aqueous solution of KOH. The reaction mixture was refluxed at 70°C for 5 hr or at room temperature for 15 hr. After separation and purification of the residue, the product was obtained. The *O*-allyl vanillin **(19)** was synthesized by the reaction of vanillin **(17)** and allyl bromide **(18)** in the presence of K_2CO_3 **(Scheme 4)**.

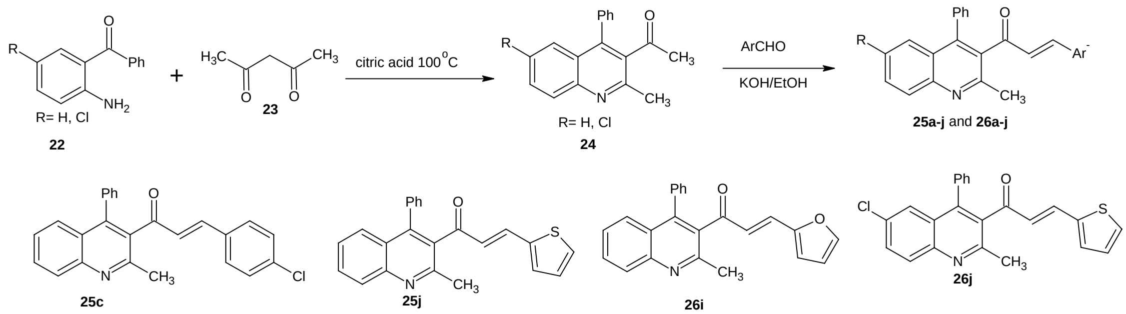
They tested the cytotoxicity of the compounds against five human cancer cell lines THP-1, HL60, HepG-2, DU-145 and MCF-7. Following US NCI screening program, which states that a compound is considered to have in vitro cytotoxicity activity if the IC_{50} value following incubation between 48 and 72 his less than 4 µg or 10 µM[78], the following compounds were considered to have cytotoxicity: compounds **21f** and **21g** (IC_{50} 10.42 and 4.76 µM) against THP-1 cell, compound **21g** also had cytotoxicity effect on DU-145 (IC_{50} 5.21 µM), HL60 (IC_{50} 7.90 µM), HepG-2 (IC_{50} 10.12 µM) and MCF-7 (IC_{50} 10.32 µM). Their work revealed compound **21g** as a good anticancer agent given its comparable IC_{50} values with doxorubicin.



Scheme 4

Synthesis of quinolinyl chalcones

The quinolinyl chalcones have been reported to show wide range of biological activities[79-85]. In view of these and the need to develop new, simple and potential anticancer agents spurred Kotra et al.[86] to synthesize new series of quinolinyl chalcones with anticancer property. To obtain the quinolinyl chalcones, a mixture of substituted *O*-amino benzophenone **(22)** with β-keto ester **(23)** and citric acid under solvent free condition was heated at 100°C. The substituted quinolines **(24)** were extracted with ethyl acetate and purified using column chromatography. They stirred mixtures of ethanolic solution of the substituted quinolines **(24)** and different substituted aromatic aldehydes in alkaline medium of KOH at room temperature for 24 hr to obtain the quinolinyl chalcones **(25a-j)** and **(26a-j)** **(Scheme 5)**.

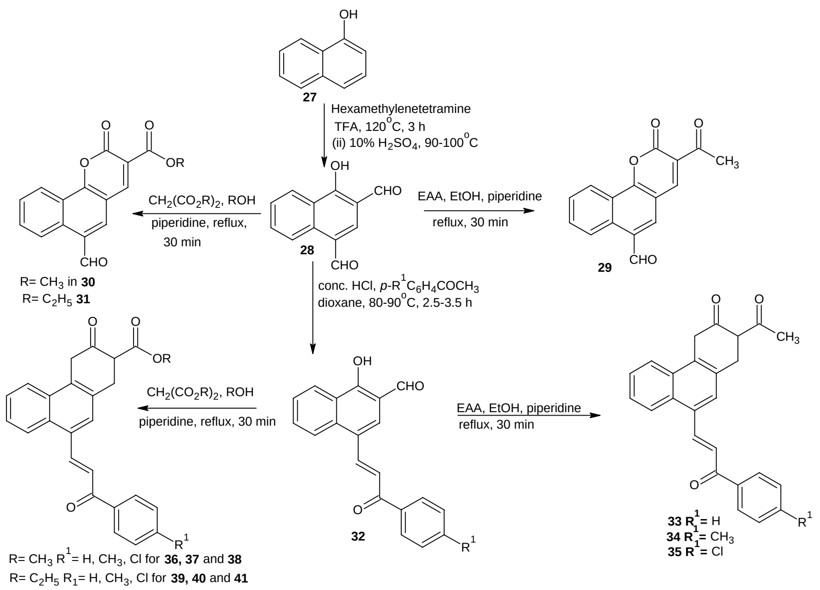


Scheme 5

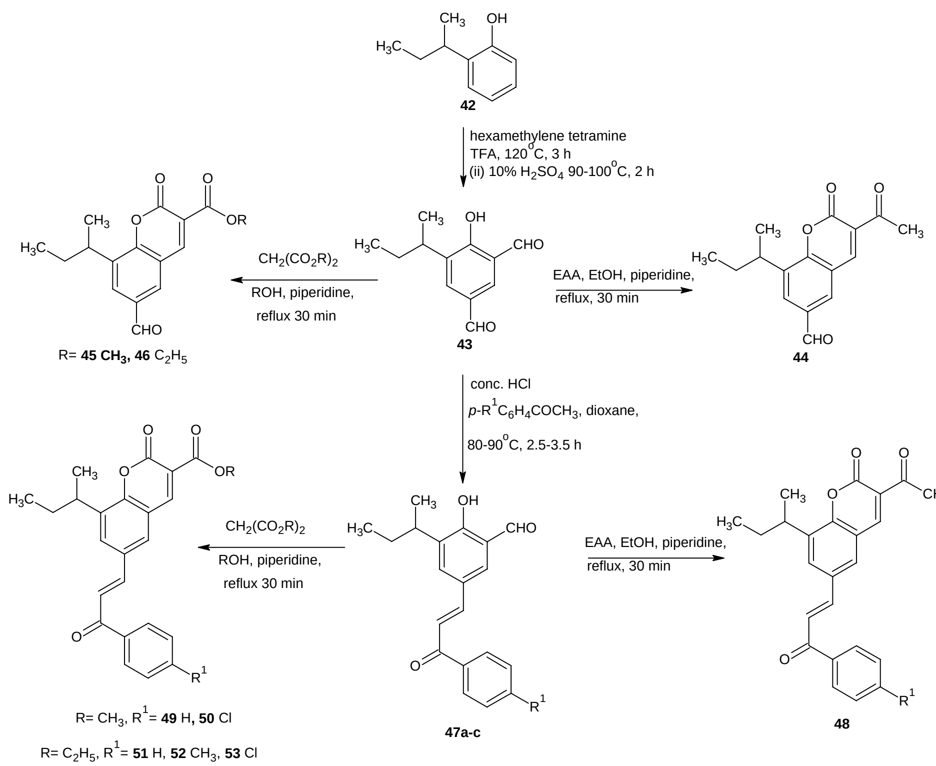
The cytotoxicity studies revealed compound **25c**, **25j**, **26i** and **26j** as having percentage inhibition of 103, 101.59, 100.20 and 100.16 against raw cell lines.

Synthesis of coumarin chalcones

Coumarins belong to the flavonoid class of plant secondary metabolites, which have been found to exhibit a variety of biological activities like anti-HIV[87], anticoagulant[88], antibacterial[89], antioxidant[90], and dyslipidemic activities[91]. Yizhou et al.[92] recently reported coumarin containing compounds that showed significant inhibition against two ER+ human breast cancer cell lines, having 10 fold more potent and 20 fold more selective than tamoxifen. In view of this, Sashidhara et al.[93] synthesized coumarin based chalcones and investigated their cytotoxicity effect against oral squamous cell carcinoma (Kβ), cervical carcinoma (C33A), breast adenocarcinoma (MCF-7), lung carcinoma (A549) and mouse embryo fibroblast (NIH3TS). They synthesized the coumarin chalcone hybrids using Duff reaction of naphthalen-1-ol (**27**) to produce compound **28** which undergo Knoevenagel-type reaction with different active methylene compounds to produce coumarinic compounds **29-31**. They also found that compound **28** on reaction with different acetophenone in refluxing dioxane in the presence of a catalytic amount of concentrated HCl gave regioselective para-condensed chalcones **(32a-c)**. Compounds **(32a-c)** on subsequent Knoevenagel-type condensation with different active methylene compounds furnished coumarin-chalcone hybrids **(33-41)** (**Scheme 6**). Similarly, they prepared another series of chalcones using 2-sec-butylphenol **(42)** which was subjected to similar protocol used in synthesizing compounds **(29-31)** and **(33-41)** to obtain coumarinic compounds **(44-46)** and coumarinic-chalcone hybrids **(48-53) (Scheme 7)**.



Scheme 6

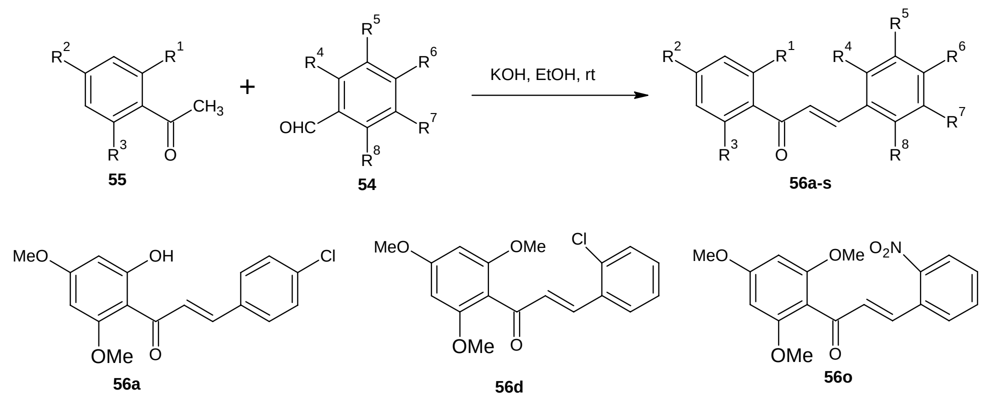


Scheme 7

Using US NCI [79] recommendation, only compounds **(49-53)** had cytotoxicity effect with IC_{50} of 6.28, 5.90, 8.12, 3.59 and 4.54 μM, respectively against C33A.

Synthesis of substituted diaryl chalcones

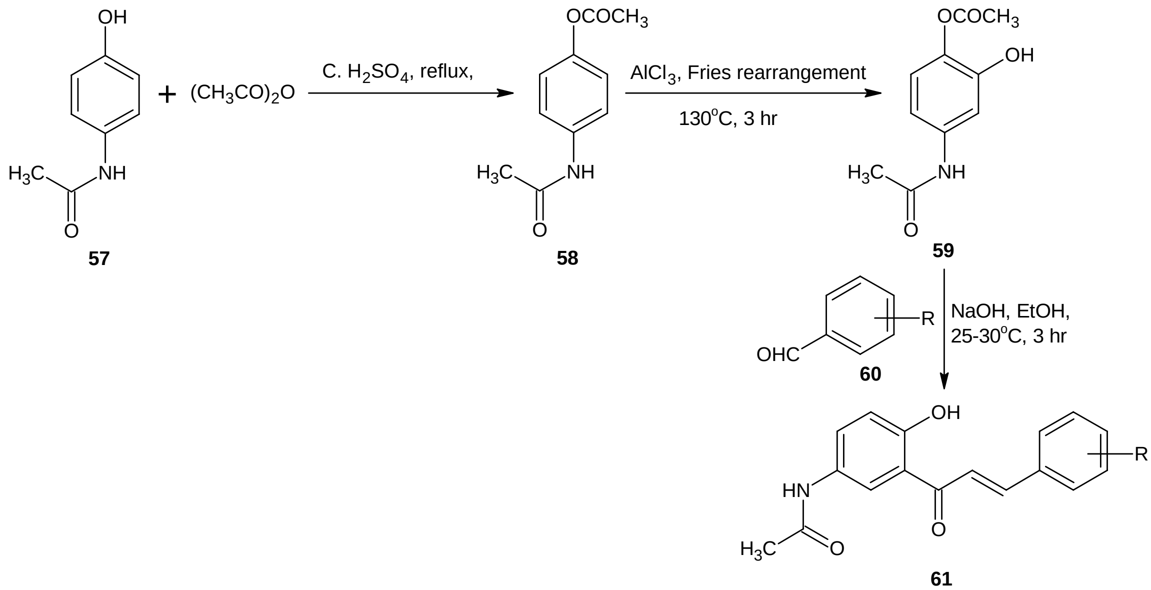
Vankadari et al.[94] synthesized novel aromatic chalcones with *in vitro* anticancer property. They achieved the synthesis following Claisen-Schmidt condensation of the appropriate aldehydes **(54)** and substituted acetophenone **(55)** using ethanol as solvent in the presence of pulverized potassium hydroxide at 5-10°C in ice bath **(Scheme 8)**.



Scheme 8

The compounds were found to be active against human T-lymphocyte leukemia (jurkat) and HL-60 human leukemia cell lines. Compound **56d** and **56o** were the only compound that had better cytotoxicity effect against Jurkat when compared with the parent compound (IC_{50} 0.016 mM, 0.017 mM and 0.018 mM respectively for compounds **56d, 56o** and the parent compound (**56a**)).

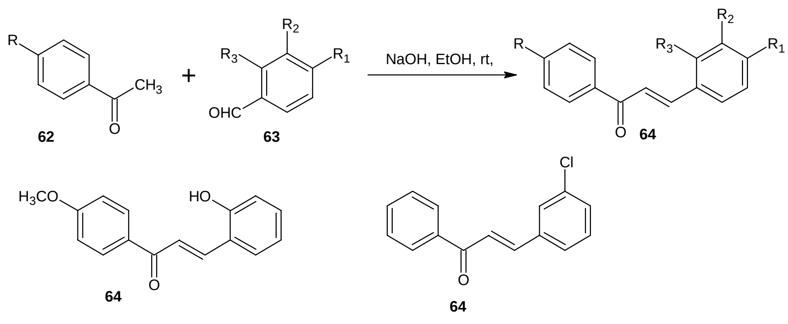
Ilango et al.[95] also reported the synthesis of substituted chalcones with anticancer potential. They prepared *O*-acetyl-*p*-acetamido phenol **(58)** by reacting a mixture of paracetamol **(57)**, acetic anhydride and concentrated sulphuric acid in a 250 mL round bottom flask equipped with a reflux condenser on a water bath at 50-60°C for 15 min. The compound **(58)** was obtained after filtration. Compound **(58)** was added drop wisely on anhydrous $AlCl_3$ and the mixture heated at 130°C for 3h. To the cooled reaction mixture, crushed ice was added and after extraction and purification 5-acetamido-2-hydroxy acetophenone **(59)** was obtained. The substituted chalcones were synthesized by reacting appropriate aldehydes **(60)** with compound **(59)** in the presence of NaOH, water and ethanol at 25-30°C for 3.5 hr **(Scheme 9)**.



Scheme 9

The *in vitro* activities of the compounds against two breast cancer cell lines MCF-7 and T47D were ascertained. The result indicates that all the compounds were active but not comparable with doxorubicin. The interesting thing in this research is that the compounds prepared had comparable activity against the two breast cancer cell lines.

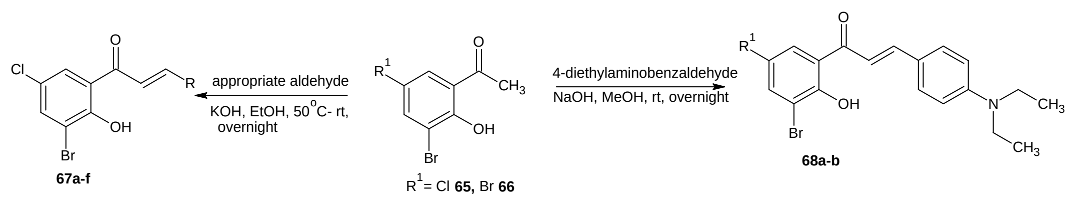
Suvitha et al.[96] synthesized twenty five chalcone derivatives of anticancer importance. Substituted acetophenone **(62)** and substituted aldehyde **(63)** were mixed in ethanol in a round bottom flask placed in an ice bath. To this mixture, they added sodium hydroxide drop-wisely with continuous stirring for 30 min and then for 2-3 hr at room temperature. They obtained the pure product **(64)** after leaving the mixture in a refrigerator overnight and recrystallized from rectified methanol **(Scheme 10)**.



Scheme 10

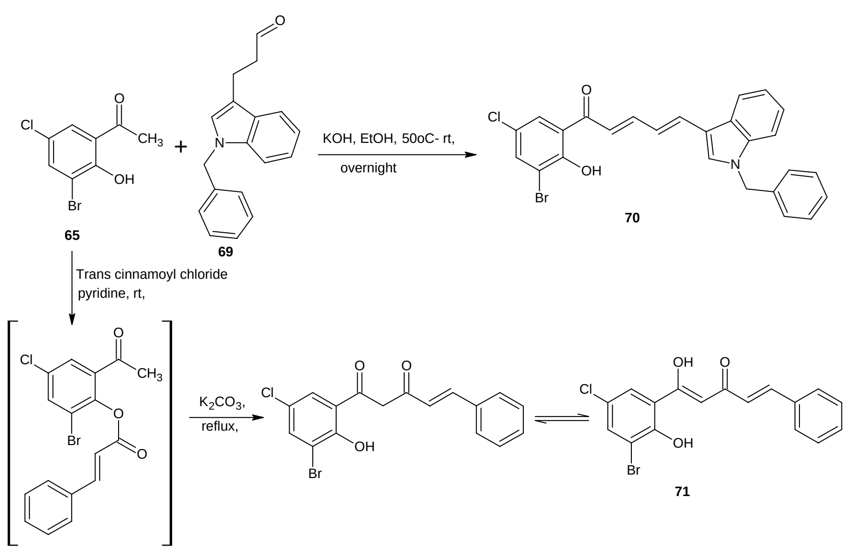
The compounds were tested against MCF-7 (breast), A549 (lung), PC3 (prostate), HT-29 (colorectal) and WRL68 (liver) cancer cell lines. Compounds **64a, 64c, 64j, 64k, 64l, 64m, 64u, 64w, 64x** and **64y** showed cytotoxicity < 20 µg/mL against all cancer cells. Except in the case of PC3, compound **64y** was the most active with IC_{50} of 14.49, 5.251, 7.772 and 7.20 µg/mL for A549, MCF-7, HT-29 and WRL68 cancer cell line, respectively. Compound **64x** had the highest activity against PC3 with IC_{50} of 5.584 µg/mL.

Christine[97] synthesized chalcones via Claisen-Schmidt condensation of 3^I-bromo-5^I-chloro-2^I-hydroxyacetophenone **(65)** and various aromatic or conjugated aldehydes with electron withdrawing or donating properties in the presence of potassium hydroxide in ethanol **(Scheme 11)**.



Scheme 11

They also synthesized dihalogenated dienone **(70)** via Claisen-Schmidt condensation of dihalogenated-2-hydroxyacetophenone **(65)** and the enol tautomer **(71)** from compound **(65)** via esterification with cinnamoyl chloride, followed by a base catalyzed intra molecular Baker-Venkataraman rearrangement (**Scheme 12**).



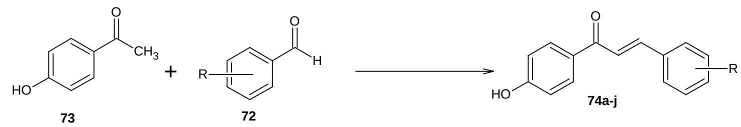
Scheme 12

They assessed the anti-proliferative activities of the chalcones using fluorometric microculture cytotoxicity assay (FMCA) against ten human cancer cell lines: RPMI 8226 (myeloma), CCRF-CEM (leukemia), U937-GTB (lymphoma), NCI-H69 (small cell lung cancer) along with drug resistant 8226/DOX40 (doxorubicin resistant myeloma), 8226/LR5 (melphalan resistant myeloma), CEM/VMI (teniposide resistant leukemia), U937/Vcr (vincristine resistant lymphoma), H69AR (doxorubicin resistant lung cancer) and primary resistant ACHN (renal adenocarcinoma) cell line. Compound **(68a)** and **(68b)** had the best cytotoxicity activity. The polymerization activity of the chalcones revealed that compounds **(67b)**, **(67e)** and **(71)** showed no significant activity toward tubulin assembly suggesting a different mechanism for their cytotoxicity effect. Other chalcones in exception of compound **(70)** displayed tubulin destabilizing activity. Compound **(70)** displayed microtubule stabilizing activity comparable to the established antimitotic chemotherapeutic drug docetaxel. Compound **(70)** so far is the first reported chalcone with microtubule stabilizing activity.

Synthesis of anti-inflammatory chalcones

Inflammation is produced due to the liberation of endogenous mediators like histamine, serotonin, bradykinin, prostaglandin etc in the body. Prostaglandins indicate and modulate cell and tissue responses involved in inflammation and even in small quantities can elicit pain response. The existence of two cyclooxygenase COX-1 and COX-2[98], that are regulated and expressed differently which are responsible for production of prostaglandins were detected independently during early 1990s. It was found that COX-1provided cyto protection in the gastrointestinal tract (GIT), whereas inducible COX-2 selectivity mediates inflammatory signals. NSAID's are widely used for treating pain and inflammation by blocking the metabolism of arachidonic acid through the enzyme cyclooxygenase. The discovery of COX-2, expressed in response to inflammatory stimuli, present in the CNS, not in the gastric mucosa has provided a unique opportunity to develop NSAIDs that lack the ulcerogenic effect[99]. Thus, it has led to the hypothesis that selective inhibitor of COX-2 over COX-1may be better anti-inflammatory agent with less adverse effects than the classical NSAIDs.

Visagaperumal et al.[100] synthesized 4-hydroxychalcones using microwave assisted synthesis and conventional methodologies. They reacted equimolar quantities of substituted benzaldehydes **(72)** and 4-hydroxyacetophenones **(73)** dissolved in alcohol with 3-4 drops of concentrated sodium hydroxide. The chalcones were obtained after stirring for 2-3 hr and leaving the mixture overnight in a refrigerator. The microwave assisted synthesis was achieved simply by irradiating the reaction mixture with 160-320 W radiation for 60-120 sec **(Scheme 13)**.

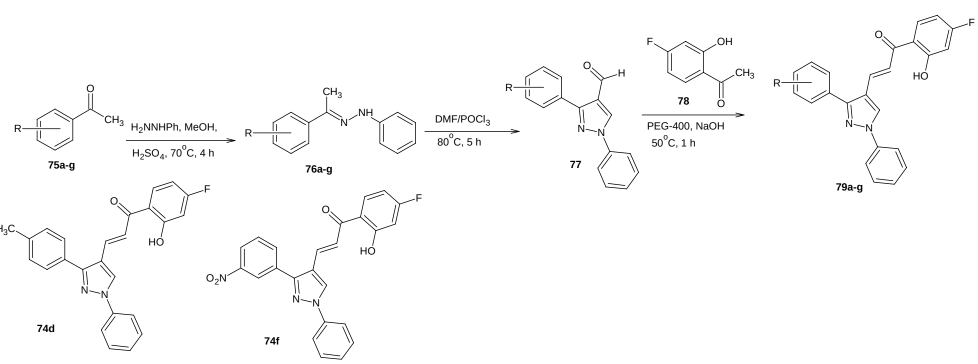


Scheme 13

They tested the anti-inflammatory activity of the chalcones and found that all the chalcones showed the inhibition of edema ranging from 4.6 to 8.05 % as against 74.71 for indomethacin showing that they had insignificant anti-inflammatory effect. The most active was compound **(74d)** with 8.05% inhibition.

Synthesis of fluoro-hydroxy substituted pyrazolechalcones

Pyrazole chalcones and their derivatives have been reported to possess antiinflammatory, analgesic, antimicrobial, antitumor, antioxidant and xanthenes dehydrogenase[101-105]. As earlier pointed out, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and indomethacin inhibits the activities of both COX-1 and COX-2, a property that accounts for their shared therapeutic and side effects[106]. Following the side effects of the lead anti-inflammatory agents, it is pertinent that a new NSAIDs with good inhibition of COX-2 than COX-1 be developed. In answer to this, Bhosale et al.[107] synthesized fluoro-hydroxy substituted pyrazole chalcones and tested their antiinflammatory activities. In their synthesis, a mixture of substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes **(77)** was first prepared by the reaction of substituted acetophenones **(75)** with phenyl hydrazine in the presence of methanol and sulphuric acid at 70^{o}C for 4 hr to obtain compound **(76)** which was subsequently treated with DMF/$POCl_3$ at 80^{o}C for 5 hr to obtain compound **(77)**. Compound **(77)** and 4-fluoro-2-hydroxyacetophenone **(78)** was dissolved in polyethylene glycol PEG-400. Sodium hydroxide was added to the mixture and then stirred for 1 hr at 40-50^{o}C. The product **(79)** was obtained after pouring the reaction mixture into 100 mL of ice and subsequent filtration **(Scheme 14)**.



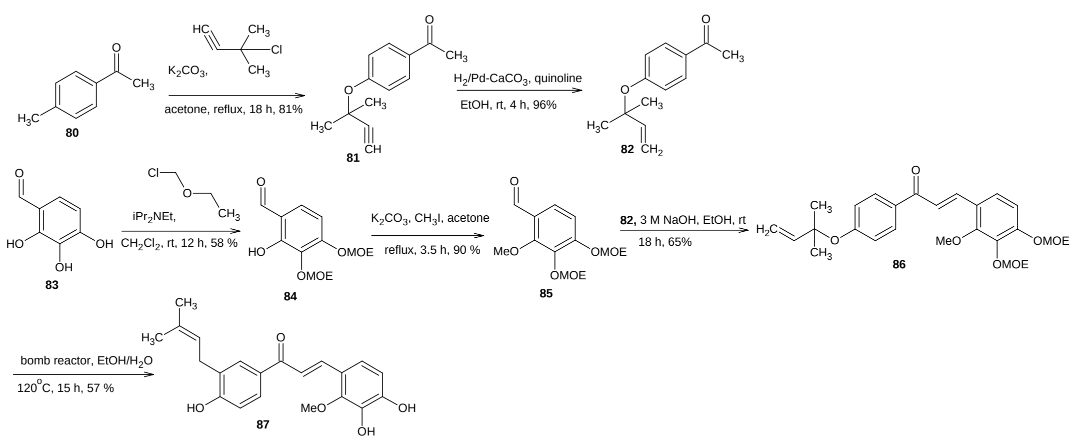
Scheme 14

The inhibition study against COX-1 and COX-2 revealed that in exception of compound **(79a)** and **(79e)** other chalcones had greater inhibition of COX-2 unlike the standard that had higher inhibition of COX-1. Compound **(79d)** and **(79f)** had two fold and three fold inhibition of COX-2: COX-1 (53.83: 28.29 and 46.58: 14.46 respectively for COX-2: COX-1 inhibition) unlike the standard COX-2: COX-1 inhibition of 28.24: 63.87.

Synthesis of licochalcones

Licochalcones separated from licorice has been reported to possess various biological activities such as chemopreventive[108], antibacterial[109], antimalarial[110], antispasmodic[111], anti-inflammatory[112], cytotoxic effect[113] etc.

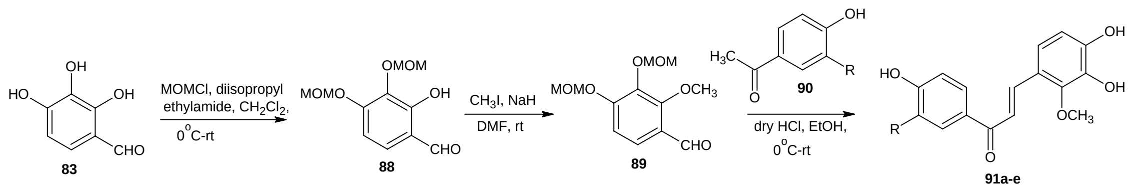
Kim and Jun[114] reported for the first total synthesis of licochalcone D. They treated 4-hydroxyacetophenone **(80)** with 3-chloro-3-methyl-1-butyne in the presence of a base to obtain compound **(81)** which was subsequently reduced to acetonephenone **(82)** using Lindlar catalyst. They protected 2,3,4-trihydroxybenzaldehyde **(83)** using 1.8eq each of diisopropryl ethylamine (DIPEA) and chloromethyl ethyl ester (CIMOE) to give 3,4-diethoxy methyletherbenzaldehyde **(84)**. Compound **(84)** was methylated with methyl iodide in basic condition to produce methoxybenzaldehyde **(85)**. Claisen-Schmidt condensation of the acetophenone **(82)** and the aldehyde **(85)** with 3 M NaOH in ethanol smoothly produced the chalcone **(86)**. The water-accelerated [3,3]-sigmatropic rearrangement of chalcones **(86)** successfully transformed to licochalcone D in a bomb reactor at 120^{o}C with ethanol/water solvent system **(Scheme 15)**.



Scheme 15

Wang et al.[115] reported a short and efficient synthesis of licochalcone B and D using acid-mediated Claisen-Schmidt condensation for biological activities of licochalcone D.

They accomplished the synthesis by selectively protecting 3- and 4-hydroxy groups in 2,3,4-trihydroxy benzaldehyde **(83)** using methoxymethyl (MOM) ether to give compound **(88)**. The 2-hydroxyl group of compound **(88)** was methylated using methyl iodide and NaH in DMF to give compound **(89)**. Claisen-Schmidt condensation of compound **(89)** and **(90)** under acidic condition gave the licochalcone B and D without further deprotection **(Scheme 16)**.

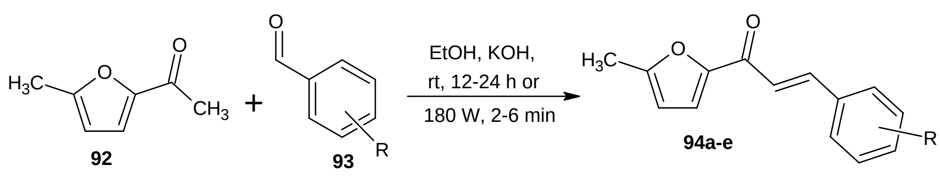


Scheme 16

Synthesis of antioxidant chalcones

Oxidative damage is implicated in various pathological events such as cancer and aging is induced by free radicals and reactive oxygen species[116]. Antioxidants are compounds that prevent oxidative damage due to their free radical scavenging ability[116]. In chalcones, such ability is attributable to phenolic –OH group attached to the ring structures[117]. Allylic substituted chalcones and pyrazolic chalcones have been reported to possess antioxidant and antimalarial activities[118-121].

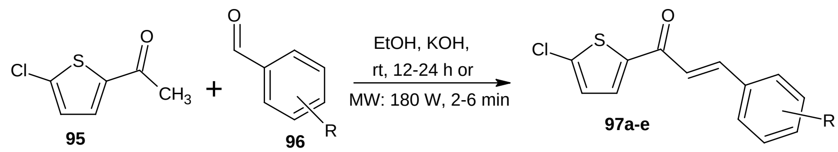
Ahmed et al.[122] synthesized new chalcone derivatives using conventional and microwave irradiation. The Claisen-Schmidt condensation of 2-acetyl-5-methylfuran **(92)** and respective aldehydes **(93)** using alcohol in the presence of potassium hydroxide was mixed with occasional stirring for 24 hr at room temperature. The microwave assisted synthesis was simply by the use of radiation of 180 W for 2-6 min **(Scheme 17)**.



Scheme 17

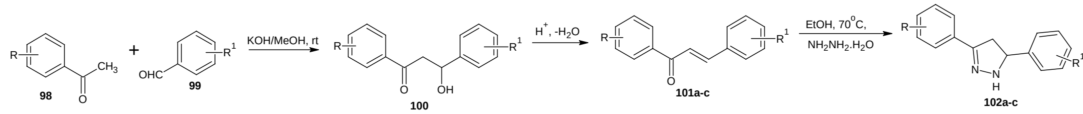
The *in vitro* antioxidant activity and scavenging effects of the chalcones using 1,1-diphenyl-2-picrylhydrazyl (DPPH). The IC_{50} indicates that none of the chalcones had comparable antioxidant effect with the standard.

Ahmed et al.[123] synthesized novel derivatives of chalcones with antioxidant activity. They reacted equimolar quantities of 2-acetyl-5-chloro-thiophene **(95)** and respective aldehydes **(96)** in minimum amount of alcohol and aqueous potassium hydroxide solution for 24 hr at room temperature. After extraction and purification, the chalcones **(97a-e)** was obtained. The microwave irradiation method employed the same reagents but instead of room temperature, the reaction was irradiated for 2-6 min at 180 W **(Scheme 18)**.

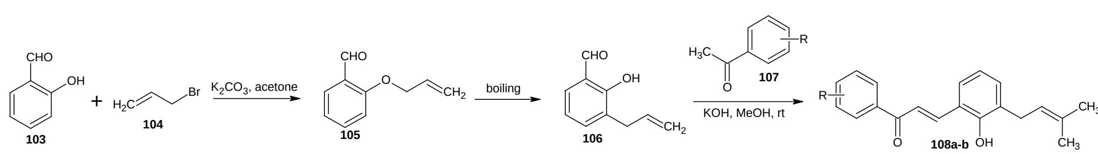


Scheme 18

The IC_{50} revealed that none of the derivatives were more active than conventional antioxidant ascorbic acid. Doan and Tron[124] synthesized novel series of chalcones, pyrazolic chalcones and allylic chalcones and screened them for antioxidant activity against DPPH radical scavenging activity. They synthesized chalcones **(101a-c)** by Claisen-Schmidt condensation of respective acetophenone **(98)** and benzaldehyde **(99)** in the presence of aq. KOH and methanol at room temperature. The chalcones (**101a-c)** were subsequently converted to corresponding pyrazolic chalcones **(102a-c)** by the addition of hydrazine hydrate in absolute ethanol to the corresponding chalcones **(101a-c) (Scheme 19)**. **The** allylic chalcones **(108a-b)** were synthesized using 2-allyloxybenzaldehyde **(105)** which was prepared by the reaction of salicylaldehyde **(103)** and allyl bromide **(104)** in the presence of potassium carbonate in anhydrous acetone. Compound **(105)** undergoing Claisen thermal rearrangement gave 2-hydroxy-3-allylbenzaldehyde **(106)**. Claisen-Schmidt condensation of compound **(106)** and respective acetophenone **(107)** in the presence of KOH and methanol at room temperature gave compound **(108a-b) (Scheme 20)**.



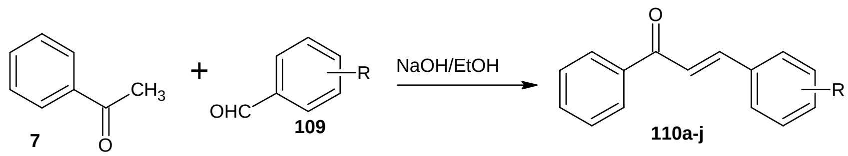
Scheme 19



Scheme 20

Their antioxidant result revealed that compounds **(101a-c)** were inactive whereas their pyrazole derivatives were the most active with compounds **(102a)** and **(102b)** having comparable antioxidant activity with vitamin C. (% DPPH scavenging activity: 89.64, 89.27 and 97.92, respectively for compound **(102a)**, **(102b)** and vitamin C).

Sandip et al.[125] using conventional Claisen-Schmidt condensation synthesized some derivatives of chalcones with antioxidant property. Their synthesis was achieved using substituted benzaldehydes **(109)** and acetophenones **(7)** in the presence of methanol and sodium hydroxide at room temperature for 45 min **(Scheme 21)**.



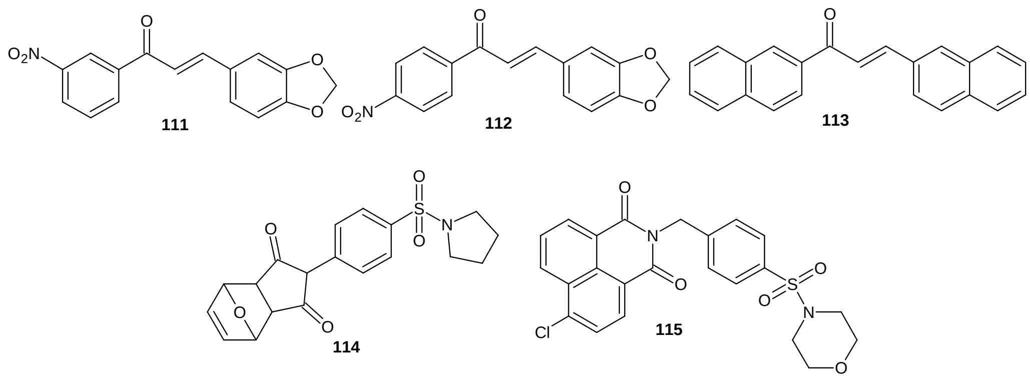
Scheme 21

The IC_{50} of the compounds showed that even though they were all potential antioxidant, none were comparable with vitamin C.

Synthesis of Yerinia enterocolitica YopH tyrosine phosphate inhibitors

Protein tyrosine phosphatases (PTPs) are an important class of enzymes that together with protein tyrosine kinases (PTKs) control the level of phosphorylation plays a critical role in signal transduction of many cellular events including immune response, metabolism, growth and gene transcription[126]. Yersinia genus are responsible for human diseases, causing different pathologies from gastrointestinal sydromes to sepsis[127]. The three pathogenic specie of Yersinia has one extra chromosal plasmid of 70kb, which is essential for their virulence[128]. This plasmid encodes the Yop (Yersinia outer protein) effector proteins and also the proteins forming the type III secretion apparatus[129]. YopH is a 51kDa protein tyrosine phosphatase that is crucial and required for Yersinia pathogenesis[130,131]. The *N*-terminal domain of this protein is accountable for substrate recognition[132] while the *C*-terminal domain has the catalytic site which is structurally similar to the eukaryotic PTPs[133]. YopH can also avoid the adaptive immune response by impairing T and B lymphocyte activation[134]. Since the pathogenicity of Yersinia specie is closely related to the activity of YopH, this enzyme is a promising target for therapeutic interventions against diseases provoked by these bacteria. Several compounds have been reported as effective YopH inhibitors, eg. α-keto carboxylic acid, aurin tricarboxylic acid, tripeptides, furanyl-salicylate derivatives, oxalyl derivatives etc[135-140].

Martins et al.[141] reported the % YopH inhibition and IC_{50} of nine chalcones, two sulphonamide and sulphonyl hydrazone. Their work revealed that at 25 μM, compound **(112)**, **(113)**, **(114)** and **(115)** had the best % inhibition of 65.5, 66.9, 76.4 and 82.1 respectively. The IC_{50} values revealed that only compound **(114)** and **(111)** had good IC_{50} values of 9.0 and 9.9 μM, respectively **(Scheme 22)**.

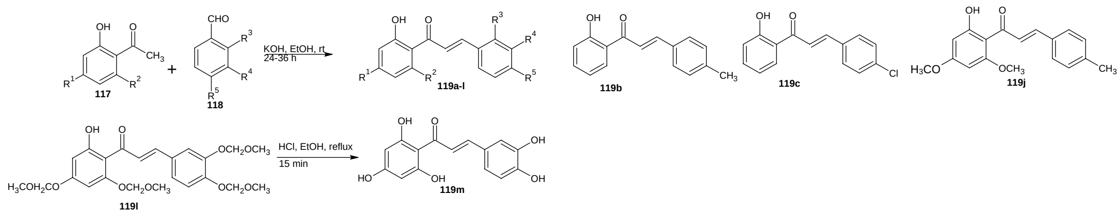


Scheme 22

Synthesis of lipoxygenase (LOX) inhibitors

Lipoxygenases are iron-containing enzymes widely distributed in plant and animals. They catalyse the oxidation of polyunsaturated fatty acids such as linoleic acid (plant) and arachidonic acid (mammals) at specific positions to hydroperoxides. Lipoxygenase inhibitors are of interest due to the implication of the enzyme to various pathophysiological conditions. Lipoxygenase plays a key role in the biosynthesis of leukotrienes, the proinflammatory mediators mainly released from myeloid cells. This implies that inhibitors of lipoxygenases could be potential agent for treatment of inflammatory and allergic diseases. The application of lipoxygenase inhibitors has recently been expanded to certain types of cancer and cardiovascular diseases[142-145]. The majority of lipoxygenase inhibitors are antioxidants or free radical scavengers, since lipoxygenation occurs via a carbon centered radical and therefore these compounds can inhibit radical formation or trap it once formed[146,147].

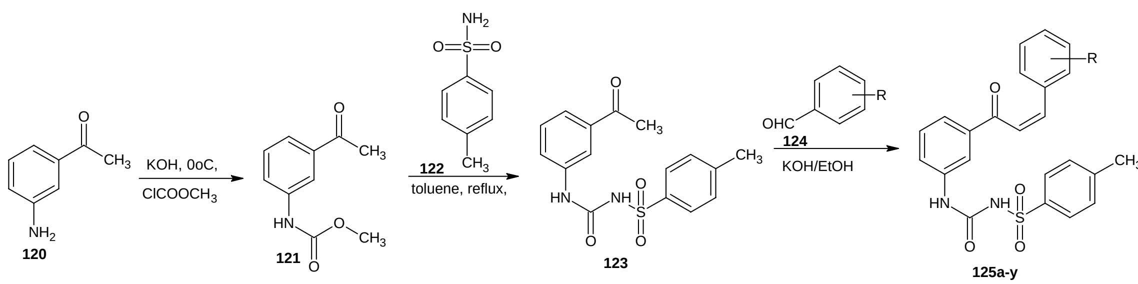
Detsi et al.[148] synthesized 2-hydroxychalcones and evaluated their inhibitory activity against soybean lipoxygenase. They synthesized 2-hydroxychalcones **(119a-m)** via Claisen-Schmidt condensation reaction between appropriate 2-hydroxyacetophenones **(117)** and benzaldehydes **(118)** in a basic medium. Compound **(119m)** which is a naturally occurring chalcone was synthesized from compound **(119l)** by simply removing the MOM (stable in basic medium) with acid by refluxing compound **(118l)** with 10% aqueous HCl in methanol for 15 min **(Scheme 23)**.



Scheme 23

The lipoxygenase inhibition revealed compounds **(119b)**, **(119c)** and **(119j)** as the most potent having IC_{50} of 52.5, 56 and 53 µM, respectively. This result is comparable with nordihydroguaiacetic acid (IC_{50} 40 µM) and far better than caffeic acid (IC_{50} 600 µM).

Bugata et al.[149] synthesized novel diaryl sulphonylurea-chalcone hybrids and screened their lipoxygenase inhibition activity. They treated 3-aminoacetophenone **(120)** with methyl chloroformate in the presence of 20% KOH at 0°C to obtain the acetoamido derivative **(121)** which was subsequently reacted with *p*-toluene sulphonamide **(122)** to obtain 1-(3-acetylphenyl)-3-tosyl urea **(123)**. Compound **(123)** on condensation with appropriate aldehydes in ethanolic solution of KOH gave the corresponding diarylsulphonylurea-chalcone hybrids **(125a-y) (Scheme 24)**.

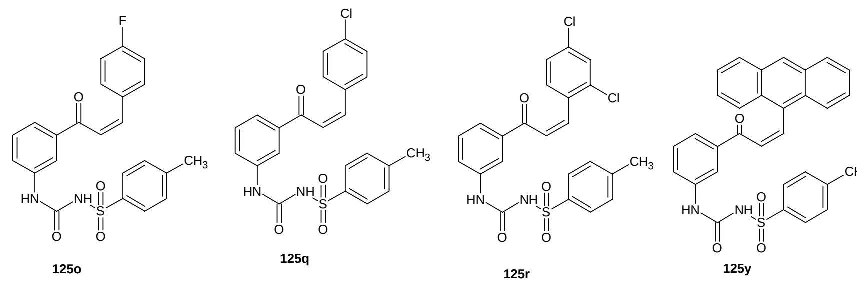


Scheme 24

The IC_{50} of the twenty five chalcones hybrid showed that only compounds **(125r)**, **(125o)**, **(125y)** and **(125q)** had comparable lipoxygenase with abietic acid (IC_{50} 7.88, 11.77, 14.91, 15.32 and 4.32 µg/mL respectively) **(Scheme 25)**.

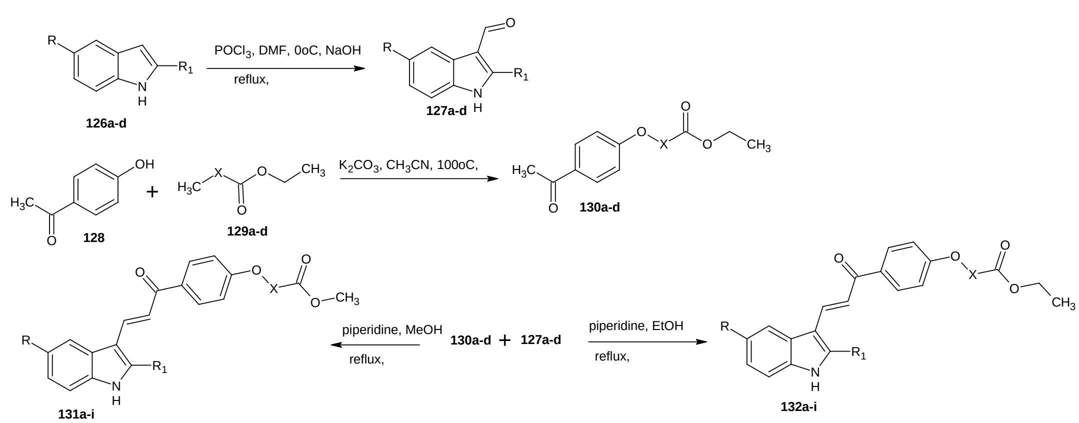
Synthesis of lipid lowering chalcones

Among the predominant risk factors for coronary heart disease are high levels of low density lipoprotein cholesterol (LDL-C), triglycerides and low level of high density lipoprotein cholesterol (HDL-C)[150]. Currently, the most common method to treat dyslipidemia is the use of statins which are HMG-CoA reductase inhibitor. The widespread clinical use of the statins is accompanied by potential dose-limiting hepatoxicity and mytotoxicity[151]. Cerivastatin, one of the second generation statins was withdrawn from the world market in 2001 due to its adverse effects[152]. The fibrate classes of lipid lowering drugs are selective activators of α-isotype of the receptors peroxisome proliferator activated receptor (PPAR)[153,154]. They lower triglyceride levels and increase HDL-C level in hyperlipidemic patients[155] and reduce the risk of coronary heart disease in patients with low HDL-C levels[156].



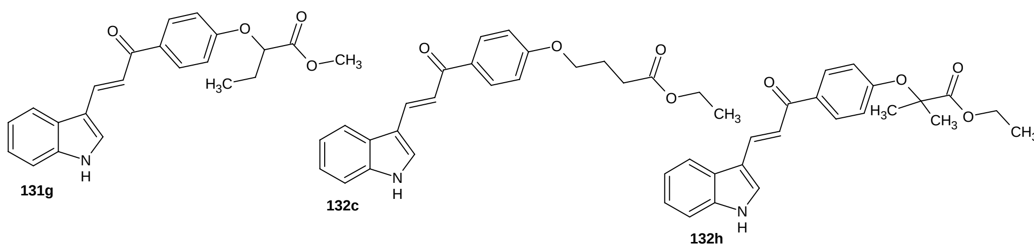
Scheme 25

Sashidhara et al.[157] synthesized indole-chalcone fibrates of lipid lowering potential. Using indoles **(126a-d)**, they carried out Vilsemeier-Haack reaction in the presence of $POCl_3$ and DMF to afford the corresponding indole-3-carbaldehydes **(127a-d)**. On the other hand, they reacted 4-hydroxyacetophenone **(128)** with the appropriate bromoesters **(129a-d)** in the presence of potassium carbonate in acetonitrile under reflux conditions to obtain substituted acetophenones **(130a-d)**. Claisen-Schmidt condensation of compound **(130a-d)** with compounds **(127a-d)** in the presence of catalytic amount of piperidine in methanol or ethanol gave the fibrates **(131a-i)** and **(132a-i)**, respectively **(Scheme 26)**.



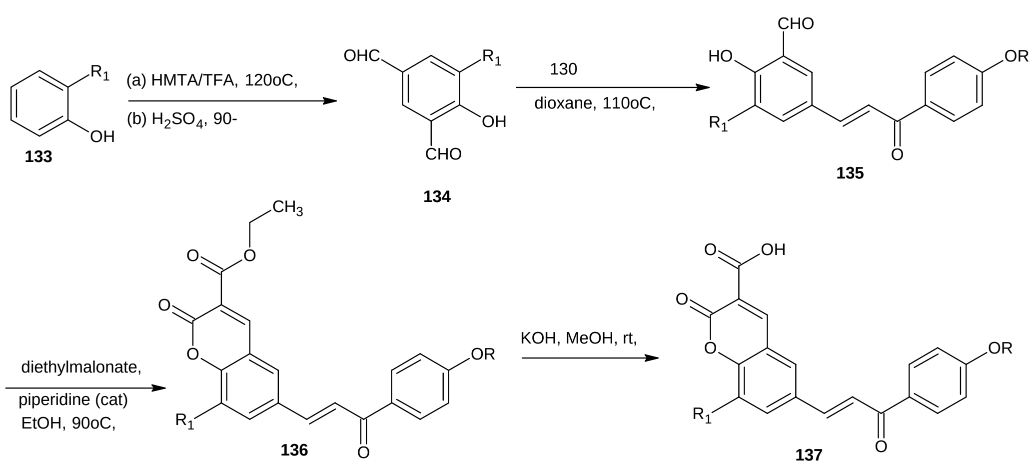
Scheme 26

The lipid lowering activity screening showed compounds **(131g)**, **(132c)** and **(132h)** as excellent antidyslipidemic agent. Compounds **(132c)** and **(132h)** had comparable lipid lowering activity with gemfibrozil (31%, 32% and 33%; 32%, 33% and 30% and 32%, 30% and 33%, respectively) for compounds **(132c)**, **(132h)** and gemfibrozil against total cholesterol, phospholipids and triglycerides **(Scheme 27)**.



Scheme 27

Sashidhara et al.[159] has also reported the synthesis of coumarin based chalcones as lipid lowering agents. Having synthesized compounds **(130a-d)** in their previous work, they treated 2-alkylphenols **(133)** using Duff formylation in the presence of hexamethylene tetramine (HMTA) and TFA at 120°C to furnish compounds **(134a-d)**. As usual, compound **(134a-d)** was subsequently reacted with acetophenones **(130a-d)** in the presence of catalytic amount of concentrated HCl in dioxane to afford the regioselective chalcones **(135a-l)**. On carrying out Knoevenagel reaction on compounds **(135a-l)** with diethylmalonate in the presence of a catalytic amount of piperidine, they synthesized coumarin-chalcone fibrates **(136a-l)**. Some of the coumarin-chalcone fibrates were converted to acid derivatives **(137a-d)** by alkaline hydrolysis of the diester **(Scheme 28)**.



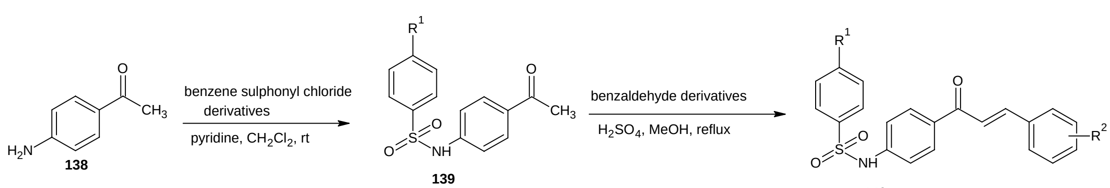
Scheme 28

None of the coumarin-chalcone fibrates had lipid lowering activity comparable to gemfibrozil.

Synthesis of β-Secretase inhibitor chalcones

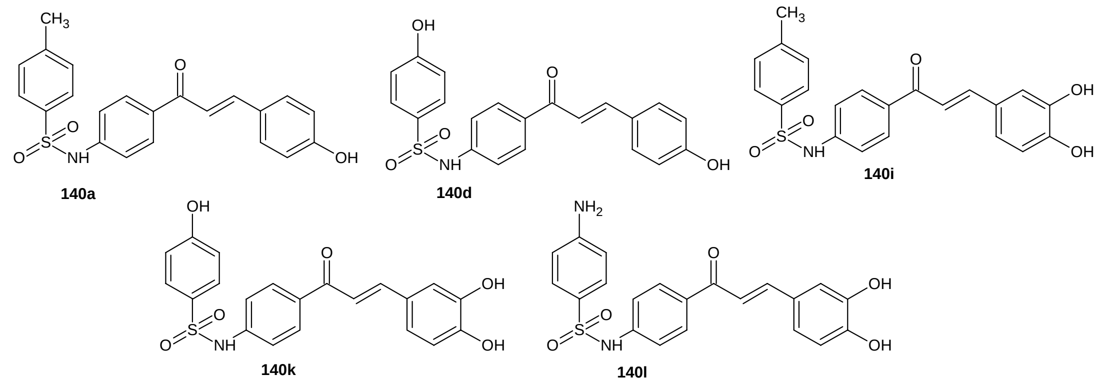
Alzheimer's disease (AD) is the major cause of dementia (1 in 8 of people over 65 has AD in the USA)[159]. This disease involves a progressive loss of neurons in the hippocampus and cortex which leads to serious loss of global cognitive ability. AD manifests itself in the brain by loss of dendrites and axons, myelin reduction, shrinkage and finally neuronal death[160]. The β-amyloid (Aβ) hypothesis for AD started from that endogenous β-secretase (BACE1) activity is increased in sporadic AD brain[161-163]. BACE1 is uniquely able to process amyloid precursor protein (APP) and thus form Aβ-peptides, because BACE1 knock-out mice are able to form Aβ peptides[164]. Over production of Aβ by BACE1 results in toxic fibrils causing neuro-degenaration. Reduced acylcholinesterase AChE expression is a common feature in AD patients. AChE catalyzes the hydrolysis of the neurotransmitter acetylcholine into choline, silencing the signal which is carried by acetylcholine[165]. Both AChE and BChE can hydrolyze acetylcholine sequel to this AChE/BChE over expression around plaques can lead to reduced neurotransmitter levels. It is then thought that AChE/BChE inhibition may alleviate AD symptoms by prolonging the half-lives of neurotransmitters. Although peptide derived structures has shown nanomolar IC_{50} against BACE1, their viability as drug candidates is hampered because of their high hydrophilicity. This is really because BACE1 inhibitors must possess sufficient lipophilicity to traverse two lipid bilayers to reach BACE1[166].

In answer to the problems of BACE1 peptide inhibitors, Park et al.[167] synthesized sulphonamide chalcones and evaluated their BACE1, AChE and BChE inhibition activity. They carried out the synthesis by treating 4-aminoacetophenone **(138)** with appropriate benzene sulphonyl chloride in the presence of pyridine to obtain *N*-sulphonylaminoacetophenone **(139)**. Claisen-Schmidt condensation of the appropriate aldehyde and compound **(139)** in the presence of catalytic amount of sulphuric acid gave the sulphonamide chalcones **(140a-n) (Scheme 29)**.



Scheme 29

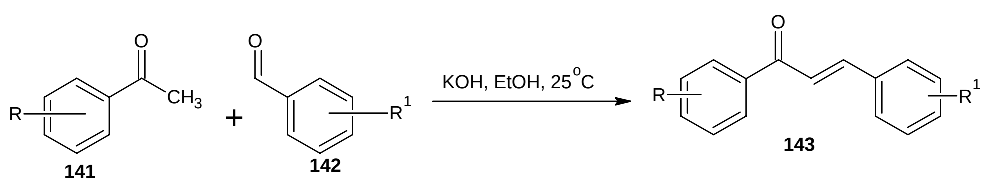
The inhibitory effects of the chalcones on BACE1 showed that compounds **(140a)**, **(140d)**, **(140i)**, **(140k)** and **(140l)** had excellent IC_{50} of 1.44, 2.88, 0.21, 0.62 and 0.69 μM respectively. In addition to their ability to inhibit BACE1, the compounds also showed good inhibition of other enzymes involved in Alzheimer's disease (AChE and BChE) **(Scheme 30)**.



Scheme 30

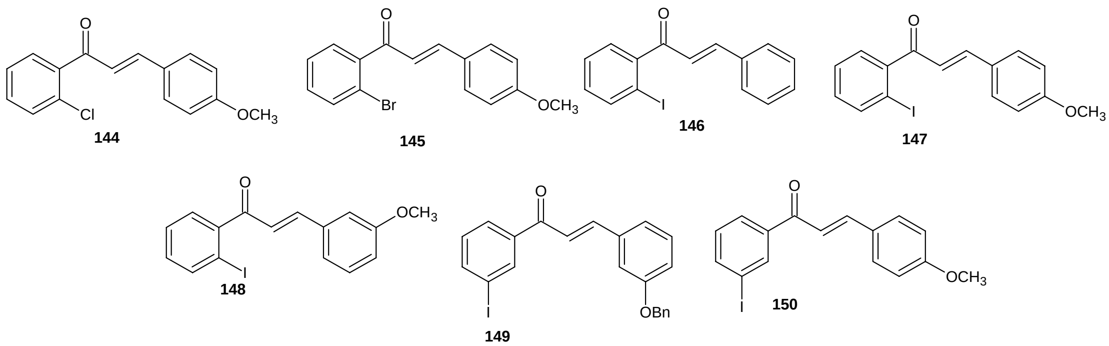
Synthesis of anti-diabetic chalcones

Peroxisome proliferator activated receptor gamma (PPARG) is a predominant molecular target for certain antidiabetic drugs such as insulin-sensitizing thiazolidinediones (TZDs). Jung et al.[168] has reported 2-hydroxychalcones and chalconyl-thiazolidinediones of antidiabetic activity through evaluating their binding potential to PPARG. In view of this finding, Hsieh et al.[169] synthesized novel chalcones by reacting acetophenones bearing hydroxyl group and or halogens with substituted benzaldehydes in the presence of aqueous KOH using ethanol as solvent **(Scheme 31)**.



Scheme 31

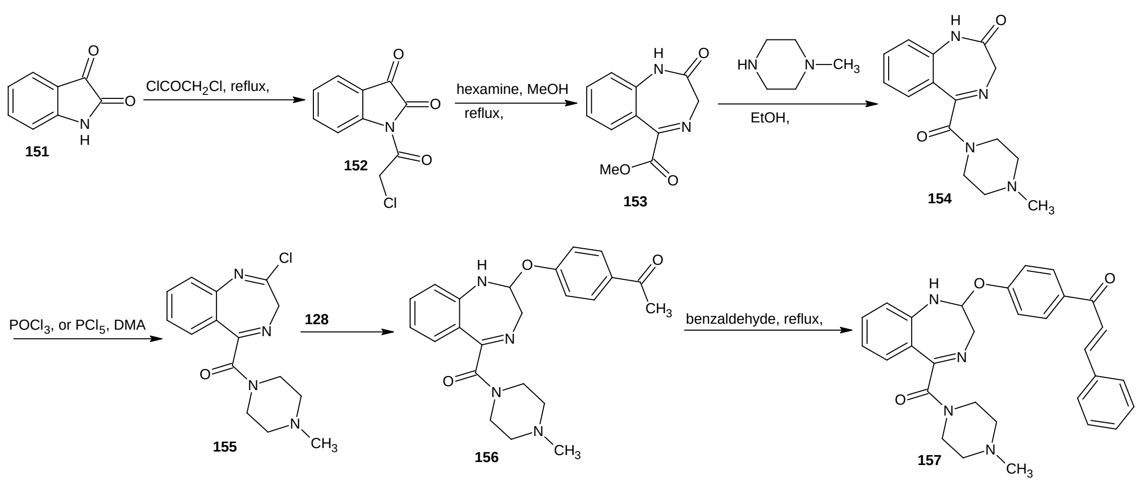
They evaluated the antidiabetic activity using glucose consumption in culture media. Seven of the chalcones **(144-150)** synthesized by this group showed better glucose consumption ability than the standard drugs rosiglitazone and pioglitazone (263 and 230 mg/dl, respectively) **(Scheme 32)**.



Scheme 32

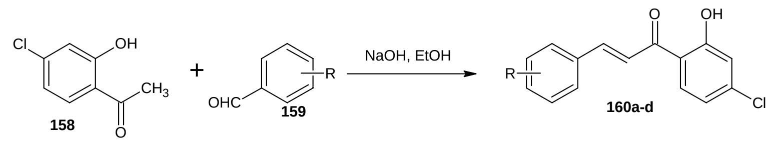
Synthesis of antibacterial chalcones

Kaur and Kishore[170] reported the synthesis of 1,4-benzodiazepine derivatives of chalcone with antibacterial activities. They used 5-carbomethoxy substituted 1,4-benzodiazepin-2-one **(153)** obtained from the reaction of *N*-chloroacetyl isatin **(152)**. Compound **(152)** was prepared by reacting indole-2,3-dione **(151)** with chloroacetyl chloride. Compound **(153)** on treatment with *N*-methyl piperazine gave the corresponding C_5-carboxamido derivatives **(154)**. Compound **(154)** on treatment with $POCl_3$ in the presence of dimethylaniline (DMA) gave the 2-chloro derivative **(155)** whose subsequent reaction with 4-hydroxyacetophenone **(128)** gave the corresponding 2-(4-acetylphenoxyl) substituted derivatives **(156)**. condensation of compound **(156)** with benzaldehyde gave the corresponding benzodiazepine chalcone **(157) (Scheme 33)**.



Scheme 33

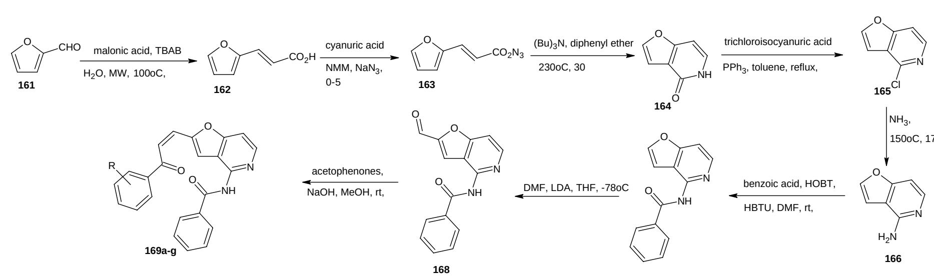
Prasadarao et al.[171] synthesized chalcone derivatives with antibacterial activities. They synthesized the chalcones by the reaction of equimolar mixture of 4-chloro-2-hydroxyacetophenone and benzaldehyde in the presence of NaOH using ethanol as the solvent **(Scheme 34)**.



Scheme 34

The four derivatives had appreciable inhibition zone diameter against *Agrobacterium tumifaciens* and *Xanthomonas campestris.*

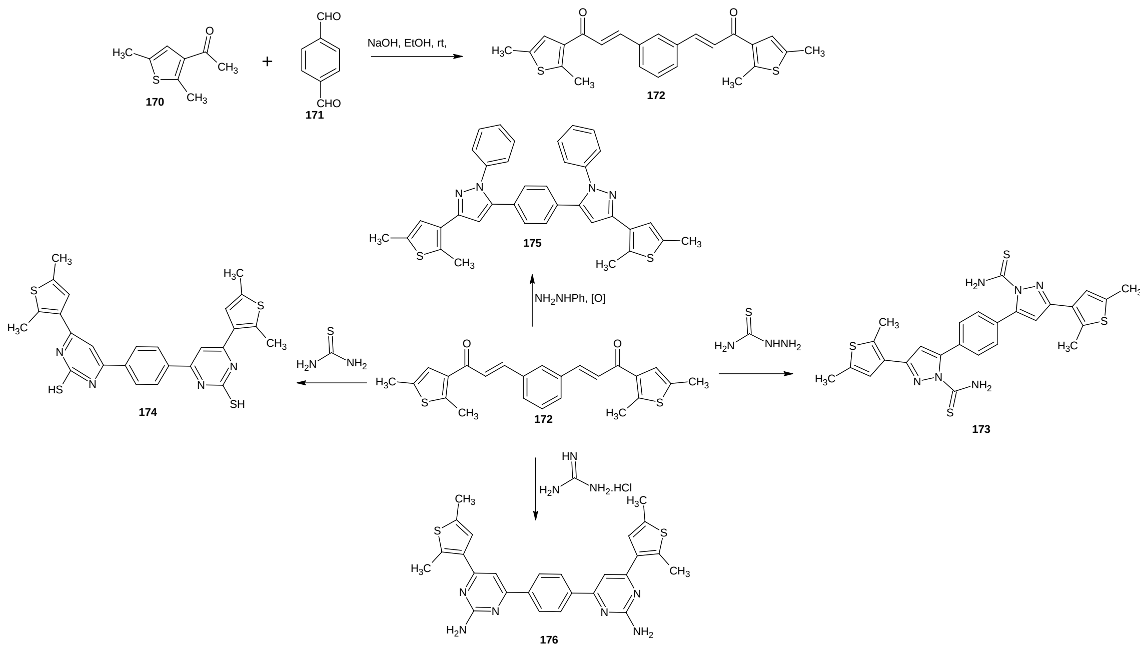
Rao and Rao[172] synthesized furo[3,2-c] pyridine chalcones with antibacterial activities. To synthesize the target chalcones, they irradiated a mixture of 2-furaldehyde **(161)**, malonic acid, TBAB, potassium carbonate and distilled water for 5 min at 100^{o}C to obtain acrylic acid intermediate **(162)** which was subsequently converted to acyl azide **(163)** using sodium azide in the presence of cyanuric chloride, *N*-methyl morpholine (NMM) in dichloromethane at room temperature for 3 h. They facilitated Curtius rearrangement of azide **(163)** to compound **(164)** by heating at 230^{o}C in the presence of diphenyl ether. Compound **(164)** was transformed to the chloride intermediate **(165)** using trichloroisocyanuric acid in the presence of triphenylphosphine in refluxing toluene. Compound **(165)** was converted to furo[3,2-c] pyridine-4-amine **(166)** by heating with aqueous ammonia at 150^{o}C for 17 hr. The coupling of compound **(166)** with benzoic acid in the presence of HOBT, HBTU and TEA in DMF gave the amide **(167)** which upon treatment with dimethyl formamide in the presence of LDA in THF afforded aldehyde **(168)**. Claisen-Schmidt condensation of compound **(168)** with acetophenones in the presence of sodium hydroxide in methanol at room temperature for 2 hr gave the chalcones **(169a-g)** **(Scheme 35)**.



Scheme 35

The antibacterial studies against *E. coli* (MTCC443), *P. aeruginosa* (MTCC424), *S. aureus* (MTCC96) and *S. pyogenes* (MTCC442) showed that while all the derivatives had antibacterial effect, only compound **(169d)** had better inhibition zone diameter on comparison with ciprofloxacin.

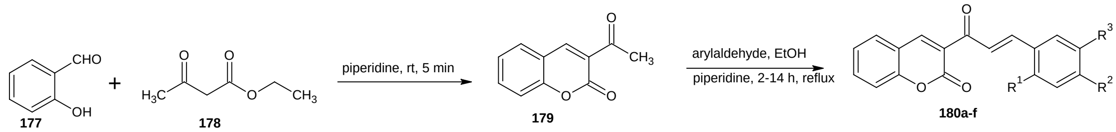
Asiri and Khan[173] synthesized bis-chalcones derived from thiophene and screened them for antibacterial activities. To synthesize the bis-chalcones, a solution of 3-acetyl-2,5-dimethylthiophene **(170)** and terephthaldehyde **(171)** in an ethanolic solution of NaOH was stirred for 20 hr at room temperature. After extraction and purification, the bischalcones **(172)** was obtained. Compound **(172)** was derivatized to compound **(173-176)** following different protocols **(Scheme 36)**.



Scheme 36

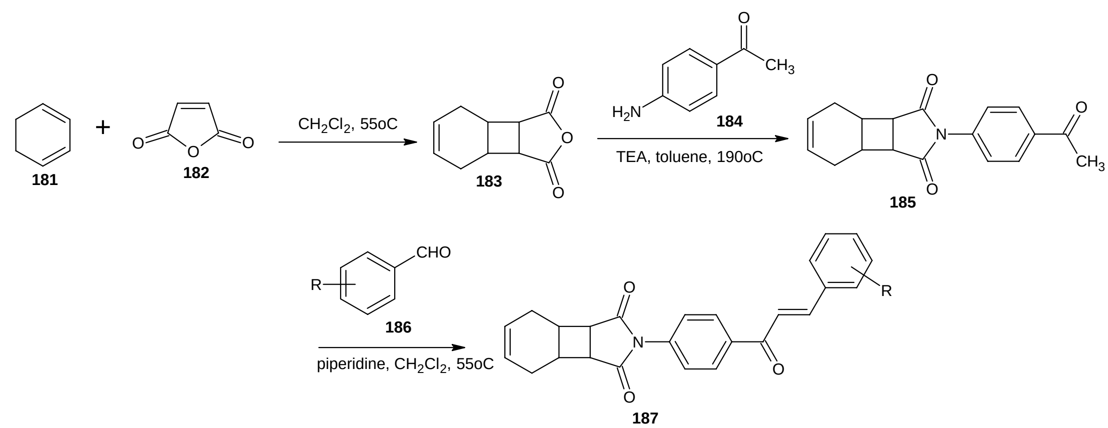
Compound **(173)** showed better antibacterial activity than chloramphenicol as evident from the inhibition zone diameter. Compound **(173)** coincidentally had the same MIC of 32 μg/mL against *S. aureus*, *S. pyogenes* and *E. coli* with chloramphenicol but against *Salmonella typhimurin* it had MIC of 16 μg/mL as against 32 μg/mL for chloramphenicol.

Vazquez-Rodriguez et al.[174] reported the synthesis of coumarin chalcone hybrids of antibacterial importance. Knoevenagel reaction of 2-hydroxybenzaldehyde **(177)** with ethylacetoacetate **(178)** in the presence of pyridine gave 3-acetylcoumarin **(179)**. Claisen-Schmidt condensation of compound **179** with arylaldehydes in the presence of piperidine gave the coumarin chalcones **(180a-f) (Scheme 37)**.



Scheme 37

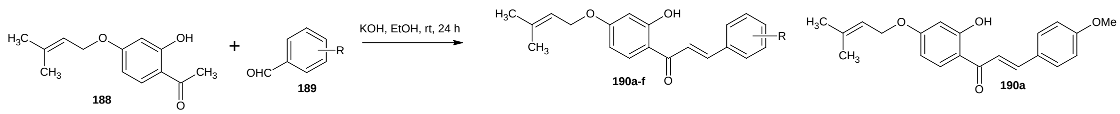
Ceylan et al.[175] reported the synthesis of 4,7-ethanoisoindole-1,3-dione chalcones with potential antibacterial activities. They achieved the synthesis by the addition of maleic anhydride **(182)** to 1,3-cyclohexadine **(181)** to produce the endo-adduct **(183)** which upon heating with 1-(4-aminophenyl) ethanone **(184)** in the presence of TEA in toluene at 110°C for 24 hr gave 2-(4-acetylphenyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-ethanoisoindole-1,3-dione **(185)**. Claisen-Schmidt condensation of compound **(185)** with benzaldehydes **(186)** in the presence of piperidine in dichloromethane at 55°C gave the chalcones **(187a-i) (Scheme 38)**.



Scheme 38

None of the active chalcones had comparable antibacterial activity with sulbactam.

Bhasker and Reddy[176] synthesized series of prenyloxy chalcones with antibacterial activity. The presence of prenyloxy group on the chalcone ring would increase their lipophilicity and consequently enhance their interaction with cellular membrane[177]. To obtain 4-prenyloxy-2-hydroxyacetophenone **(188)**, they refluxed a solution of β-resacetophenone in acetone with prenyl bromide and anhydrous potassium carbonate for 3 h. The conventional Claisen-Schmidt condensation of compound **(188)** with aromatic aldehydes **(189)** in the presence of NaOH in ethanol at room temperature for 24 hr gave the prenyoxy chalcones **(190a-f) (Scheme 39)**.



Scheme 39

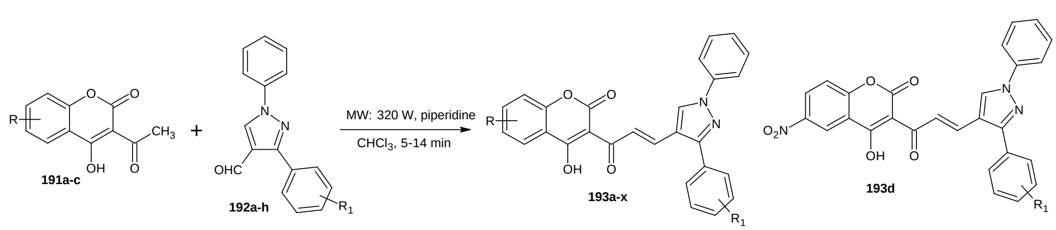
The compounds showed comparable zones of inhibition with streptomycin against *E. coli* and *S. aureus*. The most potent of the compounds was **(190a)**.

A host of other researchers have reported the synthesis and antimicrobial activities of derivatives of chalcones which cannot be reviewed in detail for want of writing space. Ziman[178], Patel and Shah[179], Shah et al.[180], Seema and Praffullkumar[181] and Patel and Patel[182] have reported derivatives of chalcones with antimicrobial activities.

Solvent free and microwave synthetic methodologies

It is undisputable that chalcones is second to none among the biologically active functionality and to a large extent the most simple medicinal compound in terms of synthesis. The studies of chalcones are still facing the synthetic problems of reactions taking up to 72 hrs and low yield in many cases. The prevailing circumstances spurred researchers to seek for the application of microwave and solvent free approach in the synthesis of chalcones.

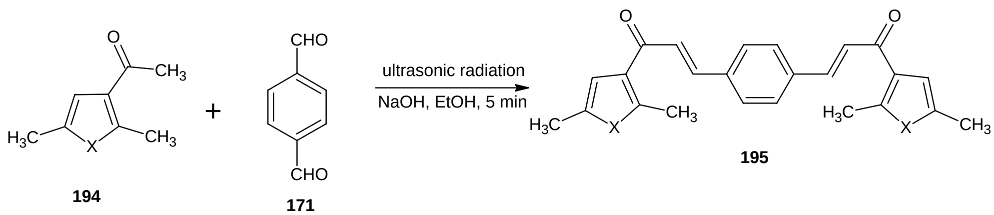
Thakrar and Shah[183] employing microwave synthesized chalcone derivatives with improved yield and drastic reduction in reaction time. The synthesis of 3-acetyl-4-hydroxycoumarin **(191a-c)** was reported by Rao and Sundaramurthy[184]. Thakar et al.[183] subjected a mixture of compound **(191a-c)** and substituted aromatic aldehyde **(192)** dissolved in chloroform in the presence of catalytic amount of piperidine to microwave at 320 W. The reaction was monitored using TLC at interval of every minute. At the completion of the reaction they obtained chalcones **(193a-x)** at excellent yield of 78-89% and time of completion ranging from 5-14 min **(Scheme 40)**.



Scheme 40

Compound **(193d)** gave the highest yield of 89%.

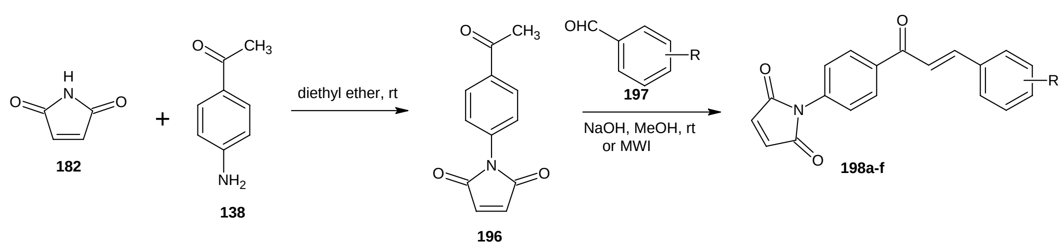
Khan et al.[185] carried out green synthesis of bischalcones via ultrasonic radiation. They synthesized the chalcones **(195)** by ultrasonic radiation aided aldol condensation reaction between 3-acetyl-2,5-dimethylthiophene/3-acetyl-2,5-dimethylfuran **(194)** and terephthalaldehyde **(171) (Scheme 41)**.



Scheme 41

It is important to note that the thiophene derivatives have been reported by Asiri et al.[173] using the conventional method without irradiation and it took them 20 hours stirring to arrive at the desired product but Khan et al.[186] synthesized the same derivatives in 5 minutes utilizing ultrasonic radiation.

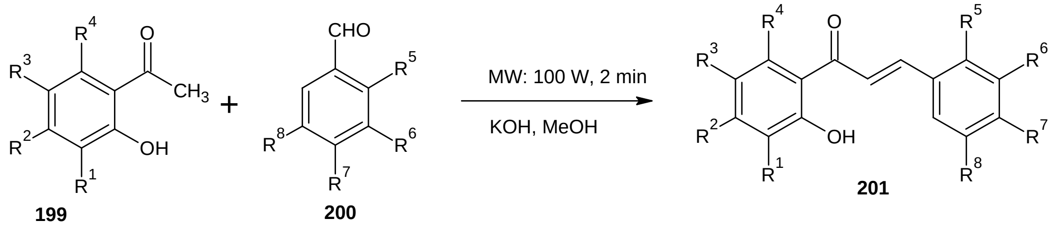
Aravind and Ganesh[186] synthesized 1-[4-(3-substituted-acryloyl)-phenyl]-pyrrole-2,5-dione derived chalcones employing both conventional and microwave irradiation. The reaction of maleic anhydride **(182)** and 4-aminoacetophenone in diethyl ether furnished 1-(4-acetyl-phenyl)-pyrrole-2,5-dione **(196)**. Compound **(196)** on condensation with substituted benzaldehydes **(197)** in the presence of alkali gave the target chalcones **(198a-f) (Scheme 42)**.



Scheme 42

A comparative analysis of the yield and time of reaction of the conventional and microwave assisted synthesis reveals approximately 20% increase in the yield and almost 99% reduction in time for the reaction.

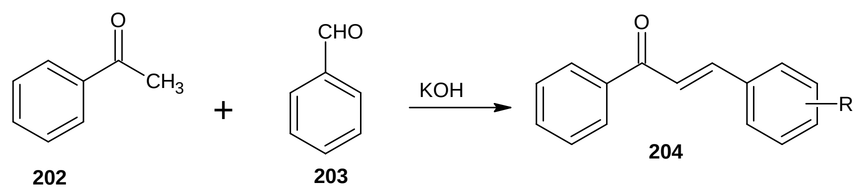
Albogami et al.[187] has reported efficient one step synthesis of functionalized chalcones **(201)**. They simply mixed the appropriate amount of 2-hydroxyacetophenone derivatives **(199)** and aromatic aldehydes **(201)** in the presence of catalytic amount of aqueous KOH in methanol and irradiating the reaction in a microwave oven at 100 W for just 2 minutes **(Scheme 43)**.



Scheme 43

Again this work underscores the improvement in the synthesis of chalcones given the time for the reaction to come to completion and also the excellent yield of 80-94%.

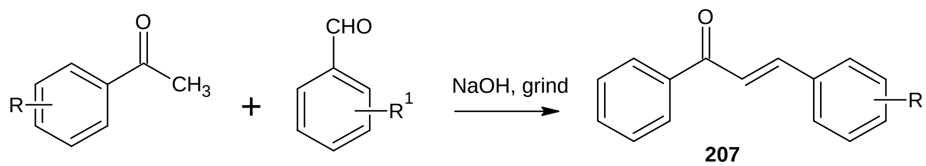
Raghav and Malik[188] reported the solvent free synthesis of chalcones. The synthesis was accomplished by mixing acetophenone **(202)**, substituted benzaldehyde **(203)** and KOH in pestle mortar. The mixture first went into solution and thereafter solidified. The solid was washed properly with water to obtain the chalcones **(Scheme 44)**.



Scheme 44

Some of the derivatives could not be synthesized via grinding technique and they stored the mixture in an ice cold solution of KOH and the reaction kept overnight. In this modification, the potassium hydroxide solution served as the solvent and catalyst. Again the solvent free synthesis provided chalcones with excellent yield and the technique is environmental friendly and economically preferred.

Dharieshwar and Dev[189] reported the synthesis of heterocyclic chalcones using solvent free technique. They achieved the synthesis by grinding equimolar quantities of (hetero) aryl methyl ketone **(205)** with (hetero) aryl aldehyde **(206)** to obtain the chalcones **(207)** **(Scheme 45)**.

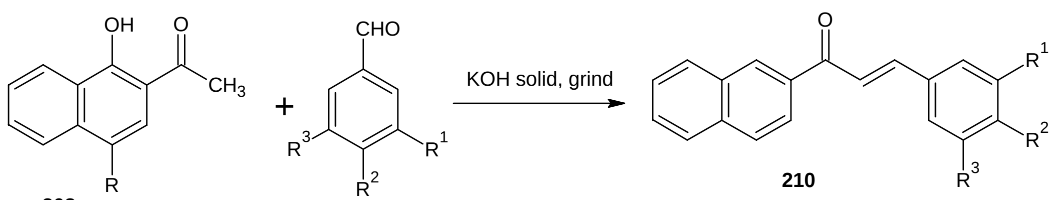


205 206 207

Scheme 45

All the twenty chalcone derivatives synthesized had yield of above 90% and the reaction time of just 2-8 minutes.

Vibhute et al.[190] reported the operationally simple synthesis of new chalcones utilizing grinding technique. It has been shown that solid state reactions occur more efficiently and selectively than does the solution reaction, since molecules in crystals are arranged tightly and regularly[191]. The new chalcones were synthesized by grinding together equimolar amounts of appropriate 2-acetyl-1-naphthol/substituted benzaldehydes **(208)** and different substituted benzaldehydes **(209)** in the presence of solid KOH in a porclain mortar for 4-8 min to afford chalcones **(210)** in excellent yield **(Scheme 46)**.



208 209 210

Scheme 46

CONCLUSION

Chalcones are pharmacologically active compounds, chemically known as derivatives of 1,3-diphenylprop-2-en-1-one. In this review, some chalcone have been reported to show good anticancer property given their ability to prevent tubulin polymerization or stabilize microtubule. Some are inhibitors of the suppressor protein P53, blockers of nitric oxide production or inhibitors of cytochrome P450 enzymes. Some chalcones have been reported to selectively inhibit COX-2 over COX-1 making them a better anti-inflammatory with less adverse effect than the classical NSAIDs which selectively inhibit COX-1 over COX-2. Chalcones have also been reported to show excellent inhibition of lipoxygenase, making this class of compound good antioxidant agent. In cardiovascular disease management, chalcones establishes a fascinating presence given their ability to lower low density lipoprotein cholesterol, triglycerides and increase the level of high density lipoprotein cholesterol. Chalcones have increased the arsenal of chemotherapy in the treatment of Alzheimer's disease owing to their ability to inhibit not just BACE1 a primary enzyme in Alzheimer's disease but also BChE and AChE. In the treatment of gastrointestinal syndromes and sepsis, chalcone has registered its presence following the findings that some chalcone inhibits Yersinia enterocolitica tyrosine phosphate a primary target for therapeutic intervention against disease provoked by Yersinia. The successful application of microwave and grinding technique in the synthetic methodologies makes the synthesis environmentally friendly and economically viable.

This article presents the synthesis of various classes of chalcones with therapeutic applications for further modifications so as to further exploit their broad biological applications. The relatively easy synthetic methodologies of this compound calls for further exploitation of their pharmacological possibilities in this era of emerging drug resistance.

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Revised : 19.11.2014 *Accepted : 21.11.2014*