Review Article

Chalcones: Synthesis, structure diversity and pharmacological aspects

Hery Suwito[1,2], Jumina[1], Mustofa[3], Alfinda Novi Kristanti[2] and Ni Nyoman Tri Puspaningsih[2]

[1]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Gajah Mada University, Jogjakarta - Indonesia*
[2]*Department of Chemistry, Faculty of Science and Technology, Airlangga University, Surabaya -Indonesia*
[3]*Department of Pharmacology and Therapy, Faculty of Medicine, Gajah Mada University, Jogjakarta - Indonesia*

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ABSTRACT

The diverse pharmacological activities of chalcones, such as antioxidant, antimicrobial, anticancer, and antihepatotoxic, attract many researchers to isolate and elucidate them from nature and to develop efficient synthetic method. In the development, chalcones do not only comprise derivatives of trans-1,3-diaryl-2-propen-1-ones, but also their analog. Chalcones isolated from nature show exotic structure, which is sometime unrecognizable directly. The structure diversity of chalcone whether from nature or synthetic origin and various synthetic method of chalcone are discussed. Furthermore the bi-electrophile character of chalcone makes them more attractive to be used as synthon in the synthesis of heterocyclic compounds, such as pyrazoline, pyrimidinone, and benzazepine, through cyclo-condensation reaction with a bi-nucleophilic species.

**Key words:** chalcone, pyrazoline, pyrimidinone, and benzazepine
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INTRODUCTION

Chalcones (*trans*-1,3-diaryl-2-propen-1-ones) are natural products belong to flavonoid, are considered as intermediate in the flavonoids biosynthesis, and are widespread in plants. The existence of the α,β-unsaturated ketone moiety in chalcones is a common part found in a large number of biological active compounds. Therefore, chalcone derivatives from nature or synthetic origin exhibit diverse pharmacological activities, such as antimicrobial [1], antitumor [2], anticancer [3,4], radical scavenger [5], and inhibitor of topoisomerase I [6]. However, isolation of chalcone derivatives from nature requires a long and usually complicated procedure which does not comparable to the yield obtained. Due to time consuming and intensive process in the isolation procedure, and to their diverse pharmacological activities, the development of an efficient synthetic protocol of chalcone derivatives attracts many researchers. A good synthetic method gives us advantages to obtain chalcone derivatives attaching various substituents in excellent yield which possibly do not exist in nature. Furthermore, chalcones are known as the key intermediate in the synthesis of various biologically important heterocyclic compounds. In this article, the preparation methods of chalcones, structure diversity, role of chalcone as synthon for the synthesis of diverse heterocyclic compounds, and their biological activity are reviewed.

SYNTHESIZE OF CHALCONES

Chalcone (**1**) and its derivatives are primarily synthesized in the laboratory using Claisen-Schmidt reaction, in which acetophenone (**2**) or its derivative is reacted with benzaldehyde (**3**) or its derivative using strong base, such as NaOH, KOH, or NaH as catalyst in a polar solvent as shown in the following reaction [7]. Other catalysts are also used, such as sodium phosphate doped sodium nitrite [8] and aluminum-magnesium hydroxide hydrate [9].
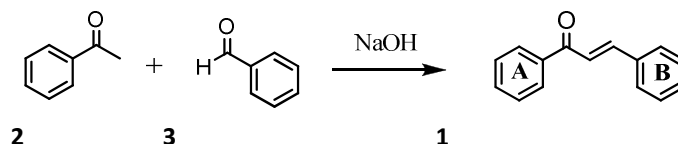
Solid phase Claisen-Schmidt reaction employing various solid catalysts was applied to synthesize chalcones by different scientific group. Cross aldol condensation catalyzed by complex of Co(II)-pyridine polymer was applied to synthesize chalcone. The complex of Co(II)-cross linking 4-vinyl pyridine-styrene showed the best performance, in which no side product was observed [10]. Solid phase synthesis of chalcones using 2-chlorotrytilchloride as supporting resin has also been performed [11]. First, the hydroxy-acetophenone (**4**) derivatives was bounded to the resin, and then treated with derivatives of benzaldehydes using NaOH as catalyst in methanol. The formed hydroxychalcones (**5**) were then released by the addition of trichloro acetic acid.
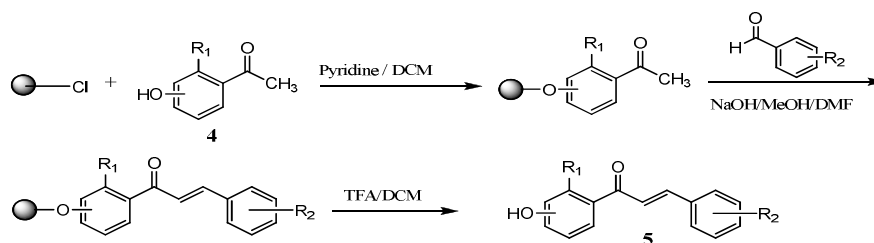
●-Cl = tritylchloride resin

Solid phase cross aldol condensation employing magnesium hydrogen sulphate was used to synthesize chalcone in good yield and self condensation products were not observed [12]. In attempt to accelerate the development of green chemistry, solvent free Claisen-Schmidt reaction was conducted using polymer as supporting material and TBD (1,5,7-trisazabicyclo[4,4,0]dec-en) as catalyst [13]. Solid phase synthesis of chalcones was also conducted using silica-sulfuric acid as catalyst. The conversion of reactants into product proceeded completely by heating the reaction mixture at 80^0C for 2 until 3 hours. The catalyst was made by the reaction of silica gel with chlorosulfonic acid [14].
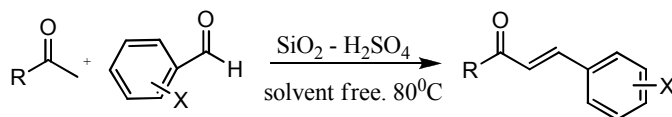

R = 4-biphenyl   X = H, *m*-NH$_2$, *p*-NH$_2$, *m*-Br, *m*-Cl, *p*-Cl,
     or 9H-2-fluorenyl   *p*-NMe$_2$, *p*-OH, *p*-OMe, *p*-Me, *o*-NO$_2$,
                                     m-NO$_2$, *p*-NO$_2$

Pursuing an environmentally benign reaction condition, the use of Zn (L-proline)$_2$ as catalyst in the synthesis of chromonyl-chalcones in water was successfully conducted. The eminence of this protocol was the use of water as solvent which is nontoxic, cheap, and non-flammable. Moreover, Zn (L-proline)$_2$ can be easily recovered and reused several time without significant loss of its performance [15].

Microwave irradiation induced reaction in the chalcones synthesis is another alternative procedure to synthesize chalcones. This reaction method can shorten the reaction time and simplify the purification procedure. Cross aldol condensation by using microwave was used for the synthesis of chalcone analog namely 2,6-bis(benzyliden)-cyclohexanone (**6**) employing BMPTO (bis-(4-methoxyphenyl)-telluroxide) as catalyst [16].
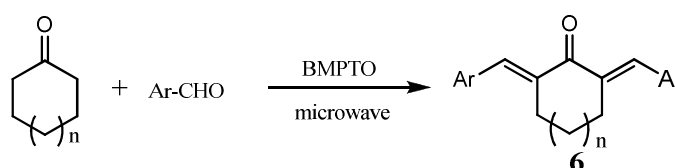
An attractive single step synthesis protocol of chalcone was reported, in which chalcones were synthesized using molecular iodine impregnated over neutral alumina as catalyst, and employing microwave irradiation as source of energy without any solvent [17]. Under this reaction condition, preparation of polyhydroxychalcones can be conducted by reacting of hydroxylated acetophenone and hydroxylated benzaldehyd without using any protecting group, which is impossible to be conducted by alkaline catalyzed reaction. The molecular iodine acts as Lewis acid, which facilitates the enolisation of the hydroxyl aryl ketone as well as activates the carbonyl group of hydroxyl benzaldehyde towards nucleophilic attack. The neutral alumina powder serves to enlarge the effective catalytic surface area.
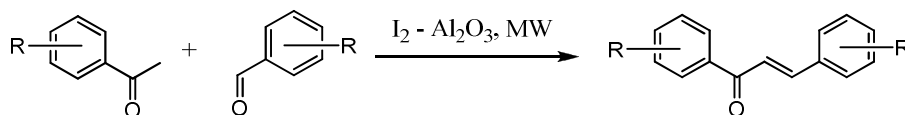

Acid catalysed of hydroxylated chalcones synthesis was successfully conducted by Jayapal and co-worker without any protecting step. The acid catalyst was prepared in situ from $SOCl_2$ and ethanol [18]. The combination of continuous flow processes and microwave technology is a relatively new method applied in organic synthesis. This technique offers many advantages, both in technical and economical aspects. Applying this technique, synthesis of chalcone derivatives were successfully conducted using mix-solution of phenyl acetylenes and benzaldehydes in 1,2-dichloroethane. Initially, the solution mixture was flowed continuously by a pump through the reaction vessel charged with amberlyst-15 as a solid acid catalyst, which was inserted in a reactor equipped with microwave generator (50 W) in a defined time. Solution of the crude product was subsequently collected from the outlet tube, and then purified chromatographically. The electron-rich or electron-poor substrates are tolerable in this reaction condition and the corresponding products are obtained in good yield [18].

More exotic synthetic protocols have also been developed to pursue high reaction yield and to minimize the side reaction. Chalcone could be synthesized using Suzuki reaction, employing cynnamoyl-chloride and phenyl boronic acids as reagents and Pd as catalyst in base reaction condition [20].
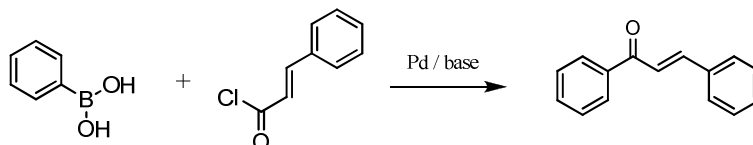

Coupling reaction between aromatic alkynes (**7**) and aldehyde in ionic solution was applied to synthesize of chalcones with high conversion. It was found that aromatic aldehydes whether attach electron withdrawing or electron donating group are able to proceed coupling reaction. However, the use of aliphatic alkynes does not give any products, even in a prolonged reaction time [21].
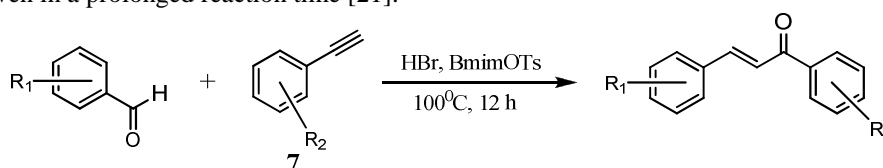
The application of Sonogashira isomerisation coupling reaction under microwave-assisted condition was used to synthesize chalcones through a reaction between aryl-halide attaching electron withdrawing group (**8**) and propargyl alcohol (**9**) [22]. Using this method, high yield was obtained in short reaction time (8 – 25 minutes).
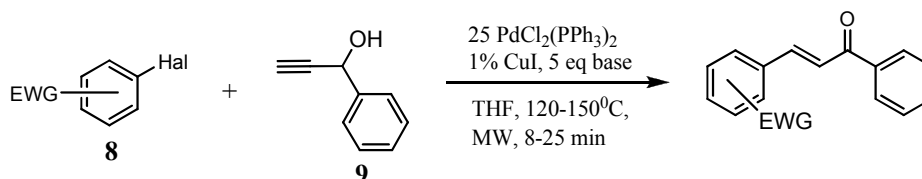
Carbonylative Heck coupling reaction employing Pd as catalyst is another protocol to produce chalcone by the reaction between aryl halide and styrene in the presence of carbon monoxide [23].
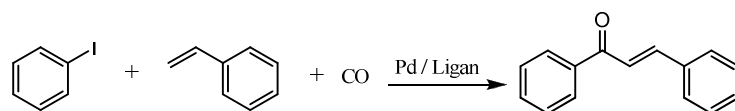
STRUCTURE DIVERSITY

Classical structure of chalcones is the derivatives of 1,3-diphenyl-2-propen-1-one and they are usually from natural products. However in the development, chalcones do not only comprise derivatives of 1,3-diphenyl-2-propene-1-one, but also derivatives of 2-propene-1-one, in which at the position 1 and 3 attached other aromatic ring or even non-aromatic ring. The structurally modified chalcones are usually obtained from the synthetic origin.

Natural origin

The classical substitution pattern of hydroxyl group in ring A of natural chalcone is 2,4,6-trihydroxy or 2,4-dihydroxy, whereas in ring B could be 4-hydroxy, 3,4-dihydroxy, 3,4,5-trihydroxy, or no substituent attached in it [23,24]. An interesting small group of natural chalcones is β-hydroxy-chalcones, which occur as the enol tautomers of dibenzoylmethane derivatives (**10**). Galliposin (**11**) isolated from the stem bark of *Galipea granulose* (Rutaceae) possessing β-hydroxy and dioxymethylene substituens is an interesting example of this group [26]
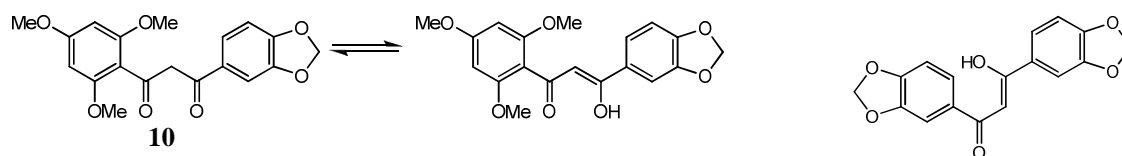
10
Tautomerization of dibenzoylmethane

11

During period 1992 until 2003, more than 80 new isoprenylated chalcones have been reported, mostly from the Leguminosae. The isoprenyl moiety exists in an open chain or in a cyclic form [25]. Spinochalcone-B (**12**) isolated from *Tephrosia* is a representative of cyclic farnesylated chalcones [27], whereas Xanthohumol-D (**13**) from *Humulus lupulus* is a representative of an open chain isoprenylated chalcones [28].

12   **13**

Chalcone dimers or oligomers are also found in plant, especially in the family of Ochnaceae and Anachardiaceae. To form a dimer, two chalcones are linked whether by a single C-C bond or by C-O-C bond. Rushchalcone VI (**14**) obtained from the twigs and stem bark of *Rhus pyroides* (Anacardiaceae) is an example of chalcone dimer formed from two molecules of isoliquiritigenin (2',4',4-trihydroxychalcone) linked by a C-C single bond between C-3 and C-5'. On the other hand Rushchalcone I (**15**) and II (**16**) represent unsymmetrical chalcone dimmers linked by C-O-C single bond, which is composed from isoliquiritigenin and its 4'methyl ether derivative [29,30].
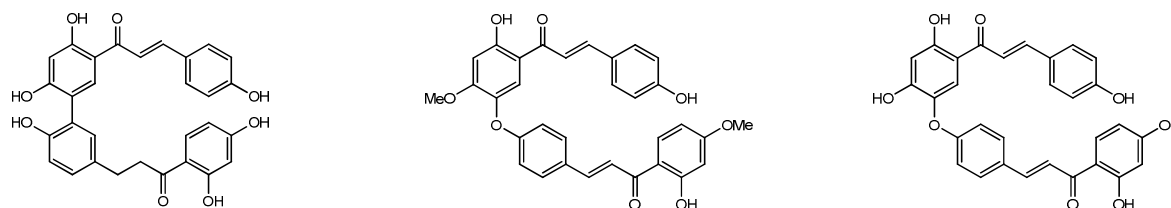

**14**   **15**   **16**

Based on their chemical structure, a characteristic feature of chalcones is their ability to act as dienophiles in an enzymatic Diels-Alder reaction. Serving as dienes in this reaction are range from isoprene, monoterpene, coumarine, and other class of flavonoid. The Diels-Alder adducts of chalcone are mostly found in family Moraceae. However, they can also be found in Annonaceae and Zingiberaceae [24]. The biosynthetic pathway of Sanggenon R (**17**) proposed by Hano et al [31] is an example of the enzymatic Diels-Alder reaction between a chalcone as dienophile and an isoprene as diene. The product of this reaction proceeds subsequently rearrangement and oxidation reaction to form sanggenon R.

The following compounds fissistin (**18**), Palodesangren C (**19**), Mulberrofuran U (**20**), Dorstenone (**21**), and Sanggenol M (**22**) are some representatives of chalcones formed through the Diels-Alder reaction between chalcone derivatives as dienophile and various kinds of diene.
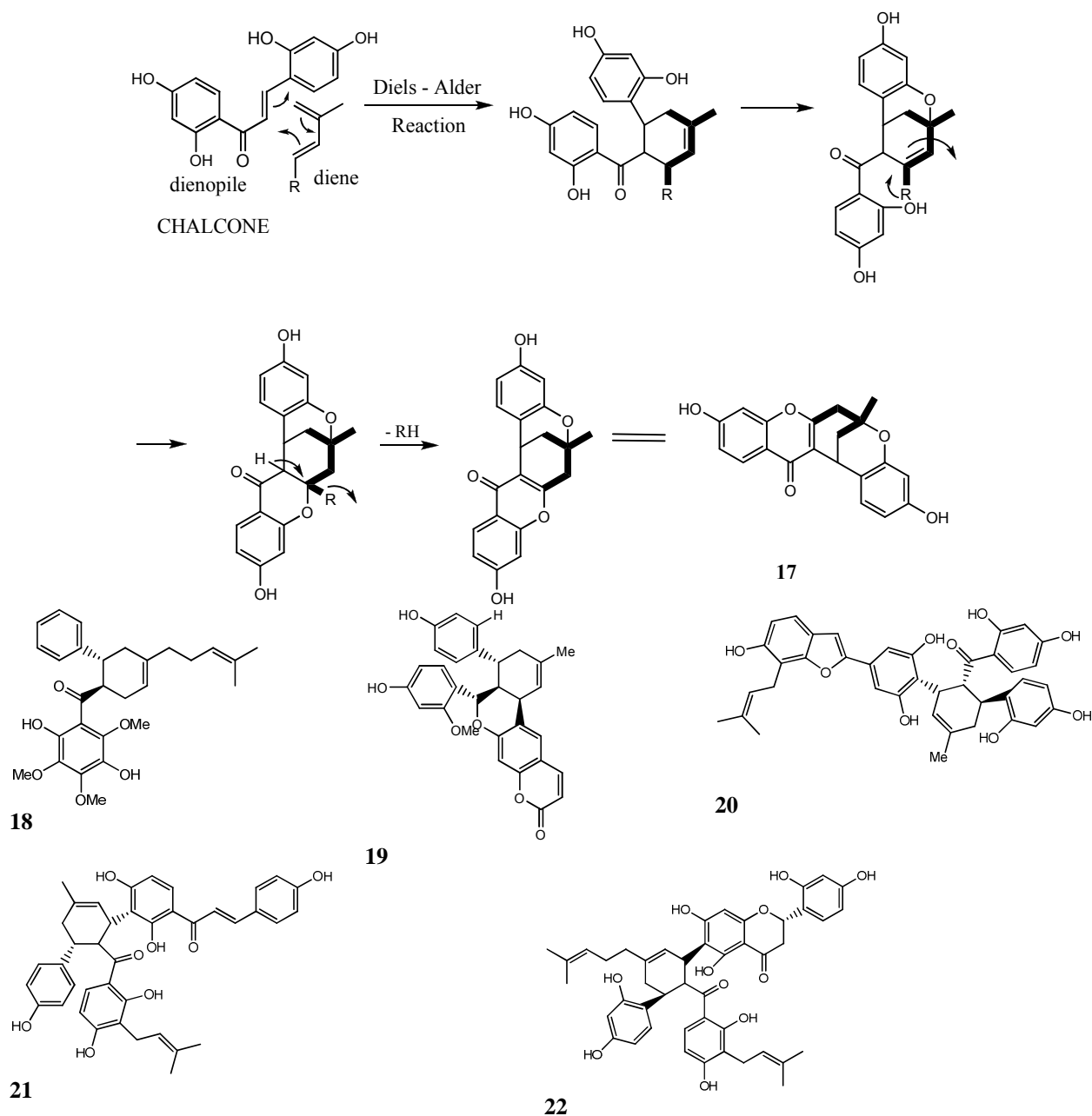

Synthetic origin

The molecular structure of chalcones of synthetic origin comprises both of derivatives of 1,3-diphenyl-2-propen-1-one and derivatives of 2-propen-1-one in which at the position 1 and 3 other aromatic or non aromatic ring attached . The classical structures of chalcones are not discussed in this part of the article. Cheng and coworkers [11] have synthesized chalcones composed of pyridine, quinoline ring, and polyhydroxy aromatic.
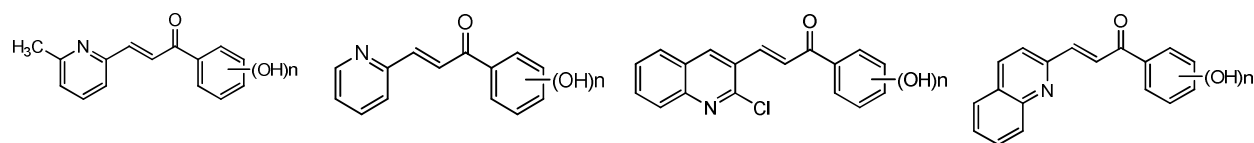
Chalcones possessing benzo-1,4-dioxane (**23**) ring have also been synthesized. The benzo-1,4-dioxane ring was made from the reaction between 1,2-dihydroxybenzaldehyde with a derivative of an epoxide. The aldehyde obtained was then treated with the derivatives of acetophenone to produce the desired products [32].
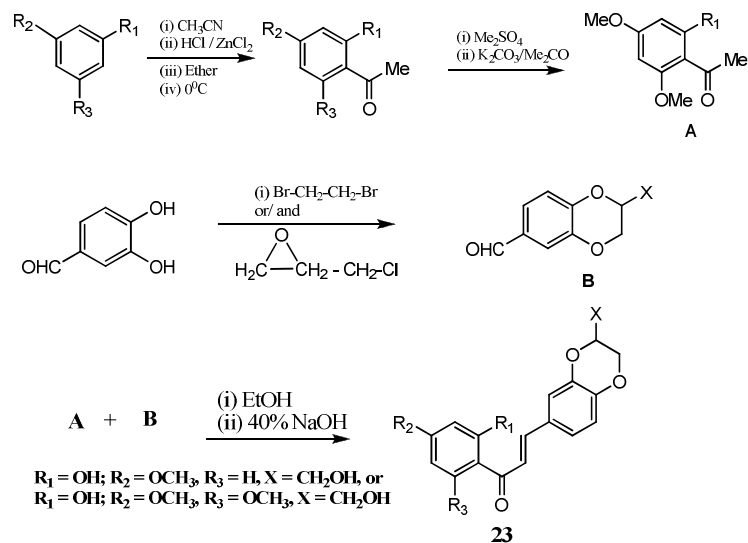
The synthesis of coumarine-based chalcones (**24**) was successfully conducted by Claisen-Schmidt condensation applying piperidine as catalyst in ethanol [1].
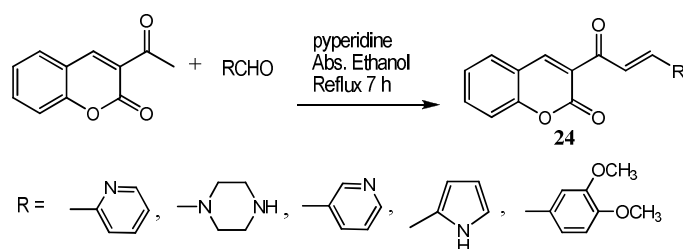
Baviskar and co-workers [33] have synthesized some novel benzimidazolyl chalcones (**25**) in attempt to gain antimicrobial agents by condensation of N-(4-(1*H*-benzo[*d*]imidazol-2-yl) phenyl)acetamide with aromatic aldehydes in presence of aqueous potassium hydroxide at room temperature.
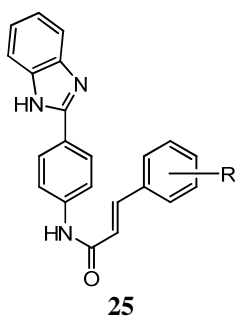
AM 58 (**26**) and AM 114 (**27**) are examples of chalcone-analogues bearing of boronic group which showed anticancer activity [34], whereas two others boronic chalcones were synthesized as fluorescent probes for saccharides signaling analysis [35].
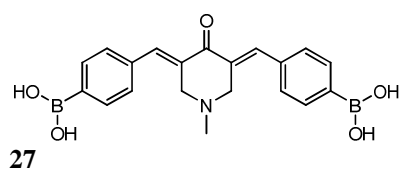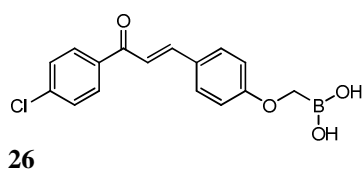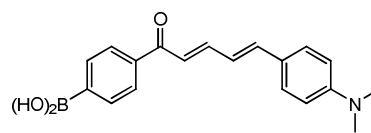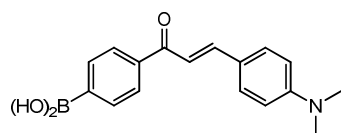
Indanocine (**28**) is an example of another chalcone analog which is classified as annulated chalcone. It is a chalcone, where the C-3 part is in a cyclic form [36].

28
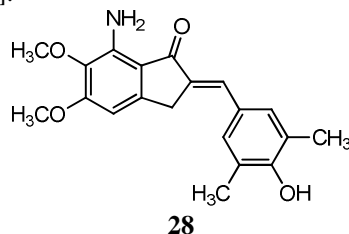
FUNCTIONAL GROUP TRANSFORMATION OF CHALCONE

Enone moiety of chalcone is an important part in functional group or structure transformation, due to its reactivity to be transformed into other functional group. The transformation can take place whether on the carbonyl or on alkenes group. The carbon-carbon double bond can be reduced into carbon-carbon single bond under hydrogen gas atmosphere using various catalyst such as Raney nickel, Adam catalyst (PtO_2), Pd/C, Rh-Al_2O_3. Although these heterogeneous catalysts are useful in the hydrogenation process, they show bad selectivity if the reduced compound possesses more than one functional group. Furthermore, the application of homogeneous catalyst in the hydrogenation of carbon double bond is also reported employing rhodium or ruthenium complex, such as Wilkinson catalyst [$(Ph_3P)_3RhCl$] and [$(Ph_3P)_3RuClH$]. It is an efficient catalyst for hydrogenation of unconjugated homogeneous alkene at standard temperature and pressure [36]. An interesting result was obtained by Alptuzun & Gozler [38] when they hydrogenated chalcone 3-(3,4-dimethoxyphenyl)-1-(3-tolyl)-2-propenone (**29**) using Zn/acetic acid in attempting to get a saturated ketone (**30**). Indeed they got the desired product, but only as side product. The major product obtained was the derivative of cyclopentanol (**31**) as the result of cyclodimerization.
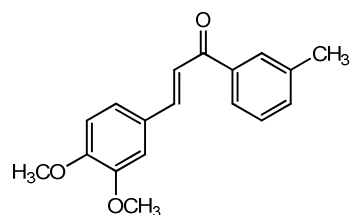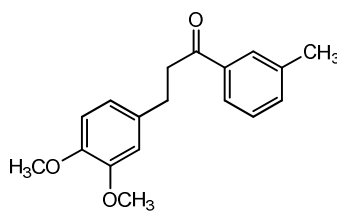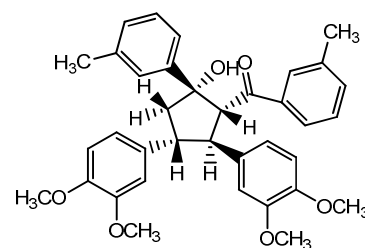
29   **30**   **31**

CHALCONE AS SYNTHON IN HETEROCYCLES SYNTHESIS

Chalcones are versatile precursors in the synthesis of heterocyclic compounds. From the organic synthesis point of view, enone moiety is important for the structural transformation of chalcones. Acting as an electrophile, chalcones can react with a nucleophile in Michael addition. In a cyclocondensation reaction, chalcones can act as a bi-electrophile which reacts with a bi-nucleophile, and this is an attractive route for the synthesis of heterocyclic compounds [22], such as derivative of pyrazoline, oxiran, pyran, oxopyrimidine, isoxazoline [39], derivatives of pyridine [40], derivatives of benzheteroazepine [41], and other heterocycles. Furthermore, substituted cyclohexenone can also be made from substituted chalcones [60].
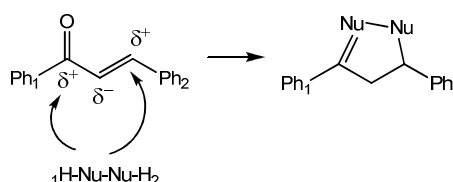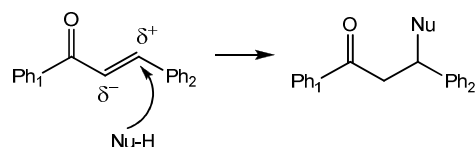
Pyrazoline (**32**) is a five-ring heterocycle which is composed of two nitrogen atoms and three carbon atoms, and several procedures of their synthesis have been developed. The most popular preparation procedure is the reaction of α,β-unsaturated carbonyl compound with hydrazine. Chalcone can be used as source of α,β-unsaturated carbonyl compound, and the reaction is conducted in weak acidic condition [42].
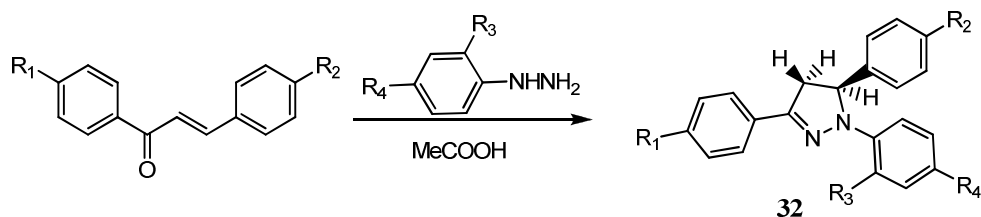
This synthesis route of pyrazoline derivatives was also reported by Katritzky and coworkers [43], Patel and coworkers [44], and Shah et al [45]. An interesting synthesis method of spiro-pyrazoline scaffold (**33**) using exocyclic α,β,γ,δ-unsaturated ketone as synthon was proposed by allowed it to react with diazomethane, and the reaction proceed regioselective and stereoselective [46].
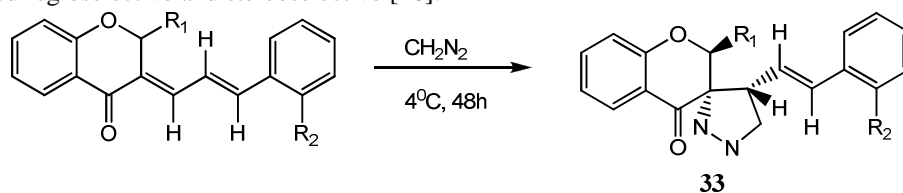
One of the most important six-member heterocyclic is pyrimidine. Pyrimidine scaffold exists in many natural and synthetic biologically active materials and also found as constituents of DNA or RNA base. Various synthesis route of pyrimidinone-nucleus has been reported by many authors, such as through one pot three-component Biginelli reaction [47], ring annulation of 2-amino-2-oxazoline acting as heteroamidine synthon by using two nucleophilic sites of the amidine moiety [48], and by tandem reaction of aza-Wittig/heterocumulene-mediated annulations [49]. However the most applied synthesis route of substituted pyrimidinones is the reaction of enone moiety of chalcone derivatives with urea or thiourea [50 - 53]. As reaction example of the transformation of a chalcone derivative into substituted pyrimidine (**34**) is displayed in the following reaction [54].
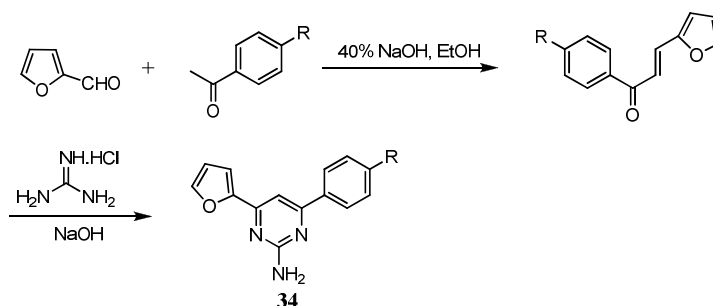
The classical method to synthesize seven-membered ring heterocyclic compound is ring enlargement reaction using Beckmann rearrangement [55]. However, due to its bi-electrophilic character, chalcone give an alternative route to build seven-membered ring through reaction with a bi-nucleophile to form derivatives of azepines, oxepines, or thiepins. Using chalcone derivative as intermediate and 1,2-diamino benzene, Bhatia et al [56] have successfully synthesized 2,4-disubstituted 1,5-benzodiazepine (**35**) as antibacterial agent. This synthesis route was also used to synthesize benzodiazepine [57].
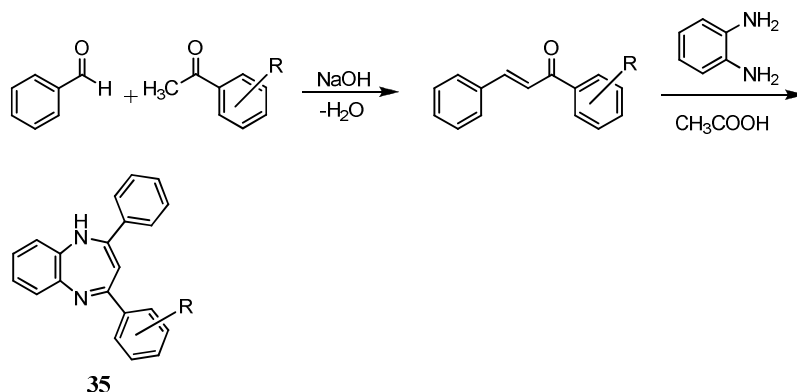
Applying the same synthesize route, many authors [58-61] have successfully synthesized benzothiazepine derivatives by the reaction of chalcone or its analog with 2-amino thiophenol,. The reaction equation of the synthesis of benzothiazepine (**36**) from chalcone derivative and 2-amino thiophenol is displayed below [62].
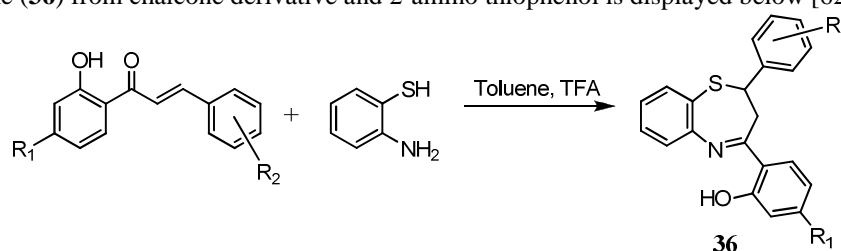

Beside used in the synthesis of heterocyclic compounds, chalcone is also applied in the synthesis of cyclohexenone derivatives (**37**). Preparation of cyclohexenone derivatives by the reaction between chalcone and 1,3-dicarbonyl compound was performed successfully and proceeded through Robinson annulations [63].
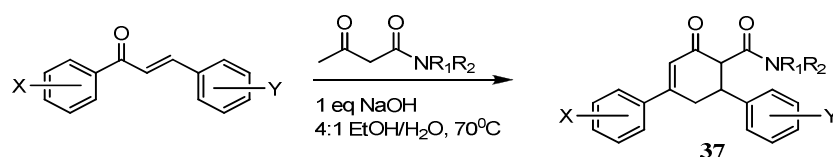

BIOACTIVITY OF CHALCONES

Chalcones are valuable chemicals because of their well known diverse pharmacological activity. A number of chalcones have demonstrated cytotoxic properties which is an implication of anticancer activity. Dimnock et al [64] have studied cytotoxic property of a number of chalcones and their related Mannich base toward murine P388 and L1210 leukemia cell lines, as well as human tumor cell lines, and they found that compound **21** exhibited the highest activity toward L1210 and human tumor cells. Compound **38** is other compound of interest due to its huge differential in cytotoxicity between P388 and L1210 cells, whereas compound **42** exhibited a high therapeutic index by comparison of the toxicity of P388 cells toward Molt 4/C8 T-lymphocytes. The study showed that in general the Mannich bases were more toxic than the corresponding chalcones.
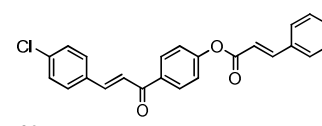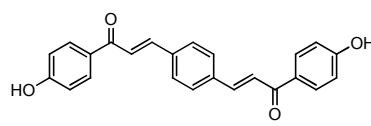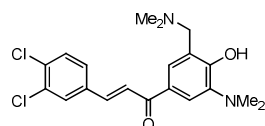
Attempting to determine the influence of relative orientation of the two phenyl rings toward cytotoxicity effect, Dimnock et al [65] studied the cytotoxicity properties of 2-arylideneindanones **41**, 2-arylidenetetralones **42**, and 2-arylidenesuberones **43** derivatives against murine P388, L1210, and Molt 4/C8 cancer cell lines, and found out that in general the order of cytotoxicity was **43** > **42** > **41**.

**41**   **42**   **43**
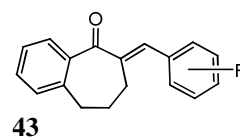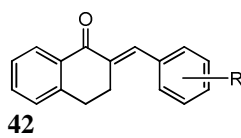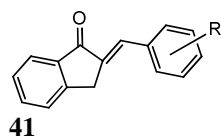
Substituted 6,7-dimethoxy-1-tetralones and 5,6-dimethoxy-1-indanones have also been synthesized and evaluated of their antitumor activity [36] and it was found that position of the lipophilic substituent affected the cytotoxic activity. 2'-amino chalcone derivatives displayed potential antitumor activity and also demonstrated significantly increased antitumor properties compared with the corresponding chalcones. Furthermore, position and the size of substituents are important for the activity of 2'amino chalcone [66].

Explorations of the mechanism of action an anticancer agent bring us to a better understanding of cancer and can lead us to design better anticancer drug. Licochalcones A (**44**) and E (**45**) are retrochalcone isolated from the root of *Glycyrrhiza inflata* exhibited the DNA topoisomerase I inhibitory activity in dose dependent manners and this property might explain the cytotoxic activity of these compounds against some human cancer cells line [6].

44   **45**   **46**
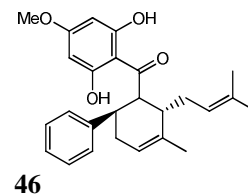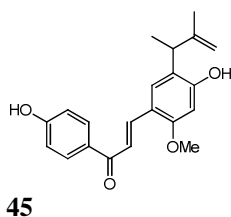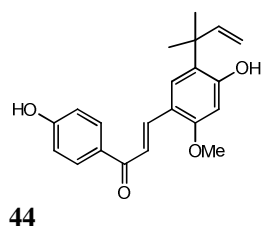
The mechanism of action of cytotoxic property toward human prostate cancer cell lines of Panduratin A (**46**) isolated form *Kaempferia pandurata* has already been explored [4]. Panduratin A was able to induce apoptosis through inhibition of procaspases 9, 8, 6, and 3 with significant increase in the ratio of Bax:Bcl-2. It indicates that the process involving a mitochondrial-dependent apoptotic pathway. Similar cytotoxic mechanism of action was shown by isobavachalcone (**47**), a constituent of *Angelica keiskei*. It reduced significantly pro-caspase-3 and pro-caspase-9 in neuroblastoma cell lines. Moreover, it can also activate Bax. These results suggested that mitochondrial-dependent pathway responsible for the apoptotic cell death in neuroblastoma by isobavachalcone application [67]. However, although the cytotoxic activity of xanthoangelol (**48**) - a major component of *Angelica keiskei* - is through apoptotic pathway, but it does not involve Bax/Bcl-2 signal transduction [68]. A boronic-chalcone derivative AM114 (**49**) also exhibited antimitotic activity through inhibition of proteasome and did not significantly disrupt the interaction of protein p53-MDM2 [34]

47   **48**   **49**
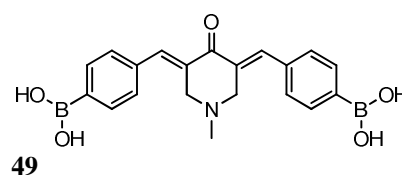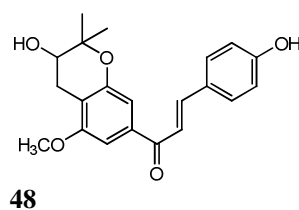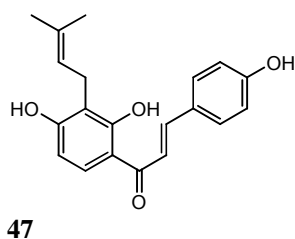
Due to the important role of 1,4-dioxane ring in displaying antihepatotoxic activity, chalcones bearing 1,4-dioxane ring system have been successfully designed, synthesized and tested to their antihepatotoxic activity. Compounds (**50**) and (**51**) exhibited potent activity compared to standard drug sylybon-70 [69]

50   **51**
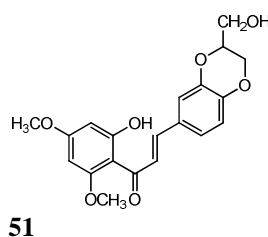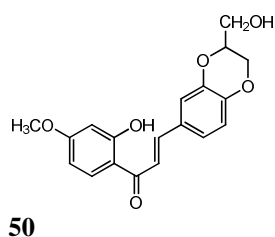
Derivatives of chalcones are also known for their antimalaria activity. Oxygenated chalcone such as 2,4-dimethoxy-4'butoxychalcone (**52**) exhibited potent activity against human malaria parasite *Plasmodium falciparum* in vitro

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[70]. Ferrocenyl chalcone derivatives (**53**) showed antiplasmodial activity in vitro. Parameters influencing antiplasmodial activity were location of ferrocene and the polarity of the carbonyl linkage. Chalcones with ferrocene adjacent directly to the carbonyl linkage were displayed more selective and potent antiplasmodial activity [71].

52
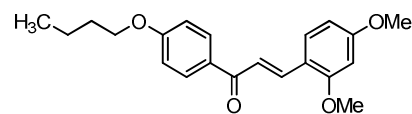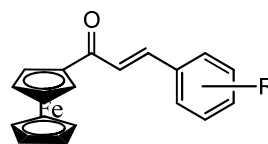
Another well known property of chalcones is their antimicrobial activity, and many authors have been reported about it. The chalcones of 2-hydroxy-1-acetonaphtone and 3-acetyl coumarin had been synthesized and tested of their antimicrobial activity. These compounds showed moderate to considerable of antibacterial and antifungal activity compared to the standard drugs chloramphenicol and fluconazole as positive control at dose of 1000 µg/mL [72]. Furthermore it was found out that chalcones attaching electron releasing group such as methoxy and hydroxyl group displayed better antibacterial activity than the others not having such functional groups [73], whereas chalcones having chloro, dichloro, or fluoro groups exhibited more antifungal activity. Chalcones bearing benzimidazolyl moiety exhibited active antibacterial and fungicidal properties [33], whereas the existence of phenyloxy moiety in chalcones is important for their antibacterial activity [74].

The existence of phenolic moiety in a compound indicates its antioxidant property. Synthesis of dihydroxylated chalcone derivatives and their radical-scavenging ability toward DPPH free radicals have been reported [5]. Furthermore study of the structure-activity relationship was also conducted. It was indicated that the very important structural factors to increase radical scavenging activity is the substitution pattern of two hydroxyl groups on ring B.

CONCLUSION

Chalcones are intermediate in the biosynthesis of flavonoid. They are valuable compounds whether from bioactivity aspects or from organic synthesis aspects. Chalcones exhibit diverse pharmacological activities and can serve as intermediate for synthesis of heterocyclic compounds. Due to these reasons, various preparation procedures were developed by many working groups, including ecofriendly protocol.

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