Chalcones: A review on synthesis and pharmacological activities

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INTRODUCTION

The chemistry of chalcone PGs is gaining intense research interest globally. The term “Chalcone” was coined by Kostanecki and Tambor (1899). Other names for chalcones are benzyl acetonaphone or benzylideneacetophenone. In the structure of a chalcone, two benzenoid rings are joined by an aliphatic chain of three carbons. Chalcone is an α, β-unsaturated ketonic compound consisting of two benzenoid rings with a wide variety of groups. Aromatic groups are connected to each other by three carbons, α, β-unsaturated ketonic system, highly electrophilic in nature having a linear structure (Awasthi et al., 2009; Cheng et al., 2000; Liu et al., 2001). They have ketoethylenic moiety (–CO–CH=CH–) in their structure. They have a conjugated double bond and an entirely delocalized π-electron-containing order on aromatic rings. Chalcones have been utilized as a precursor for the synthesis of compounds which possess pharmacological importance (Straub, 1995). The chalcones’ chemistry remains a major interest for scientists in the 21st century, producing a diversity of promising pharmacological activities like anti-inflammatory (Dhar et al., 2018; Fu et al., 2019; Gan et al., 2018; Li et al., 2017; Mahapatra et al., 2017; Md Idris et al., 2018; Sayed et al., 2018), analgesic (Fu et al., 2019), antigout as xanthine oxidase inhibitors (Hofmann et al., 2016), antihistaminic (Padaratz et al., 2009; Rossi and Avellino, 1957), anticancer (Gan et al., 2018; Hsieh et al., 2019; Khanapure et al., 2018; Özdemir et al., 2017; Pingaew et al., 2014; Sashidhara et al., 2010), antileishmanial (Insuasty et al., 2015), antimalarial (Pingaew et al., 2014), antiviral (Wan et al., 2015), antiulcer (Choudhary et al., 2012), antimicrobial (Benouda et al., 2019; Lal et al., 2018; Monga et al., 2014; Özdemir et al., 2017; Sayed et al., 2018), antioxidant (Bandgar et al., 2010), antibacterial (Balú et al., 2019; Emayavaramban et al., 2013; Gaur et al., 2014; Hsieh et al., 2012; Rammohan et al., 2020; Shukla et al., 2017), etc. Metochalcones increase bile secretion by stimulating the liver (Sahu et al., 2012) and sofalcone as an antiulcer agent, which increases the concentration of Prostaglandins from the mucosa causing a gastroprotection from Helicobacter pylori-induced ulcers (Higuchi et al., 2010). It is also found through clinical trials that hesperidin methylchalcone was tested and found effective for chronic peripheral venous lymhatic insufficiency (Beltramino et al., 1999, 2000) and hesperidin trimethylchalcone was found effective for trunk or branch varicosis (Weindorf and Schultz-Ehrenburg, 1987).
Chalcones have been known from earlier times to have an interesting moiety which is associated with a wide range of pharmacological activities. The majority of commonly found food chalcones are phloretin (Gerhauser, 2008; Mariadoss et al., 2019; Min et al., 2015) and its glucoside phloridzin, i.e., phloretin 2′-O-β-glucopyranoside which are present in apples, chalconaringenin in tomatoes (Echeverria et al., 2009; Kolot et al., 2019; Slimestad and Verheul, 2011), Arbutin in pears (Reiland and Slavin, 2015; Sasaki et al., 2014), and flavokavains in kava plants (Liu et al., 2018; Pinner et al., 2016). Chalcone possess a very good moiety due to which a variety of novel heterocyclic compounds with better pharmacological properties can be designed.

**METHODS OF SYNTHESIS OF CHALCONES**

Chalcones possess a simple moiety which makes its substitutions easy with simple and easy methods of synthesis. Currently, a wide range of schemes are available to synthesize various chalcone analogs.

**Claisen–Schmidt’s condensation**

It is a commonly employed and easy method (Scheme 1). In the method, chalcones are synthesize by condensing substituted or unsubstituted benzaldehyde with substituted or unsubstituted acetophenone with the use of bases or acids as catalysts in an appropriate solvent at about 50°C–100°C for few hours (Kaur and Narasimhan, 2018; Khanapure et al., 2018; Monga et al., 2014; Özdemir et al., 2017; Rahman et al., 2007; Reddy and Kathale, 2018). It is normally carried out in the liquid phase, but some syntheses occur in the solid phase, like resin was bound with acetophenone compounds and then reacted with benzaldehyde compounds (Mahapatra et al., 2015) or under solvent-free conditions such as catalytic condensation in the presence of triazabicyclodecene (Fringuelli et al., 2004). Additionally, microwave-assisted liquid and solvent-free condensation decrease synthesis time and elevate the production yield (Kakati and Sarma, 2011; Srivastava, 2008).

**Carbonylative Heck’s coupling reaction**

Chalcones have been synthesized by vinylation of aryl halide (such as phenyl halide) with styrene under carbon monoxide and the catalyst palladium can undergo carbonylative coupling (Bianco et al., 2003; Wu et al., 2010) (Scheme 2).

**Suzuki–Miyaura’s coupling reaction**

This coupling reaction takes place by combining benzoyl chloride and styryl boronic acid using Pd(PPh₃)₄, CsCO₃, and anhydrous toluene or by combining phenyl boronic acid and cinnamoyl chloride using Pd(PPh₃)₄, CsCO₃, and anhydrous toluene (Selepe and Van Heerden, 2013) (Scheme 3).

**Sonogashira’s isomerization coupling**

This reaction involves the synthesis of chalcones by the microwave coupling of the electron-insufficient group, like phenyl halide, and prop-2-yn-1-ol and catalyst PdCl₂(PPh₃)₄ and solvent like tetrahydrofuran (THF) (Braun et al., 2006; Takahashi et al., 1980) (Scheme 4).

**Continuous-flow deuteration reaction**

Ynones basically were synthesized by the process available in the literature by the reaction of benzoyl chloride and phenylacetylene under Sonogashira’s conditions and then for deuteration, which was carried out in an H-Cube system caused by replacing H₂O with D₂O as the deuterated source (Hsieh et al., 2015; Ötvös et al., 2016) (Scheme 5).

**Solid acid catalyst-mediated reaction**

Chalcones are prepared by using a solid acid catalyst which is heterogeneous in nature (Scheme 6). It involves the addition of aromatic aldehyde (such as benzaldehyde) and ethynyl benzene in ethylene dichloride solvent using a microwave condition and using ion-exchange resin, like amberlyst-15, as the solid acid catalyst (Rueping et al., 2011).

**Coupling reaction**

Chalcones are prepared by coupling benzaldehyde with phenylacetylene in hydrogen bromide and ionic liquids like BmimOTs (1-butyl-3-methyl-1H-imidazolium 4-methylbenzene-sulfonate) for about 12 hours at 100°C (Xu et al., 2004) (Scheme 7).
One-pot synthesis

It is an easy, efficient, and green method that allows the chalcone synthesis in a single reactor (Scheme 8). The reaction mixture consists of phenyl methanol and acetophenone with an oxidizing agent such as CrO₃. CrO₃ generates the benzaldehyde from phenyl methanol, which then involves the reaction with the acetophenone to give chalcone (Mahapatra et al., 2015).
Synthesis of chalcones using Schiff bases

Schiff bases result in aryl amino ketones, which in the presence of an acid lead to hydramine breakdown and produce products such as primary aromatic amine and chalcones (Abe et al., 2003; Gaonkar and Vignesh, 2017).

Microwave-assisted synthesis of chalcone

In this method, heterogeneous catalysts, such as $K_2CO_3$, $Ba(OH)_2$, p-Toluenesulfonic acid, $KF-Al_2O_3$, piperidine, and aqueous alkali, are employed to synthesize chalcones and their derivatives under microwave conditions (Blass, 2002; Gall et al., 1999; Mistry and Desai, 2004).

Ultrasound irradiation-assisted synthesis of chalcone

Ultrasound-assisted synthesis is another advantageous technique like microwave irradiation-assisted synthesis due to the fact that it completes the reaction within short period of time and yields a high percentage of products. For the synthesis of chalcones and their derivatives under ultrasound irradiation, heterogeneous catalysts like $K_2CO_3$, pulverized potassium hydroxide (KOH), NaOH, basic $Al_2O_3$, $KF-Al_2O_3$ are used productively (Adole et al., 2020; Calvino et al., 2006; Cancio et al., 2019; Li et al., 2002; Polo et al., 2019; Rammohan et al., 2020).

PHARMACOLOGICAL ACTIVITIES

Various chalcones and their derivatives have been synthesized and reported to have pharmacological activities like antimicrobial, antimalarial, anticancer, antifungal, anthelmintic, anti-inflammatory, anti-HIV, monoamine oxidase inhibition, antiangiogenic, antileishmanial activities, etc. A brief outline of some of the selected pharmacological activities is presented in the following sections.

Chalcone as an antimicrobial agent

α, β-unsaturated keto functions as highly reactive species, which shows nucleophilic conjugate addition of important protein due to which it shows antimicrobial activity.

The synthesis of a new chalone series with benzimidazolyl group was carried out to produce antimicrobial agents by condensing N-(4-(1H/benzo[d]imidazol-2-yl)phenyl)acetamide with benzaldehyde-related compounds using aqueous KOH at room temperature (Baviskar et al., 2009).

Novel nitrochalcones were synthesized to produce antimicrobial agents by condensing nitroacetophenone with some aromatic aldehydes by using a base at room temperature (Monga et al., 2014).

Chalcones AA (1–6) were prepared by Claisen–Schmidt’s condensation of 2-acetyl pyridine and aldehyde derivatives in diluted ethanolic KOH at room temperature (Prasad et al., 2008).
Physical properties of chalcones are presented in Table 1. Chalcones AB are synthesized by condensing aldehydes with o-hydroxy acetophenone, followed by reaction with I₂ and dimethyl sulfoxide (DMSO), which results in the synthesis of flavones and which shows antimicrobial property (Rathore et al., 2015).

Some of the novel fluorinated chalcones, AC, AD, AE (1–13), have been synthesized and tested for antitubercular activity for Mycobacterium tuberculosis H37Rv and antimicrobial activity for fungi and pathogenic bacteria (Burmaoglu et al., 2017).

Recently, chalcones AF (1–5) have been reported by the coupling of 1-(2,6-dichloro-4-trifluoromethyl-phenyl)-pyrolidine-2,5-dione, 1-(2,6-dichloro-4-trifluoromethyl-phenyl) piperidine-2,6-dione, and various aromatic aldehydes in the acetic acid. The resultant products had shown antimicrobial properties (Rajput and Sayyed, 2017).

Chalcones AG (1–10) were prepared by carrying out Claisen–Schmidt’s condensation between 2-acetyl-1-methylpyrrole and 5-(aryl)-furfural analogs. The consequential products were tested to possess antimicrobial activities for five pathogenic bacteria and four fungi (Özdemir et al., 2017).
A novel series of dehydroacetic acid chalcone-1,2,3-triazole analogs AH (1–16) was designed and synthesized. The synthesized compounds were evaluated for antimicrobial activities against four bacterial and two fungal strains (Lal et al., 2018).

![AH (1-16)](image)

Chalcones as anticancer agents

The synthesis of a novel sequence of 2',5'-dialkoxyl chalcones BA (1–10) was carried out by condensing various aromatic ketones with various suitable and substituted benzaldehydes. The compounds were evaluated to show antitumor and chemopreventive activities (Cheng et al., 2008).

![BA (1-10)](image)

Quinazolinone-Chalcone

A novel series of chalcones BB (1–12) with 3-aryl thiophene-2-aryl and hetero aryl moieties was prepared and tested to show in vitro anticancer property for human colon cancer cell lines (Venkataramireddy et al., 2016).

| Compound | R | Compound | R |
|----------|---|----------|---|
| 1        | H | 9        | 3-BrC₆H₄CH₂- |
| 2        | 2-CH₃C₆H₄CH₂- | 10 | 4-BrC₆H₄CH₂- |
| 3        | 3-CH₃C₆H₄CH₂- | 11 | 2-FC₆H₄CH₂- |
| 4        | 4-CH₃C₆H₄CH₂- | 12 | 3-FC₆H₄CH₂- |
| 5        | 2-NO₂C₆H₄CH₂- | 13 | 4-FC₆H₄CH₂- |
| 6        | 3-NO₂C₆H₄CH₂- | 14 | 4-OCH₃C₆H₄- |
| 7        | 4-NO₂C₆H₄CH₂- | 15 | 4-BrC₆H₄- |
| 8        | 2-BrC₆H₄CH₂- | 16 | 4-NO₂C₆H₄- |

A new quinazolinone–chalcone derivative was prepared by condensing the substituted aromatic aldehyde and substituted aromatic ketone in Ba(OH)₂ and testing it for possessing anticancer activity (Wani et al., 2015).

| Compd. | R | R₁ | R₂ | Compd. | R | R₁ | R₂ |
|--------|---|----|----|--------|---|----|----|
| 1      | O | Me | OCH₃ | 7      | Me | H | OCH₁ |
| 2      | MeO | H | OCH₃ | 8      | | | |
| 3      | MeO | H | OCH₃ | 9      | | | |
| 4      | Br | H | OCH₁ | 10     | | | |
| 5      | I | H | OCH₁ | 11     | | | |
| 6      | H | OCH₁ | 12   | | | |
Ngameni et al. (2013) synthesized O-allyl chalcones BC (1–8) by condensing O-allyl vanillin with various acetophenones and reported antiproliferative activity of the synthesized chalcone derivative.

\[
\begin{array}{cccc}
\text{Compd.} & R_1 & R_2 & R_3 \\
1 & H & H & H \\
2 & OMe & H & H \\
3 & Me & H & Me \\
4 & H & Me & H \\
5 & H & H & Me \\
6 & H & Me & H \\
7 & Me & H & Me \\
8 & Me & H & Me \\
\end{array}
\]

Novel derivatives of chalcones BD were prepared by condensing appropriate acetophenones and various benzaldehydes, followed by the reaction of the produced product (chalcone) with sodium acetate in ethanol to give flavanones BE, which were evaluated as antiproliferative agents (Ketabforoosh et al., 2014).

Chalcones as anti-inflammatory agents

A novel chalcone 20-hydroxy-3,4-dichlorochalcone was synthesized which was evaluated for anti-inflammatory activity (Won et al., 2005).

\[
\begin{array}{cc}
\text{NaOAc, EtOH} & \text{Reflux} \\
\end{array}
\]

R = H; R_1 = H, OMe, Cl, Br

Dichlochalcone

Fluorinated chalcone analog was prepared by Claisen–Schmidt’s condensation and by reacting with SOCl/EtOH, which possesses a powerful anti-inflammatory property (Hasan et al., 2012).
Chalcones as antioxidants

A sequence of novel derivatives of chalcones DA (1–6) with heterocyclic moiety was prepared by Claisen–Schmidt’s condensation of 2-acetyl-5-chlorothiophene and various benzaldehyde derivatives with a catalytic amount of NaOH and methanol as solvents at room temperature and evaluated as antioxidant agents (Kumar et al., 2013).

\[
\text{DA (1-6)}
\]

| Compound | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | Compound | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> |
|----------|-----------|-----------|-----------|----------|-----------|-----------|-----------|
| 1        | H         | H         | H         | 4        | OCH<sub>3</sub> | H         | H         |
| 2        | H         | H         | H         | 5        | H         | OCH<sub>3</sub> | H         |
| 3        | H         | H         | H         | 6        | H         | H         | OCH<sub>3</sub> |

A new series of 2,4-dihydroxy chalcones DB (1–5) was prepared by the condensation of dihydroxy acetophenone and various benzaldehydes, followed by reaction with DMSO in the presence of iodine to give flavonoids DC (1–5), which were evaluated for antioxidant activity (Murti et al., 2013).

\[
\text{DB (1-5)}
\]

\[
\text{DC (1-5)}
\]

Chalcones as an antiepileptic

A new series of chalcones was prepared through Claisen–Schmidt’s condensation, which was further tested for antiepileptic property (Sharma et al., 2013).

\[
\text{DD}
\]

\[
\text{DE}
\]

\[
\text{DF}
\]

A new series of derivatives of chalcones was synthesized and tested for antioxidant activity (Wu et al., 2014).

where \( R_1 = \text{H, OCH}_3 \); \( R_2 = \text{CH}_3, \text{C}_2\text{H}_5, \text{H}_2\text{C=CH}, \text{Ph}, 4\text{-ClPh, 2-FPh, and Benzyl.} \)

A novel chalcone, i.e., glycyglabrone, was isolated from the roots of liquorice (Glycyrrhiza glabra), along with three known derivatives, viz. licoagrochalcone, licochalcone, and kanzonol. The obtained chalcones DD, DE, and DF were found to possess antioxidant property (Chen et al., 2017).

\[
\text{Chalcone derivatives}
\]
A new series of 3,5-diphenyl-2-pyrazoline-1-carboxamide analogs 1–20 were prepared by the reaction of substituted chalcones with semicarbazide hydrochloride, which were evaluated to be potent antiepileptic derivatives (Siddiqui et al., 2010).

(i) \( \text{CH}_3\text{OH} \), Conc. \( \text{H}_2\text{SO}_4 \), (ii) \( \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \), and (iii) \( \text{CH}_3\text{OH}; \text{Glacial acetic acid.} \)

| Compound | \( R_1 \) | \( R_2 \) | Compound | \( R_1 \) | \( R_2 \) |
|----------|------|------|----------|------|------|
| 1        | H    | H    | 6        | 4-N(Me)  | 4-OH |
| 2        | 3-NO | H    | 7        | 3-N\( \text{O}_2 \) | 4-Cl |
| 3        | 4-Cl | H    | 8        | 4-N(Me)  | 4-F |
| 4        | 4-Cl | 4-OH | 9        | 4-Cl    | 4-F |
| 5        | 2-Cl | 4-OH | 10       | 4-N\( \text{O}_2 \) | 4-F |

Chalcones as antidiabetic agents

A novel series of chalcone-based aryl oxypropanolamine FA, FB, FC, and FD was synthesized and evaluated as powerful antidiabetic and antidysslipidemic agents (Shukla et al., 2017).

A new chalcone series EA (1–10) was synthesized which incorporated hydrazide derivatives and were evaluated as anticonvulsant agents (Kumar and Chauhan, 2015).

A new series of 60 derivatives of chalcone were synthesized having substitutions on Ring A or were unsubstituted by Claisen–Schmidt’s condensation of some aromatic ketones with various benzaldehydes in 50% w/v KOH/H\(_2\)O with solvent ethanol. Out of these 60 derivatives, 12 derivatives were found to be active as antidiabetic agents (Hsieh et al., 2012).

\( R_1 \) = H, OH, F, Cl, Br, I; \( R_2 \) = H, OMe, OBn, -OCH\(_3\)O-

A series of chalcone FE and its 2-pyrazoline analogs FF, FG, FH, FI, and FJ was prepared and tested to be antidiabetic agents (Emayavaramban et al., 2013).
A novel series of chalconeimines, FV, FW, FX, FY, and FZ, was prepared and evaluated for antidiabetic activity via *in-vitro* α-amylase inhibition activity (Balu et al., 2019).

Chalcones as antihypertensive agents

Novel chalcones GA (1–7) were synthesized, consisting of pyrimidine as the basic moiety, and tested to be potent antihypertensive agents (Bukhari et al., 2013).
Studies were carried out on vasorelaxant and antihypertensive properties of dihydrospinochalcone and isocordoin isolated from Lonchocarpus xuul (Avila-Villarreal et al., 2013).

Novel chalcones with quinoline in their structure GB were prepared and tested to have powerful antihypertensive moiety (Kumar et al., 2015).

**Chalcones as antimalarial agents**

Three aminoalkylated derivatives of chalcones HA (1–3) were synthesized by Claisen–Schmidt’s condensation between chloroacetophenone and vanillin. After this reaction, addition of the amine group was carried out through Mannich’s reaction. The synthesized derivatives were evaluated for antimalarial activity against Plasmodium falciparum strain (3D7) and molecular docking was also performed. Molecular docking and biological evaluation shows that compound HA2 was the most active derivative among the synthesized derivatives (Syahri et al., 2020).

**CONCLUSION**

From this review, it can be stated that chalcones and their derivatives show a wide spectrum of biological activities, viz anticancer, antimicrobial, anticonvulsant, antioxidant, anti-inflammatory activities, etc. That is why the attention of scientists has increased towards chalcones in searching for novel and biologically potent derivatives from them.

**CONFLICT OF INTEREST**

None.

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**Table 1.** Physical properties of chalcone.

| IUPAC name     | trans-1,3-diaryl-2-propen-1-one |
|----------------|---------------------------------|
| Molecular formula | C₁₅H₁₂O                         |
| Molar mass       | 208.26 g mol⁻¹                  |
| Exact mass       | 208.088815                      |
| Density          | 1.071 g/mol                     |
| Melting point    | 55°C–57°C                       |
| Boiling point    | 345°C–348°C                     |
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