Recent Advances in Chalcones: Synthesis, Transformation and Pharmacological Activities

Oluwaseyi Bukky Ovonramwen¹ *, Bodunde Joseph Owolabi¹ and Amowie Philip Oviawe¹

¹Department of Chemistry, University of Benin, P.M.B. 1154, Benin City, Nigeria.

Authors’ contributions

This work was carried out in collaboration among all authors. Author OBO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors BJO and APO managed the analyses of the study. Author OBO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOCS/2019/v6i318996

Editor(s):
(1) Prof. Pradip K. Bhowmik, Department of Chemistry, University of Nevada, Las Vegas 4505 Maryland Parkway, USA.

Reviewers:
(1) Mamoona Rauf, Abdul Wali Khan University Mardan, Pakistan.
(2) B. C. Revanasiddappa, Nitte Deemed to be University, India.
Complete Peer review History: https://sdiarticle4.com/review-history/50935

Received 09 June 2019
Accepted 18 August 2019
Published 21 September 2019

ABSTRACT

Chalcones are useful intermediates in the synthesis of heterocyclic compound and the unique reagents in organic synthesis. The usual approach to obtain chalcones is through Claisen-Schmidt condensation. Several novel heterocyclic chalcone analogs have emerged. Chalcones are multifunctional molecules that possess promising pharmacological activities. Chalcones are known for anti-cancer, antioxidant, anti-inflammatory, anti-microbial, anti-tubercular, antileishmanial, antimalarial, anthelmintic, osteogenic activities. This review article focuses on recent applications of Claisen-Schmidt condensation reaction employed in the synthesis of chalcone, its transformation to heterocyclic compounds and pharmacological activities.

Keywords: Chalcone; heterocycles; synthesis; pharmacological activities.

*Corresponding author: E-mail: adebuloyeoluwasey@yahoo.com;
1. INTRODUCTION

Chalcones, unsaturated aromatic ketones are natural products, group of biaryl propenones of C6-C3-C6 precursors. 1,3-Diphenyl-2-propene-1-one is the main pharmacophore and benzylideneacetophenone as a parent member of chalcones (Fig. 1). They are electrophile (Michael acceptor) with three reactive carbons (α,β-unsaturated ketone) and a diverse array of substituents that cause both carbons to be readily attacked by nucleophiles. They contain conjugated double bonds with a completely delocalized π electron system on the structure which enables them to undergo electron transfer reactions. Chalcones transformation might proceed either by 1,4-addition or 1,2-addition. Examples of heterocyclic compounds from chalcones are pyrazoles [1,2], pyroles [3-5], pyrazoline [6], isoxazoles [7-9], pyrimidines [10,11], pyridines [12-16], indoles, indazoles, triazoles [17,18], imidazoles [19,20], thiazines [21], 1,5-benzodiazepines, 1,3,4-thiadiazepines, benzazepines, and 1,5-benzodiazepines [22]. Chalcones are multifunctional molecules that possess promising pharmacological activities. Chalcones have been found useful as anticancer [23-25], antioxidant [26-29], anti-inflammatory [30-32], anti-microbial [23,33-36], anti-tubercular [34,37,38], antileishmanial [39], antimalarial [40-42], anthelmintic [27], osteogenic activity [43]. This review article focuses on recent applications of Claisen-Schmidt condensation reaction employed in the synthesis of chalcone, its transformation to heterocyclic compounds and pharmacological activities.

![Fig. 1. Structure of chalcone](image)

2. PREPARATION OF CHALCONES

The usual approach to obtain chalcones is through Claisen-Schmidt condensation, several novel heterocyclic chalcone analogs have emerged [23,43,44]. Rajkumar and co-workers synthesized 1-hydroxynaphthalene-2-ylchalcones 3 from 1-hydroxynaphthalene-2-yl ethanone 1 with substituted benzaldehydes 2 [45]. Meanwhile, Díaz-Carrillo et al. obtained chalcones 6 from substituted aceto phenone 4 and substituted benzaldehydes 5 catalyzed by BF₃•OEt₂ in dry dioxane [27]. Dhananjayulu et al. used silica gel supported piperidine as an alternative base to prepare 2-hydroxychalcone 9 from 2-hydroxyacetophenone 7 and substituted benzaldehyde 8 [46]. In another work, Ali et al. produced heterocyclic analogs 12 from acetylated benzimidazoles 10 with benzaldehyde derivatives 11 [44]. Whereas indolyl chalcones 15 were synthesized from N-methyl indole-3-carboxaldehyde 14 and different acetophenones 13 [43]. Likewise, Wang et al. reported chalcone 18 from substituted aromatic aldehydes 17 and acetophenone 16 catalyzed by NaOH or HCl [29] (Scheme 1).

2.1 Mechanism of Claisen-Schmidt’s Chalcone Synthesis

Steps in chalcone formation are from first enolization, C=C bond, proton equilibration, second enolization, and hydroxide elimination and C=C bond formation [47] (Scheme 2).

3. CHALCONES TRANSFORMATION IN HETERO CYCLES SYNTHESIS

Chalcones are useful precursors in producing heterocyclic compounds (Scheme 3).

Meanwhile, Aswin et al. reported pyrimidine-2(1H)-thione 20 from the condensation of chalcone 19 with thiourea using triphenylphosphine (PPh₃) as a catalyst [10]. Pyrimidine derivatives 22 were also reported from chalcones 21 with urea in the presence of ethanolic potassium hydroxide solution [11] (Scheme 4).

In another work, Rajaguru et al. described the synthesis of condensation of substituted imidazoles 26 from the reaction of azidochalcones 23, aryl-aldehydes 24 and anilines 25 with erbium triflate as a catalyst [19]. Likewise, Zhu et al. developed tetrasubstituted imidazoles 29 from oxidative coupling of chalcones 27 and amides [48]. Moreno, polysubstituted aminimidazoles 32 were via alkene vicinal C-N bonds formation of 2-bromo-2-alkenones 30 with guanidine 31 [20] (Scheme 5).

4,6-Diphenyl substituted thiazine derivatives 34 were prepared in two steps through chalcone 33 and thiourea via a conventional and microwave irradiation methods [21] (Scheme 6).
Scheme 1. Chalcones synthesis
Scheme 2. Mechanism of chalcone synthesis

Scheme 3. Heterocyclic compounds from chalcone
Scheme 4. Synthesis of pyrimidine from chalcone

\[
\text{Ar}^1 + \text{Ar}^2 + \text{Ar}^3 \xrightarrow{\text{reflux, 1-3 h}} \text{Ar}^4
\]

\[
\begin{align*}
\text{Ar}^1 &= \text{Ph, 4-ClPh, 4-CH}_3\text{Ph, 4-CH}_2\text{OPh, 4-NO}_2\text{Ph} \\
\text{Ar}^2 &= \text{Ph, 3-ClPh, 4-ClPh, 4-CH}_3\text{Ph, 2-thiazolyl} \\
\text{Ar}^3 &= \text{Ph, 4-ClPh, 4-BrPh, 4-CF}_3\text{Ph, 4-CH}_3\text{Ph, 3-CH}_2\text{OPh, 4-CH}_3\text{OPh, 4-NO}_2\text{Ph} \\
\text{Ar}^4 &= \text{Bz, Ph, 4-ClPh, 2-BrPh, 2-Cl-3-CH}_3\text{OPh, 4-BrPh, 4-FPh, 4-CF}_3\text{Ph, 4-CH}_3\text{OPh, 4-morpholinyl}
\end{align*}
\]

Scheme 5. Synthesis of substituted imidazoles from chalcones

\[
\begin{align*}
\text{Ar}^1 + \text{Ar}^2 + 1.2 \text{eq } \text{HN-} + 3 \text{eq } \text{H}_2\text{NCl} & \xrightarrow{\text{dioxane, 100 °C, ~ 16 h}} \\
\text{Ar}^1 &= \text{Ph, 4-CH}_3\text{Ph, 4-CNPh, 4-NO}_2\text{Ph} \\
\text{Ar}^2 &= \text{Ph, 4-ClPh, 4-CH}_3\text{Ph, 4-CH}_2\text{OPh, 4-NO}_2\text{Ph}
\end{align*}
\]
Furthermore, Osman et al. reported pyrazoline-1-carbothioamide 36 from the cyclization reaction of chalcones 35 and thiosemicarbazide [6] (Scheme 7).

Yang et al. studied the reaction of enaminone 37 and tosyl azide to produce NH-1,2,3-triazole 38 [17]. Meanwhile, Wan et al. obtained a series of N-substituted 1,2,3-triazoles 41 from NH-based secondary enaminones 39 and tosyl azide 40 [18] (Scheme 8).

Likewise, El-Gamil described the synthesis of 1,5-benzodiazepines 45 and 46 from α-phenylenediamine 44 and variously substituted chalcones 42 and 43 [22] (Scheme 9).
In another approach, Dou and co-workers synthesized 5-arylisoaxazole derivatives 50 from 3-(dimethyl-amino)-1-arylprop-2-en-1-ones 49 treated with hydroxylamine hydrochloride in aqueous media without using any catalyst [7]. Also, chalcone 51 was used to obtain 3,5-diphenylisoaxazole 52. Isoxazole substituted 9-anilino acridines 54 were synthesized from some novel chalcone 53 using microwave irradiation [9] (Scheme 10). Zhang and co-workers reported di-, tri-, and tetrasubstituted (aryl, alkyl, and or vinyl) pyrazoles 57 from readily available α,β-unsaturated aldehydes/ketones 55 and hydrazine salts 56 without isolation of the less stable intermediates hydrazones [1]. Meanwhile, Ding et al. obtained polysubstituted pyrazoles 60 from hydrazine 59 and chalcones (Michael acceptors) 58 in good yields [2] (Scheme 11).
Scheme 11. Pyrazoles from chalcones

Scheme 12. Synthesis of pyridines from chalcones
In another work, Huang and co-workers produced 2-aryl-substituted pyridines 63 from chalcones 61 with oxime-based 62 [12]. Likewise, di-, tri-, tetra-, and pentasubstituted pyridines, as well as fused pyridines 66, were obtained from chalcones 64 and 2-fluoro-1,3-dicarbonyl-initiated 65 in one-pot Michael addition of [5 + 1] [13]. In another approach, Chen et al. reported the synthesis of 3-acylpyridines and pyridine-3-carboxylates 69 from the saturated ketone substrate 68, followed by [3+3] annulation with β-enaminone or β-enaminoester 67 [14]. More so, 7-exo-dig cyclization reaction of N-propargyl enaminones 70, with alcohols/thiols and aldehydes 71 were used to prepare 2-alkoxy/2-sulfenyl pyridines and dihydrofuro[2,3-b]pyridines 72 [15]. While Abd El-Sattar et al. reported pyridine 74 from chalcone 73 and malononitrile [16] (Scheme 12).

Imbri et al. reported pyrrole-2-carboxylates and -carboxamides 77 from chalcones 75 and glycine esters or amides 76 [3]. In another paper, Wang et al. obtained polysubstituted pyroles 80 from iodine-catalyzed tandem Michael addition/oxidative annulation of enamines 78 and allenes 79 in good yields under mild conditions [4]. Likewise, substituted indole/azaindole-3-acetic acid derivatives 83 synthesized from the coupling of 4-acetoxy-2-butenonic acid derivatives 81 with N-Ts o-bromoanilines 82 [5] (Scheme 13).

\[
\begin{align*}
\text{Ar} + \text{EtO}_2C\text{NHCl} & \overset{\text{1 eq AcOH, pyridine reflux 23-53 h}}{\rightarrow} \text{EWG} \\
\text{R}^1\text{OR} & \overset{\text{2 eq DDQ reflux 22-66 h}}{\rightarrow} \text{X, Br}
\end{align*}
\]

\[
\begin{align*}
\text{R}^\text{NH} + \text{CO}_2\text{Me} & \overset{5 \text{ mol}-\% \text{I}_2, 2 \text{ eq TBHP, } 5 \text{ mol}-\% \text{K}_2\text{CO}_3, \text{DCE, 60 °C, 1-12 h}}{\rightarrow} \text{R}^{\text{11}}\text{O}_2\text{C} \\
\text{R}^{\text{1}} & \overset{\text{R = Et, Bn, R}^{\text{11}} = \text{alkyl}}{\rightarrow} \text{X = H, Br}
\end{align*}
\]

\[
\begin{align*}
\text{AcO} + \text{Y} & \overset{5 \text{ mol}-\% \text{Pd(OAc)}_2, 0.1 \text{ eq } \text{P(o-tol)}_2, 3 \text{ eq DIPEA, DMA, 100 °C or 120 °C 12-24 h}}{\rightarrow} \text{Ts}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{C} + \text{Y} & \overset{\text{X = Br (120 °C), I (100 °C)}}{\rightarrow} \text{Ts}
\end{align*}
\]

**Scheme 13. Pyrrole from chalcones**
4. PHARMACOLOGICAL ACTIVITIES

Chalcones have broad and multiple pharmacological activities because of the α, β-double bond, and the presence and the positions of chemical substituents which help in viral disorder, cardiovascular diseases, parasitic infections, pain, gastritis, stomach cancer, cosmetic formulation ingredients. They are useful as anticancer, antidiabetic, anti-inflammatory, and antidiuretic agents.

4.1 Antimalarial Activities

Chalcones with inhibitory activity against in vitro Plasmodium parasites provide a useful marker to identify a potential antiplasmodial. Syahri et al. synthesized and evaluated several chalcones for antiplasmodial potential, and found compound 84 actives with an IC50 (0.59 mM) [40]. In another work, 4-Benzimidazole chalcone 85 was a potent antimalarial agent because of the OCH3 moieties at position two and four in the chalcones [41]. In another paper, chalcone 86 exhibited promising antiplasmodial activities (50% inhibitory concentration [IC50] values 7.45±0.65 and 6.01±0.29 µg/ml, respectively) [42] (Fig. 2).

4.2 Anti-inflammatory Activities

Rücker and co-workers used electrophilicity of alpha-substituted chalcone analog 87 and 88 (CF3, Br, and Cl) to fine-tune therapeutic effects as potent anti-inflammatory agents in-activating nuclear factor erythroid 2 (NFE2)-related factor 2 (Nrf2) and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), with corresponding effects on their respective transcriptional gene products with significant reduction observed in Inducible nitric oxide synthase (iNOS) at a nanomolar range of IC50 values [30]. Debarshi and Ruchi also reported imidazole containing Murrayanine based chalcone 89 as a promising anti-inflammatory agent [31]. Synthetic halo-azachalcones 90 exhibited more significant inhibition [32] (Fig. 3).

![Chalcone derivatives with antimalarial activities](image1)

![Chalcone derivatives with antiinflammatory activities](image2)
4.3 Anti-microbial Activities

In their paper, Thasneem and co-workers concluded that chalcone 91 with NH$_2$ and NO$_2$ showed excellent activity against *Staphylococcus aureus* (ATCC5922) and *Escherichia coli* (ATCC6633) respectively whereas OH showed excellent activity against *Saccharomyces cerevisiae* [33]. In another paper, compounds 92 with substituents H, 2-F, and 2,5-diF displayed activities against the *S. aureus*, *S. pyogenes*, *E. faecalis*, *E. coli*, and *P. aeruginosa* while 92 substituent H and compound 93 were active against tested *C. albicans* [34]. The presence of halogens in chalcone 94 increases microbial susceptibility [35]. Özdemir et al. found compound 95 (4-Cl, 2,5-diCl) significantly active against *C. krusei* than the reference drug (ketoconazole) in ATP bioluminescence assay, whereas flow cytometry analysis revealed that the percentage of dead cells treated with substituent 4-Cl was more than that treated with 2,5-Cl and ketoconazole. According to Ames MPF assay, compound 95 (4-Cl, 2,5-diCl) was found to be non-genotoxic against TA98 and TA100 with/without metabolic activation [23]. In another work, compound 96 shown similar antifungal activity to ketoconazole against *C. albicans* (ATCC 24433), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), and *C. glabrata* (ATCC 90030) and as found potential ergosterol biosynthesis inhibitor [36] (Fig. 4).

4.4 Antileishmanial Activity

In another work, compound 97 showed good antileishmanial activity [39] (Fig. 5).

![Fig. 4. Chalcone derivatives with antimicrobial activities](image1)

![Fig. 5. Chalcone derivative with an antileishmanial activity](image2)
4.5 Anti-cancer Activities

In another investigation, Özdemir and co-workers found compound 98 (4-NO$_2$ and 2-NO$_2$) active and selective on the A549 human lung adenocarcinoma and HepG2 human hepatocellular carcinoma cell line respectively than cisplatin in MTT assay [23]. Meanwhile, compound 99 potently inhibited CYP1B1 with an IC$_{50}$ (~0.2 μM) in Sacchrosomes™ and CYP1B1-expressing live human cells [24]. While compound 100 possessed both anti ligase (inhibit human DNA Ligase I) and antiproliferative activity (enhanced cytotoxicity against colon cancer (DLD-1 at IC$_{50}$ 4.6µM)) [25] (Fig. 6).

4.6 Anti-Tubercular (TB) Activities

Alam et al. evaluated heterocyclic chalcones 101 for anti-tubercular activity [37], while, Solankee and Tailor found chalcone 102 to exhibit promising activity [38]. In another work, compound 103 with trimethoxy on ring A and fluoro groups on the B showed enhance activity with IC$_{50}$ (≤16,760) against *Mycobacterium tuberculosis* H37Rv compared to the standard drugs Ethambutol (EMB) and Isoniazid (INH) [34] (Fig. 7).

4.7 Osteogenic Activity

In another investigation, compound 104 displayed significant bone matrix mineralization from alkaline phosphatase (ALP) activity and mRNA expressions of osteogenic marker genes (BMP2, RUNX-2, and OCN) at 1 pM concentration [43] (Fig. 8).

4.8 Anthelmintic Activity

Díaz-Carrillo et al. found out the number and position of hydroxyl substituent in ring B to be responsible for the chalcone antiparasitic activity of chalcones 105 and 106 which at 20 mg/mL was able to kill the parasite at the lesser treatment time about six times lower than the control drug Praziquantel. In conclusion, at least one meta or para hydroxyl group in ring B was adequate for the activity of the synthetic chalcones against *H. nana* parasite [27] (Fig. 9).

![Fig. 6. Chalcone derivative with anti-cancer activities](image1)

![Fig. 7. Chalcone derivative with anti-tubercular activities](image2)
Fig. 8. Chalcone derivatives with osteogenic activity

![Chemical structure](image)

Fig. 9. Chalcone derivatives with anthelmintic activities

![Chemical structure](image)

Fig. 10. Chalcone derivatives with antioxidant activities

![Chemical structure](image)

4.9 Antioxidant Activity

In another investigation, Lahsasni and co-workers, surprisingly found compound 107 (68.58% at C = 2μg/ml) more effective as an antioxidant agent than the ascorbic acid [26]. Meanwhile, the meta- and para-dihydroxy substitution patterns in ring B of chalcones (catechol structure in ring B) 108 were the best combinations for the highest antioxidant activity compared to caffeic acid (positive control) [27]. Stepanic et al. found compound 109 potent in 1,1-diphenyl-2-picrylhydrazyl (DPPH+) radical scavenging activity, through single electron transfer followed by a proton transfer (SET-PT) mechanism as revealed by density functional theory (DFT) modeling [28]. Likewise, compound 110 played protective and therapeutic roles against ischemia/reperfusion-related brain injury for both in vitro and in vivo as free radical scavengers or Nuclear factor erythroid 2-related factor 2 (NRF2) pathway stimulators [29] (Fig. 10).

5. CONCLUSION

In summary, chalcones are a real intermediate in the synthesis of heterocyclic compounds, a multifunctional molecule of great pharmacological activities that are usually synthesized via Claisen-Schmidt synthetic method. Chalcones play a functional role in agricultural, medicinal, and industrial chemistry. Therefore, chalcones and their derivatives required further progresses through a modification to achieve more of these unique precursors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.
REFERENCES


35. Batheimerly N, Charles FN, Pantaleon A, Azeh NN, Estella T, Hortense GK, Aghem FK, Ronel TA, Olivier AK, Ngadjui BT.
DOI: 10.9734/BJPR/2016/28243
DOI: 10.3390/molecules23040831
DOI: 10.1016/j.aptb.2017.07.004
DOI: 10.1111/j.1747-0285.2012.01383.x 
Epub 2012 Apr 13.
DOI: 10.1021/acs.joc.6b00959
DOI: 10.1021/acs.orglett.5b01854
© 2019 Ovonramwen et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.