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# Recent Advances in Chalcones: Synthesis, Transformation and Pharmacological Activities

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***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.*

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## 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.*

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## 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], pyrroles [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, benzoazepines, and 1,5-benzodiazepines [22]. Chalcones are multifunctional molecules that possess promising pharmacological activities. Chalcones have been found useful as anti-cancer [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.

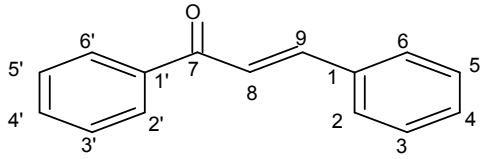



**Fig. 1. Structure of chalcone**

## 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-hydroxynapthalen-2-ylchalcones **3** from 1-hydroxynapthalen-2-yl ethanone **1** with substituted benzaldehydes **2** [45]. Meanwhile, Díaz-Carrillo *et al.* obtained chalcones **6** from substituted acetophenone **4** and substituted benzaldehydes **5** catalyzed by $BF_3$•$OEt_2$ 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).

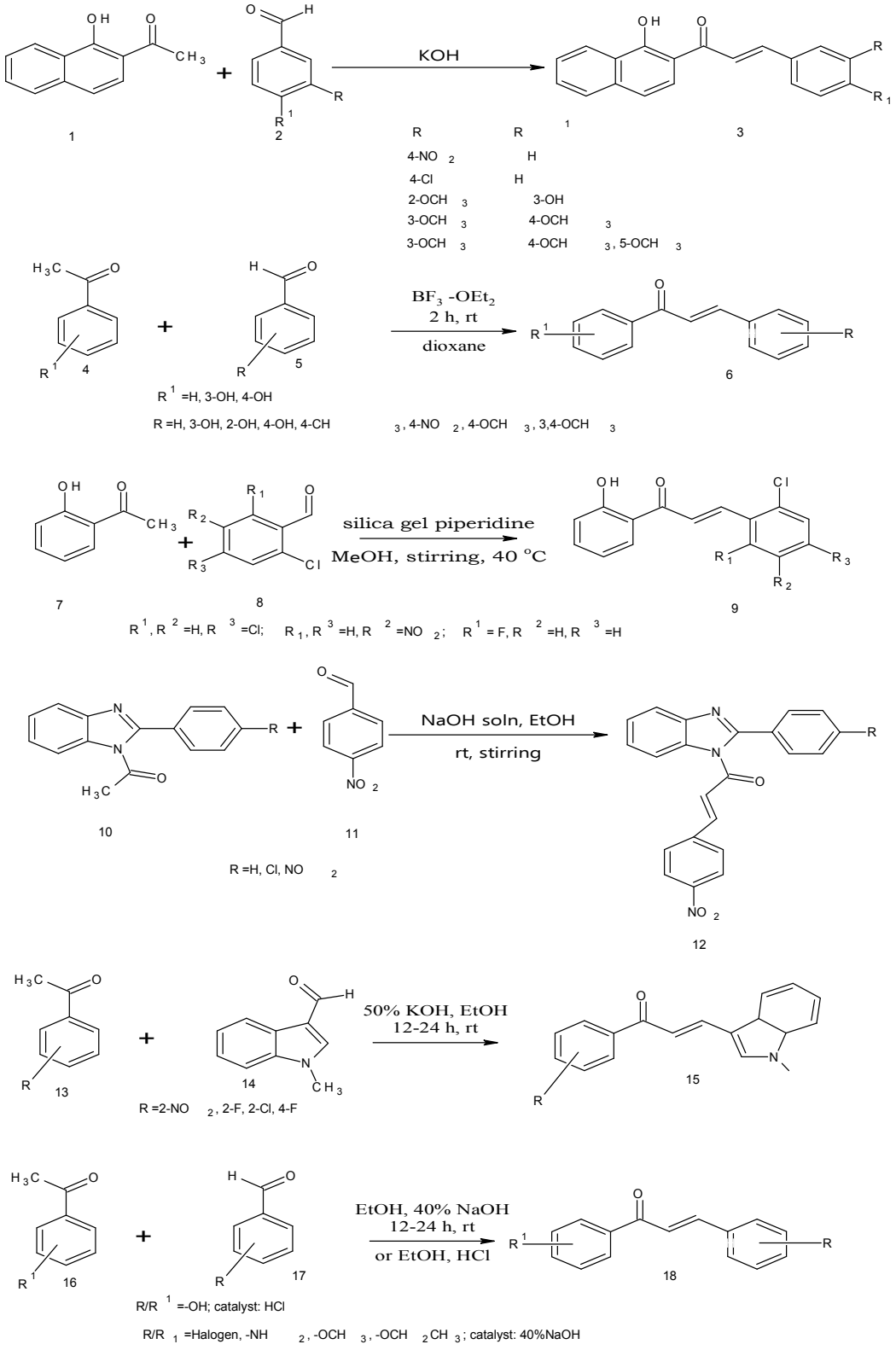
## 3. CHALCONES TRANSFORMATION IN HETEROCYCLES SYNTHESIS

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

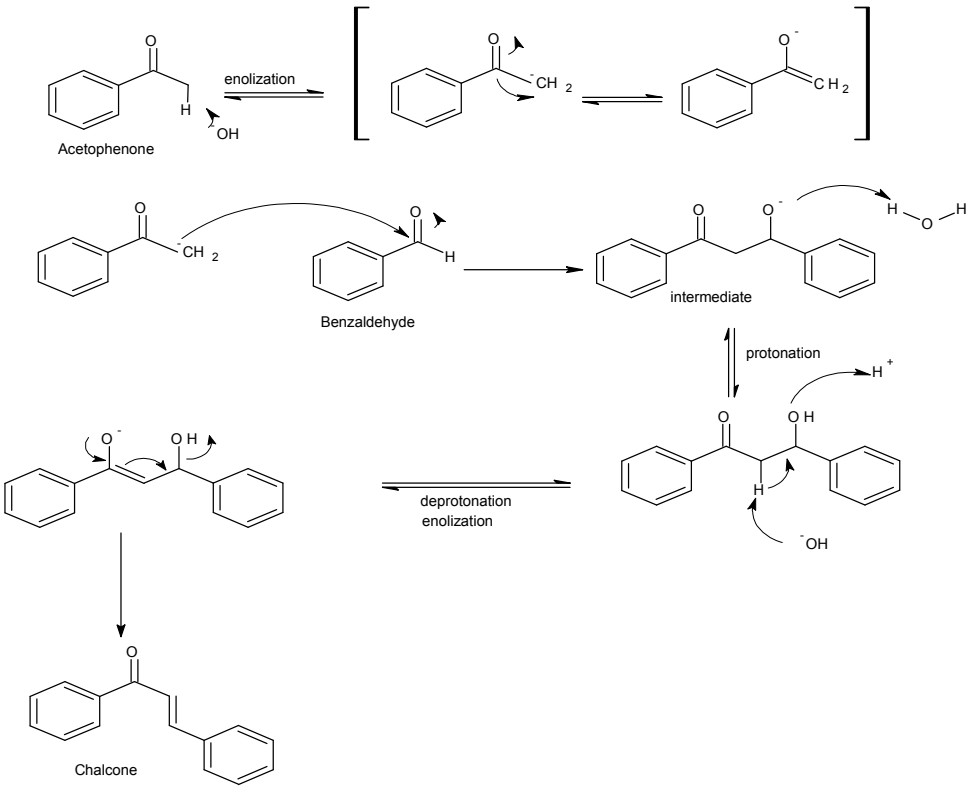
Meanwhile, Aswin *et al.* reported pyrimidine-2(1*H*)-thione **20** from the condensation of chalcone **19** with thiourea using triphenylphosphine ($PPh_3$) as a catalyst [10]. Pyrimidine derivatives **22** were also reported from chalcones **21** with urea in the presence of ethanolic potassium hydroxide 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 amidines [48]. Moreso, polysubstituted aminoimidazoles **32** were via alkene vicinal C-N bonds formation of 2-bromo-2-alkenones **30** with guanidine **31** [20] (Scheme 5).

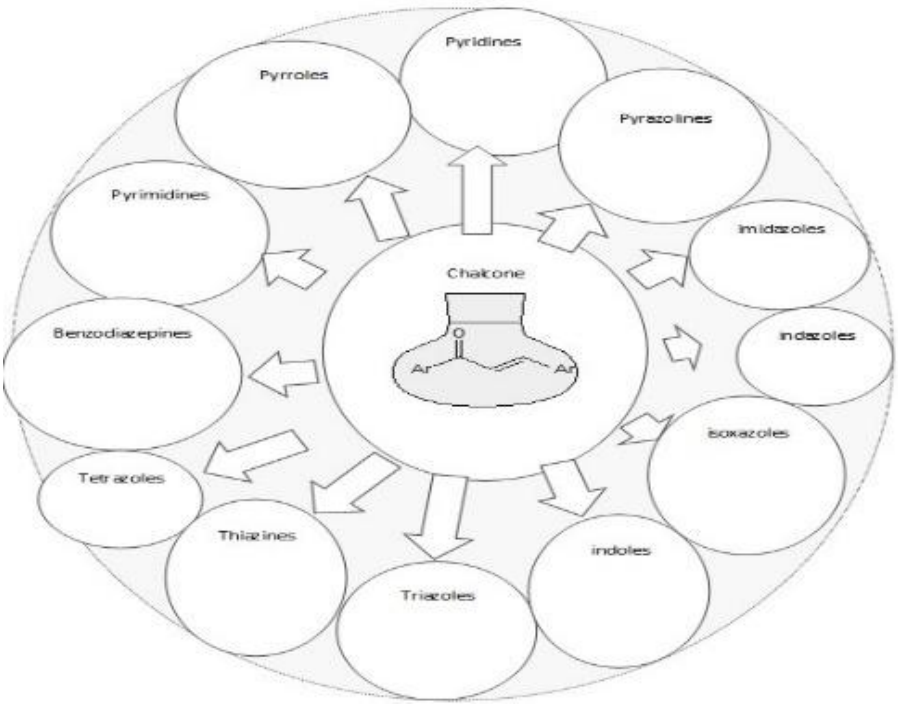
4,6-Diphenyl substituted thiazine derivatives **34** were prepared in two steps through chalcone **33** and thiourea via a conventional and microwave irradiation methods [21] (Scheme 6).



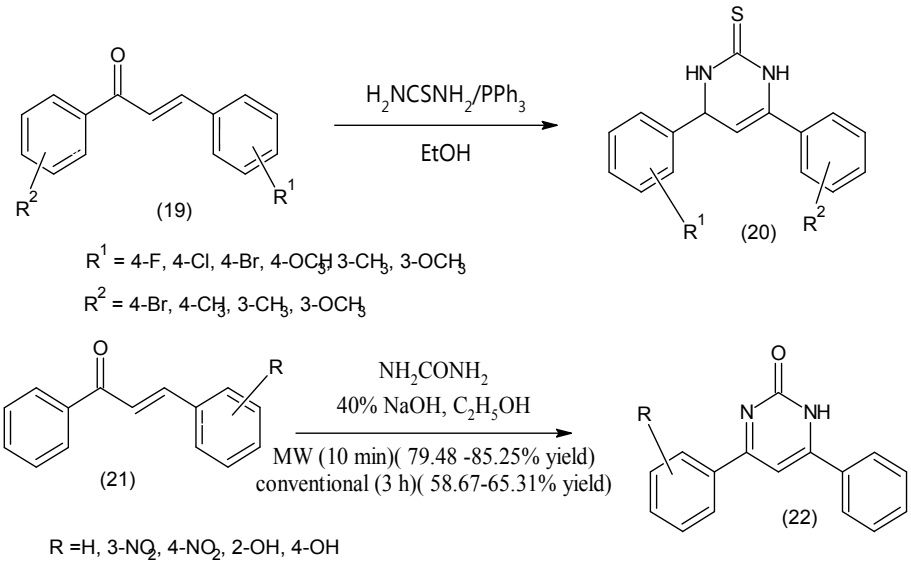

**Scheme 1. Chalcones synthesis**



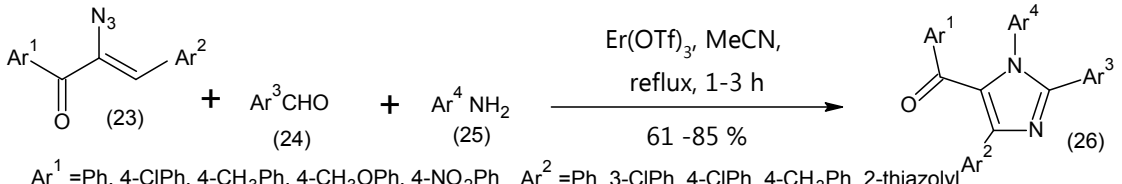

**Scheme 2. Mechanism of chalcone synthesis**



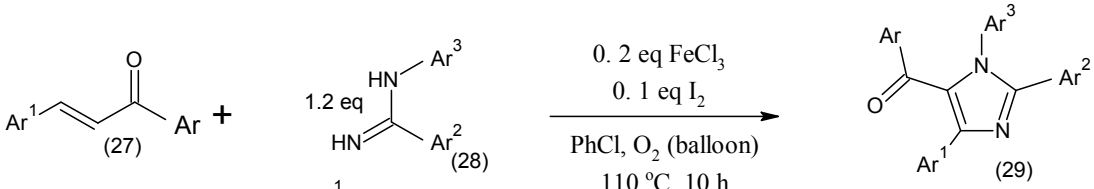

**Scheme 3. Heterocyclic compounds from chalcone**



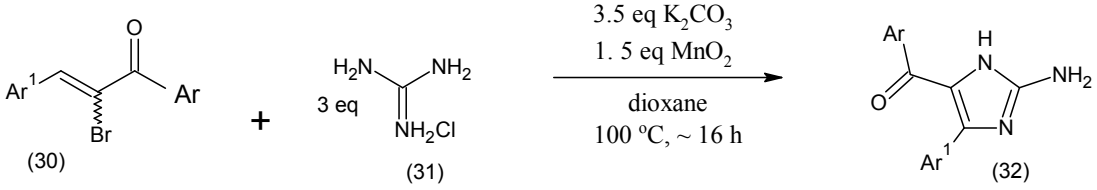

**Scheme 4. Synthesis of pyrimidine from chalcone**




Ar1 =Ph, 4-ClPh, 4-CH3Ph, 4-CH3OPh, 4-NO2Ph Ar2 =Ph, 3-ClPh, 4-ClPh, 4-CH3Ph, 2-thiazolyl
Ar3 =Ph, 4-ClPh, 4-BrPh, 4-CF3Ph, 4-CH3Ph, 3-CH3Ph, 3-CH3OPh, 4-CH3OPh, 4-NO2Ph
Ar4 =Bz, Ph, 4-ClPh, 2-BrPh, 2-Cl-3-CH3OPh, 4-BrPh, 4-FPh, 4-CF3Ph, 4-CH3Ph,4-CH3OPh, 4-morpholinyl




Ar =Ph, 4-ClPh, 4-CH3OPh; Ar1 =Ph, 4-ClPh, 4-CH3OPh, 2-thiazolyl
Ar2 =Ph, 2-ClPh, 4-BrPh, 4-CH3OPh; Ar3 =Ph, 4-ClPh, 2-CH3OPh, 2-CH3Ph



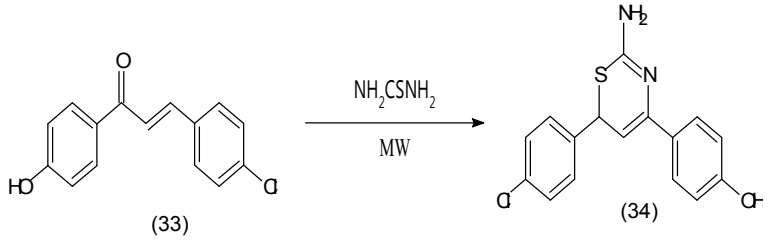

Ar =Ph, 4-CH3Ph, 4-CNPh, 4-NO2Ph
Ar1 =Ph, 4-ClPh, 4-CH3Ph, 4-CH3OPh, 4-NO2Ph

**Scheme 5. Synthesis of substituted imidazoles from chalcones**

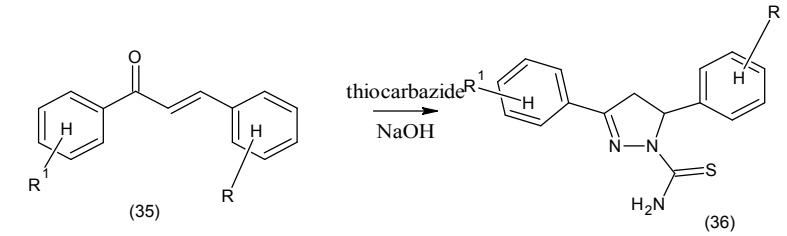
Furthermore, Osman et al. reported pyrazoline-1-carbothioamide **36** from the cyclization reaction of chalcones **35** and thiosemicarbazide [6] (Scheme 7).

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-Gaml described the synthesis of [1,5]benzodiazepines **45** and **46** from *o*-phenylenediamine **44** and variously substituted chalcones **42** and **43** [22] (Scheme 9).



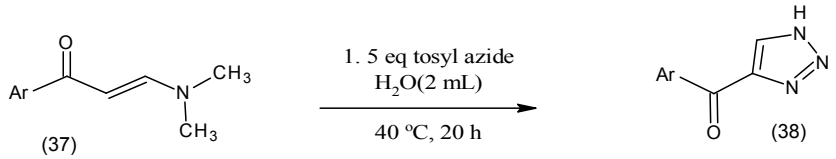

**Scheme 6. Thiazine derivative from chalcone**




R=H, 4-CH 3O, 4- *N,N*(CH 3)2, 3-NO 2

Ar =H, 4-NH 2, 4-Br, 4-NO 2

**Scheme 7. Pyrazoline derivative from chalcone**

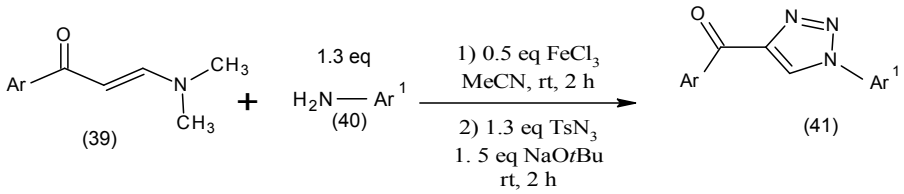



58-96% yield

Ar =Ph, 4-MeOPh, 4-ClPh, 4-BrPh, 4-MePh, 4-CNPh, naphthan-2-yl, thiophen-2-yl

3-NO 2Ph, 4-NO 2Ph, 2-benzodioxolane, 4-CF 3Ph, 3-ClPh, 3-MeOPh, naphthan-1-yl

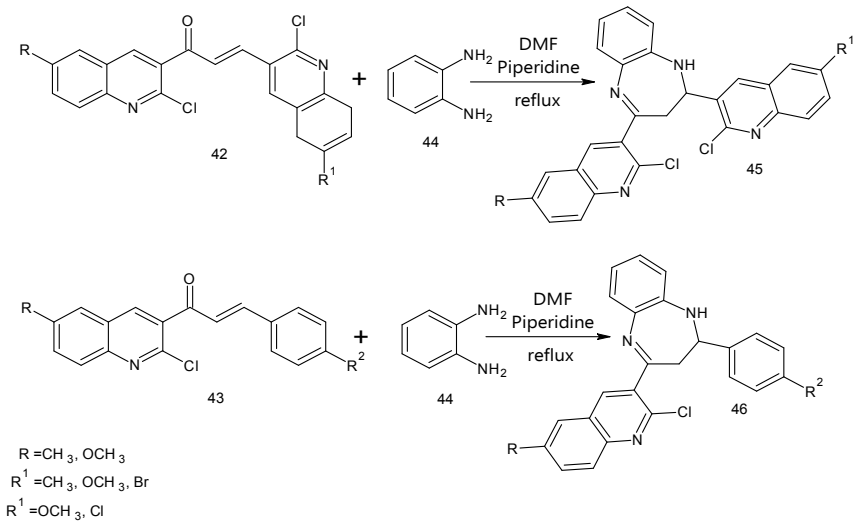
2-NO 2Ph, 2-MePh, 3,4-diMeOPh, 3,4-diClPh, furan-2-yl



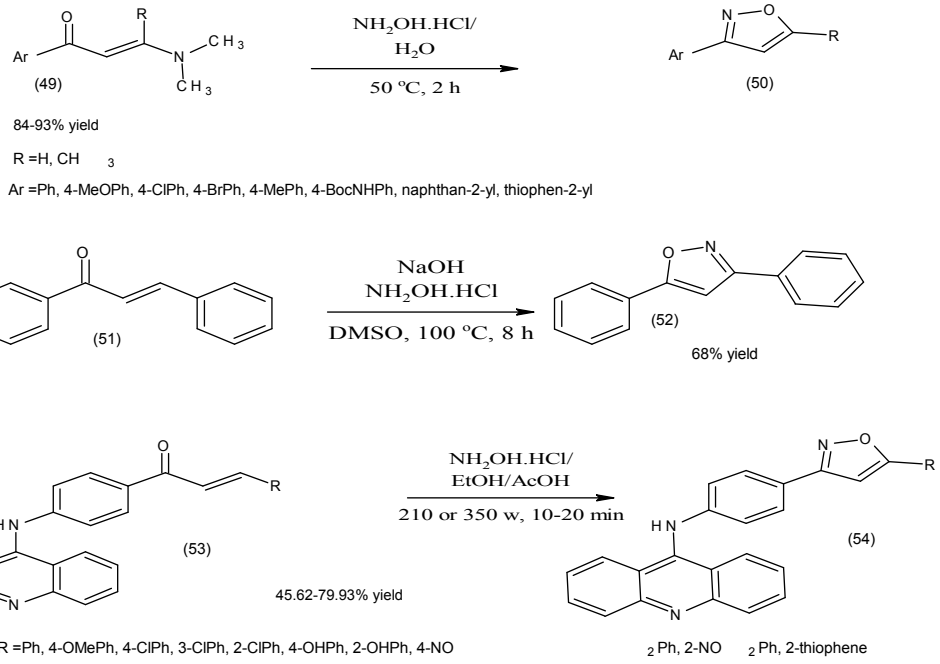

**Scheme 8. Triazoles from chalcones**

In another approach, Dou and co-workers synthesized 5-arylisoxazole 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-diphenylisoxazole **52**.8 Isoxazole substituted 9-anilino acridines **54** were synthesized from some novel chalcone **53** using microwave irradiation [9] (Scheme 10).

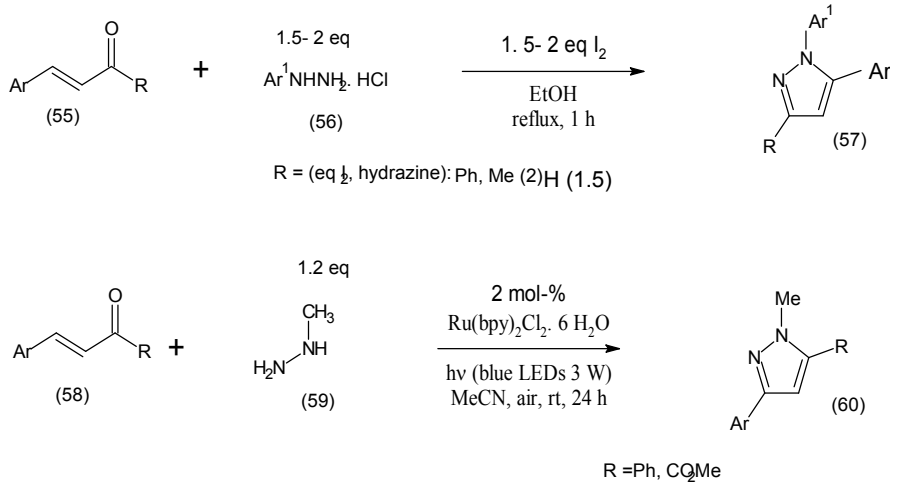
Zhang and co-workers reported di-, tri-, and tetrasubstituted (aryl, alkyl, and or vinyl) pyrazoles **57** from readily available α,β-unsaturated aldehydes/ketones **55** and hydrazine salts **56** without isolation of the less stable intermediates hydrazones [1]. Meanwhile, Ding *et al.* obtained polysubstituted pyrazoles **60** from hydrazine **59** and chalcones (Michael acceptors) **58** in good yields [2] (Scheme 11).



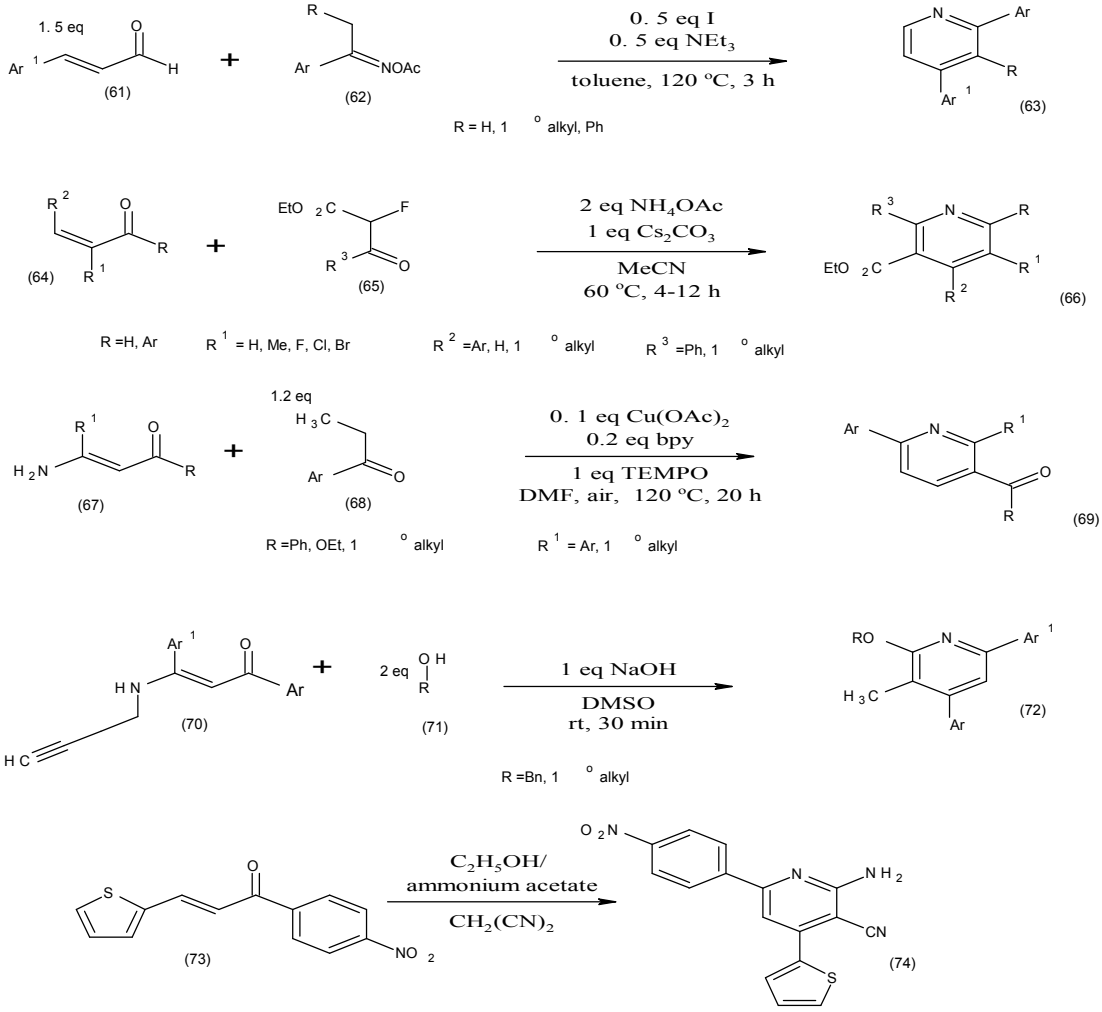

**Scheme 9. Synthesis of [1,5]-benzodiazepines from chalcones**




**Scheme 10. Isoxazoles derivatives from chalcones**



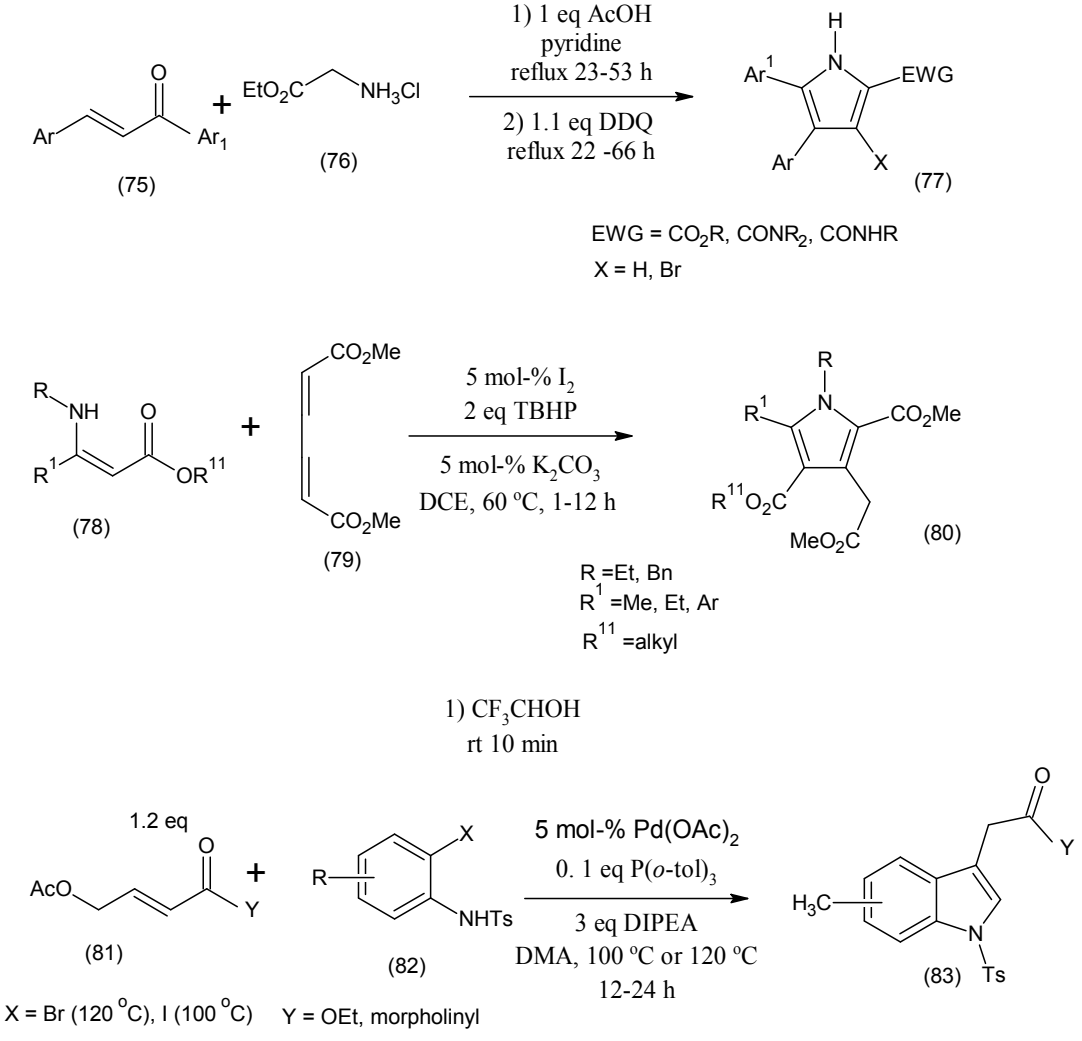

**Scheme 11. Pyrazoles from chalcones**




**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 pyrroles **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).




(75) (76) (77) (78) (79) (80) (81) (82) (83)

**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 $IC_{50}$ (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 [$IC_{50}$] 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).

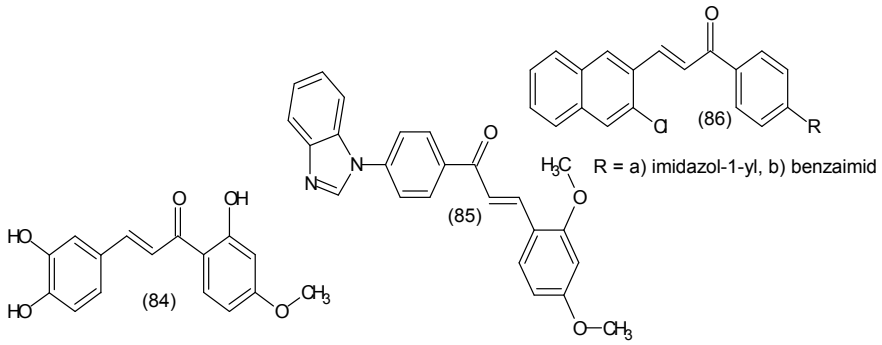



**Fig. 2. Chalcone derivatives with antimalarial activities**

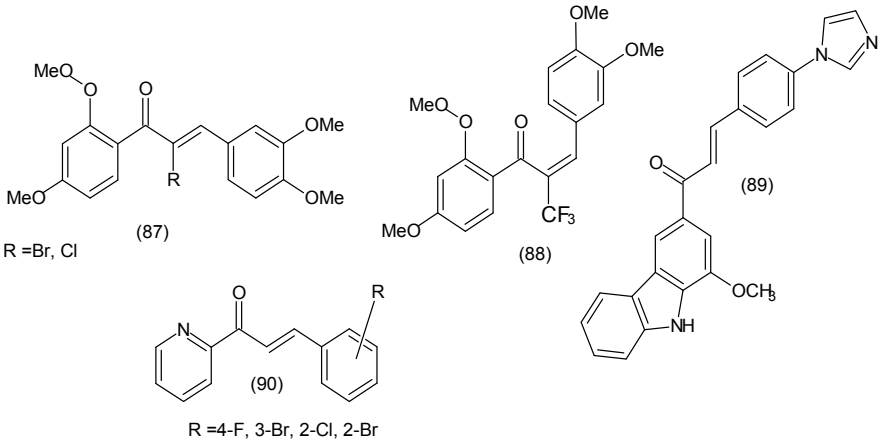



**Fig. 3. Chalcone derivatives with antiinflammatory activities**

### 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 anticandidal 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).

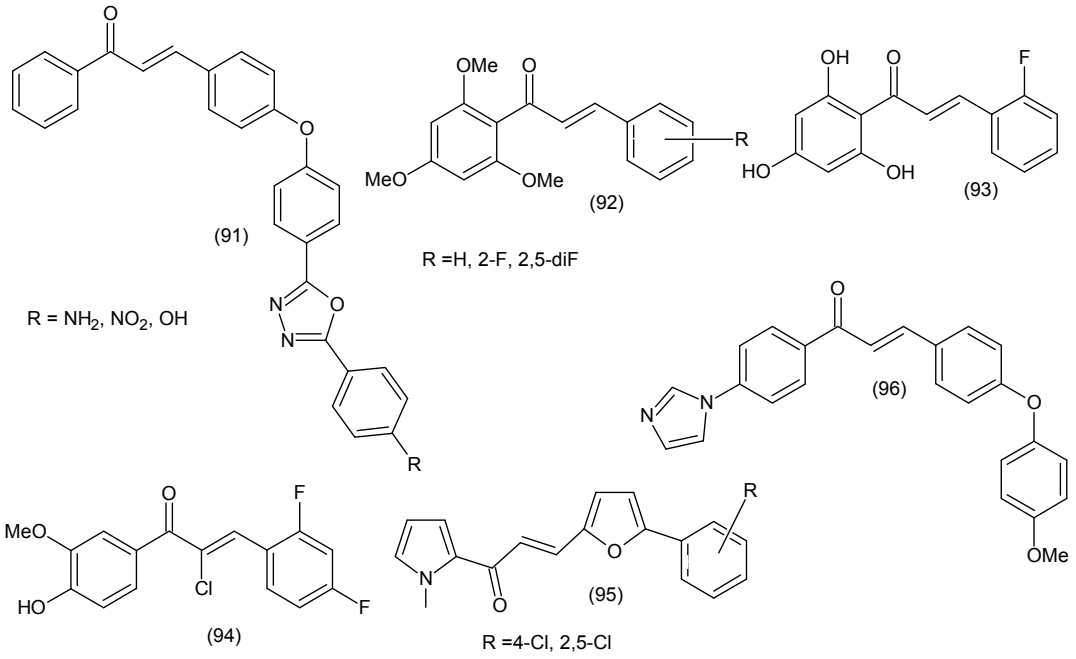



**Fig. 4. Chalcone derivatives with antimicrobial activities**

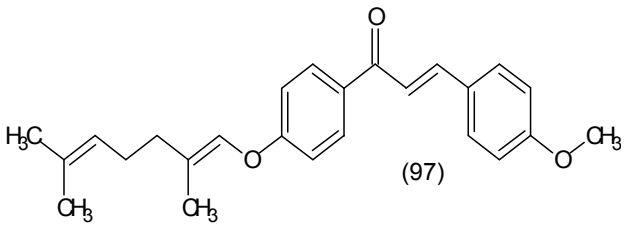



**Fig. 5. Chalcone derivative with an antileishmanial activity**

### 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 IC50 (~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 *p*M 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).

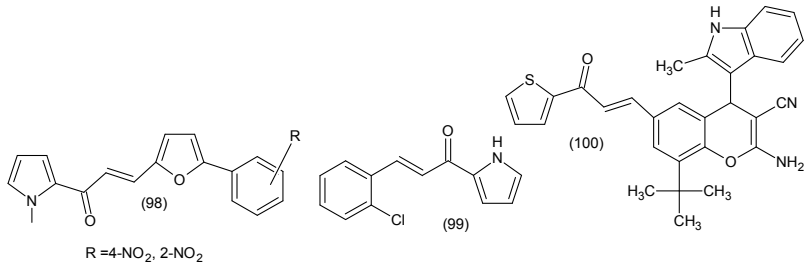



**Fig. 6. Chalcone derivative with anti-cancer activities**

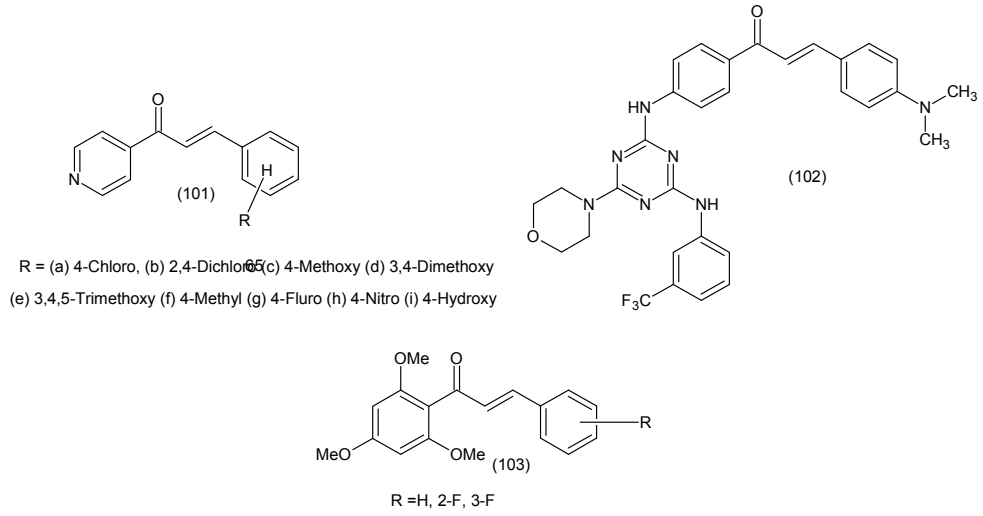
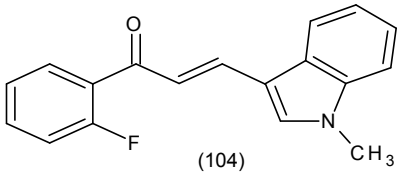
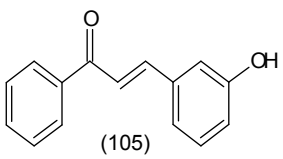



**Fig. 7. Chalcone derivative with anti-tubercular activities**

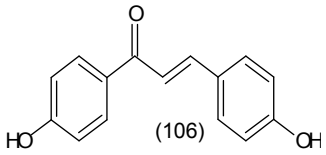


(104)

**Fig. 8. Chalcone derivatives with osteogenic activity**

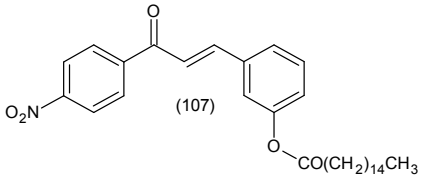


(105)

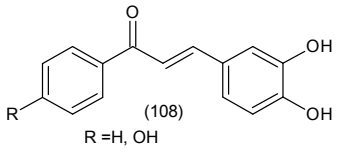


(106)

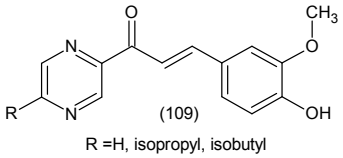
**Fig. 9. Chalcone derivatives with anthelmintic activities**



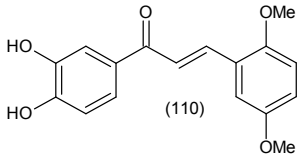
(107)



(108)
R =H, OH



(109)
R =H, isopropyl, isobutyl



(110)

**Fig. 10. Chalcone derivatives with antioxidant activities**

## 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.

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