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Synthesis, reactions, and applications of chalcones: A review

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REVIEW ARTICLE

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ABSTRACT

Considering the essential biological and medicinal properties of chalcones, the synthesis of these compounds has attracted the interest of medicinal and organic chemists. This review aims to describe the different strategies developed so far for the synthesis of chalcones and their applications. After a brief introduction of the chalcones and their biological activities, different synthetic approaches such as chemical and other methods are described and organized on the basis of the catalysts and the other reagents employed in the syntheses. Some of the reactions have been applied successfully to the synthesis of biologically important compounds. Moreover, the biological and pharmacological activities of chalcones have been shown.

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1. Introduction

Chalcone the name was coined by the two authors, Stanislaw Kostanecki and Joseph Tambor [1]. Chalcones (aromatic ketones and enones, α,β-unsaturated ketone) consist of two aromatic rings joined by a three-carbon α,β-unsaturated carbonyl system [-CO-CH=CH-] [2]. It has the general structural formula as shown in Figure 1. Chalcone may be called some names as benzylideneacetophenone, phenyl styryl ketone, benzalacetophenone, α-phenyl-β-benzoylethylene, and others [3,4].

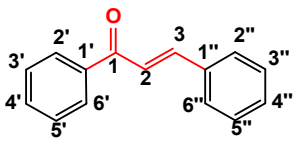

Figure 1. General structural formula of chalcone.

Many of chalcones possess interesting pharmacological properties such as antibacterial [5], antifungal [6], antiviral [7], anti-HIV activity [8], 5-lipoxygenase inhibitor [9], anticancer [10-12], cytotoxic activity [13], antimalarial [14], antiulcer [15], antileishmanial [16], and anti-inflammatory [17]. Recently, several chalcone-based compounds have been approved for clinical use, for example Metochalcone I was once marketed as a choleretic drug, while Sofalcone II was previously used as an antiulcer and nucoprotective drug (Figure 2) [18]. In addition, chalcones and their derivatives have great applications as sweeteners [19,20], fluorescent whitening factor [21], heat maintenance [22], and brightening agent [23].

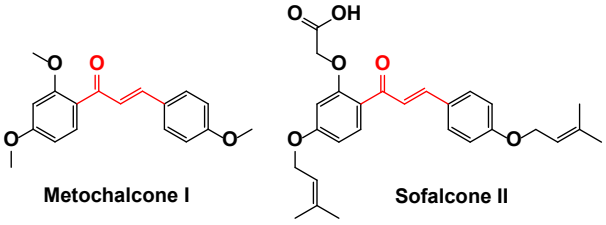

Figure 2. Structures of approved chalcone-based drugs.

Based on the above arguments, in continuation of our program [24-61], and related work [62-67], therefore, this review aims to highlight and summarize the synthetic methodologies, reactions, applications, and biological activities of chalcones.

2. Synthetic methodology of chalcones

2.1. Claisen-Schmidt condensation

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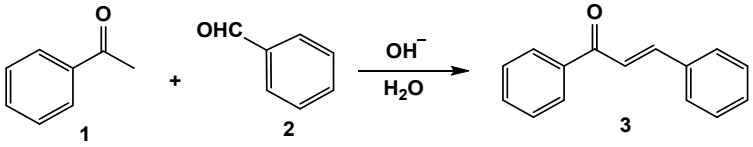
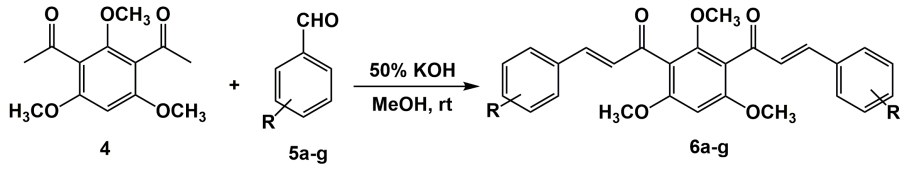


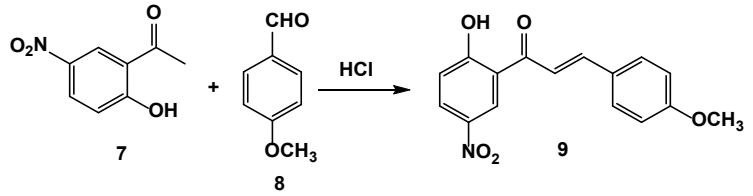
Scheme 1



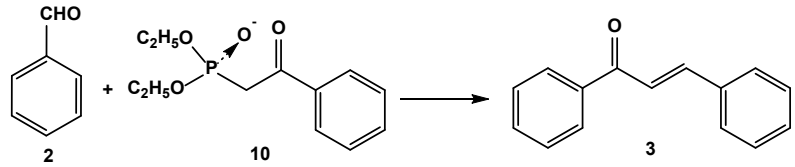
5a, R= H; 5b, R= 2-F; 5c, R= 3-F; 5d, R= 4-F; 5e, R= 2, 3-di-F; 5f, R= 2, 4-di-F; 5g, R= 2, 5-di-F, 5h, R= 3, 4-di-F

6a, R= H; 6b, R= 2-F; 6c, R= 3-F; 6d, R= 4-F 6e, R= 2, 3-di-F; 6f, R= 2, 4-di-F; 6g, R= 2, 5-di-F; 6h, R= 3, 4-di-F

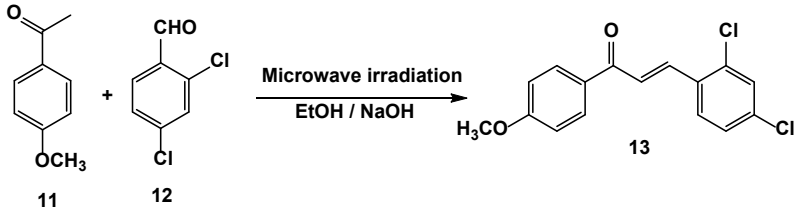
Scheme 2



Scheme 3



Scheme 4



Scheme 5

2.1.1. Synthesis of monochalcone

This method was used for the preparation of chalcone **3** (with a yield of approximately 85%) by adding an equimolar amount of acetophenone **1** to benzaldehyde **2** in the presence of aqueous alcoholic alkali (10 to 60% alkali) at 50 ° C for 12-15 hours or one week at room temperature (Scheme 1) [68].

2.1.2. Synthesis of bis-chalcone

Di-ketone (**4**), 1,1'-(2,4,6-trimethoxy-1,3-phenylene)diethanone, was reacted with aldehyde **5a-g** in the methanol as a solvent in the presence of 50% potassium hydroxide to give *bis*-chalcones **6a-g** (Scheme 2) [69].

2.2. Using hydrochloric acid

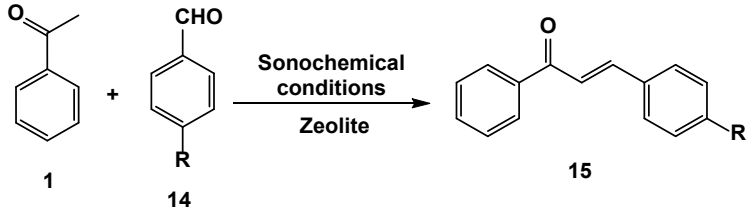
2-Hydroxy-5-nitro-acetophenone (**7**) was reacted with 4-methoxybenzaldehyde (**8**) to give 1-(2-hydroxy-5-nitrophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**9**) *via* using hydrochloric acid (Scheme 3) [70].

2.3. Chalcone synthesis from phosphonate carbanion

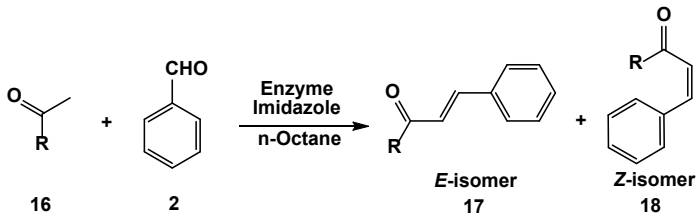
Chalcone **3** was obtained by the reaction of benzaldehyde (**2**) with phosphonate carbanion (**10**) which was produced from diethyl phenacyl phosphonate (Scheme 4) [71-74].

2.4. Using microwave conditions

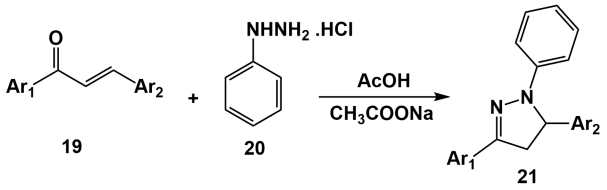
Chalcone **13** was prepared by adding of *p*-methoxyacetophenone (**11**) to 2,4-dichlorobenzaldehyde (**12**) in the presence of sodium hydroxide (1-2 pellets) in absolute ethanol under microwave irradiation conditions (a microwave oven for 50 seconds) (Scheme 5) [75].



Scheme 6



Scheme 7



a) Ar_1= C_6H_5, Ar_2= 4-$CH_3OC_6H_4$; b) Ar_1= C_6H_5, Ar_2= 4-$CH_3C_6H_4$; c) Ar_1= C_6H_5, Ar_2= C_6H_5
d) Ar_1= C_6H_5, Ar_2= 4-ClC_6H_4; e) Ar_1= C_6H_5, Ar_2= 3-ClC_6H_4; f) Ar_1= C_6H_5, Ar_2= 2-ClC_6H_4
g) Ar_1= C_6H_5, Ar_2= 3-BrC_6H_4; h) Ar_1= C_6H_5, Ar_2= 4-$O_2NC_6H_4$; i) Ar_1= 4-ClC_6H_4, Ar_2=C_6H_5
j) Ar_1= 3-$O_2NC_6H_4$, Ar_2= C_6H_5

Scheme 8

2.5. Using solvent-free conditions

Sonochemical conditions were used in the synthesis of chalcones **15** from acetophenone (**1**) with aldehyde derivatives **14** in the presence of zeolite as a catalyst (the catalyst was prepared by grafting amino groups on sodium and cesium exchanged X zeolite, a new type of amino grafted zeolite) under solvent-free conditions (Scheme 6) [76].

2.6. Using the biocatalysts

Lipases are industrial biocatalysts, which are involved in several novel reactions occurring in both aqueous and non-aqueous mediums. The reaction of aliphatic ketone **16** and benzaldehyde (**2**) was catalyzed by using recombinant *D*-amino-acylase (EC 3.5.1.81) and imidazole in the presence of *n*-octane as a solvent for the formation of the *E*-isomer of alkyl-but-3-en-2-ones (**17**) and the *Z*-isomer of alkyl-but-3-en-2-ones (**18**) with yields of 74 and 26%, respectively (Scheme 7) [77].

3. Reactions of chalcones

3.1. Reaction with phenylhydrazine

Chalcones **19** were reacted with phenylhydrazine (**20**) in the presence of a mixture of acetic acid-sodium acetate aqueous solution at room temperature. The optimum reaction condition was the molar ratio of chalcone: phenylhydrazine: sodium acetate was 1:3:0.15 for the formation of 1,3,5-triaryl-2-pyrazolines **21** in 83–96% yield (Scheme 8) [78].

3.2. Reactions with hydrazine hydrate

3.2.1. Bis-chalcones with hydrazine hydrate

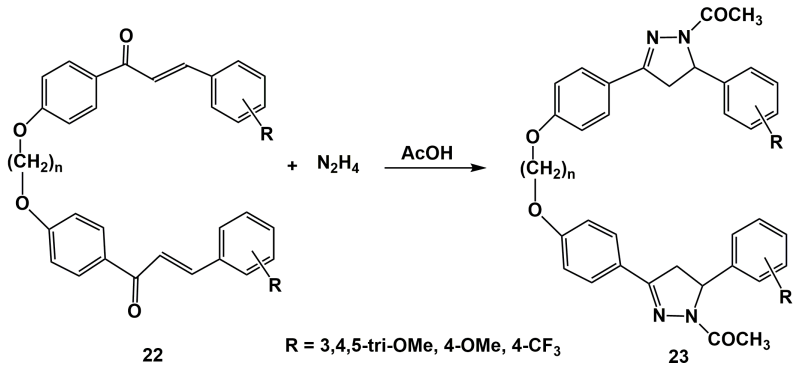
Bis-chalcones (**22**) were reacted with hydrazine hydrate in the presence of acetic acid to give *bis*-3,5-diphenyl pyrazoline (**23**) (Scheme 9) [79].

3.2.2. Chalcones with hydrazine hydrate using ultrasound irradiation conditions

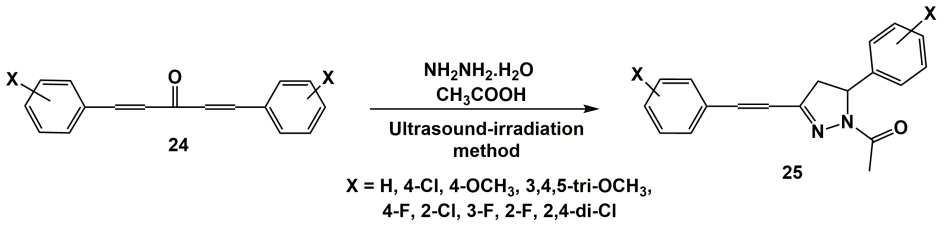
The cyclo-condensation of 1,5-substituted diphenyl-1,4-pentadien-3-ones **24** with hydrazine hydrate in a cyclizing agent such as acetic acid in ethanol under the ultrasound irradiation method. The reaction mixture was sonochemically irradiated for 10 to 25 minutes to give N^1-acetyl-5-aryl-3-(substituted styryl)pyrazolines **25** (Scheme 10) [80].

3.2.3. Chalcones with hydrazine hydrate using microwave irradiation

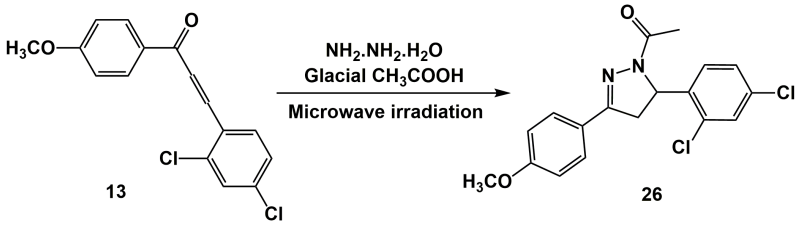
Chalcone **13** reacted with hydrazine hydrate in glacial acetic acid and absolute ethanol under microwave conditions. The reaction mixture was placed in a microwave oven for 160 seconds for the formation of 1-(5-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone **26** (Scheme 11) [75].



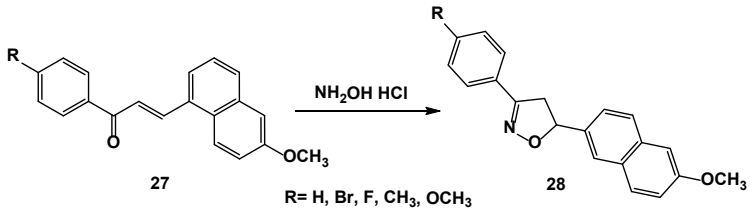
Scheme 9



Scheme 10



Scheme 11



Scheme 12

3.3. Reaction of chalcones with hydroxylamine

3.3.1. Synthesis of methoxynaphthaline isoxazole derivatives

When 1-(4'-substituted-phenyl)-3-(6″-methoxynaphthaline) -2-propene-1-one **27** were reacted with hydroxylamine, the isoxazole derivative **28** were formed (Scheme 12) [81].

3.3.2. Synthesis of benzofuryl isoxazole derivatives

Benzofuryl chalcone derivatives **29** were condensed with hydroxylamine hydrochloride in ethanol as a solvent in the presence of sodium hydroxide to form isoxazole derivatives **30** (Scheme 13) [82].

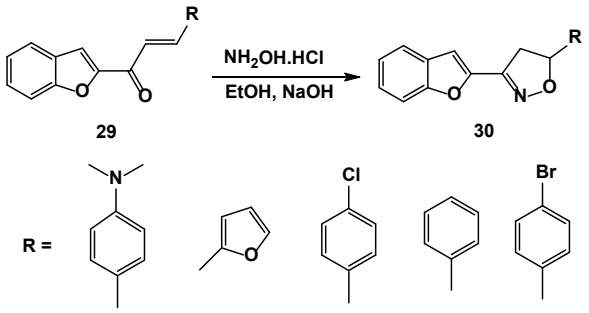
3.4. Reactions of chalcones with urea and thiourea

3.4.1. Synthesis of pyrimidine and theinopyrimidine derivatives

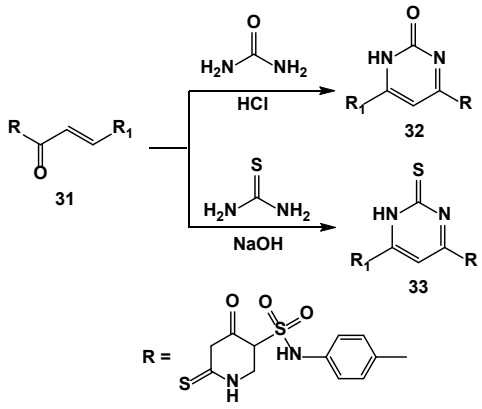
Some chalcones **31** were reacted with urea in acidic medium to give the derivative pyrimidine-2-one **32**, while it can give the derivatives pyrimidine-2-thione **33** when reacted with thiourea in basic media (Scheme 14) [83].

3.4.2. Reaction with thiourea using microwave irradiation

Pyrimidine-2-thione derivatives **35a-j** were produced from the condensation of chalcone **34a-j** with thiourea dissolved in ethanol and in the presence of diluted HCl. These reactions were carried out using the microwave technique. The reaction mixture was placed in a microwave oven for 55-60 seconds (Scheme 15) [75].

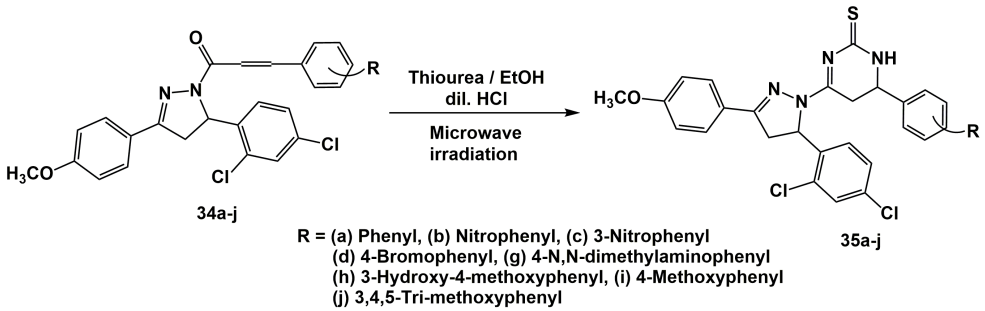


Scheme 13

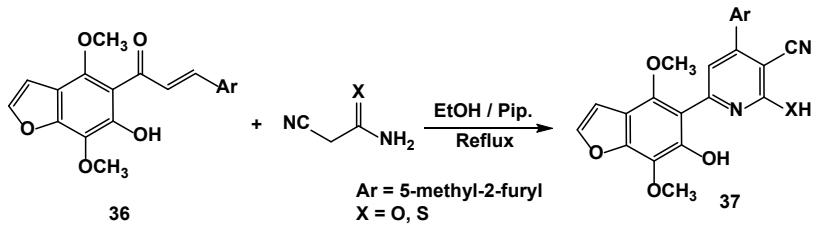


R_1= *p*-nitrophenyl, *p*-chlorophenyl, 3-indolyl. and *p*-*N*-dimethylaminophenyl

Scheme 14



Scheme 15



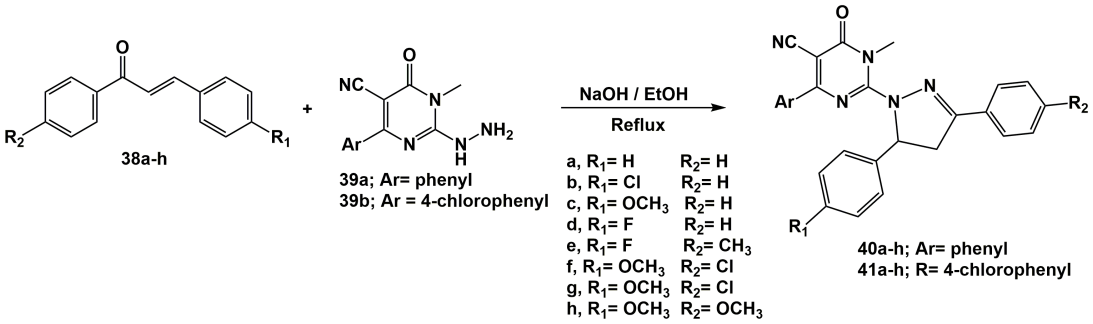
Scheme 16

3.5. Reaction with 2-cyanoacetamide or 2-cyanothio acetamide

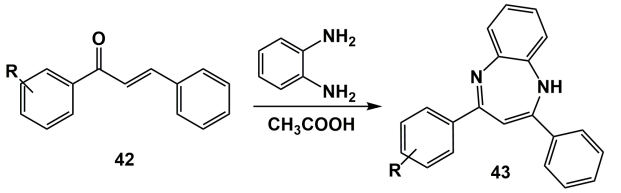
Chalcone **36** and 2-cyanoacetamide or 2-cyanothio acetamide were reacted together in ethanol in the presence of piperidine to give 6-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-4-(5-methylfuran-2-yl)-3-cyanopyridine derivatives **37** (Scheme 16) [84].

3.6. Reaction with 1-methyl-6-oxo-4-aryl-pyrimidine-5-carbonitrile

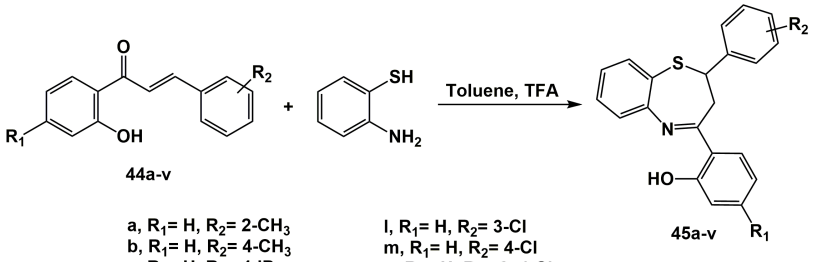
Chalcones **38a-h** were reacted with 2-hydrazino-1-methyl-6-oxo-4-phenylpyrimidine-5-carbonitrile (**39a**) and 2-hydrazino-1-methyl-6-oxo-4-(4-chlorophenyl)-pyrimidine-5-carbonitrile (**39b**) [85] in absolute ethanol and in the presence of sodium hydroxide.



Scheme 17



Scheme 18



Scheme 19

The reaction was then heated under reflux conditions for 72 hours to give 2-(substituted)-1-methyl-6-oxo-4-aryl-pyrimidine-5-carbonitrile derivatives **40a-h** and **41a-h**, respectively, (Scheme 17) [86].

3.7. Reaction with 1,2-diaminebenzene

Chalcone derivatives **42** were reacted with *o*-phenylenediamine to give 2,4-disubstituted-1,5-benzodiazepine **43** (Scheme 18) [87].

3.8. Reaction with 2-aminothiophenol

Benzothiazepine derivatives **45a-v** were prepared from the reaction of chalcones **44a-v** with 2-aminothiophenol in toluene and in the presence of TFA (Scheme 19) [88-92].

3.9. Reactions with thiosemicarbazide and isonicotinic acid

Chalcones **46** were dissolved in absolute ethanol in the presence of sodium hydroxide and added to thiosemicarbazide, then glacial acetic acid was added and the mixture was refluxed for 7 hours to give 4,5-dihydro-pyrazole-1-carbothioamide derivatives **47.** Furthermore, chalcones **46** were added to a mixture of isonicotinic acid and glacial acetic acid in ethanol, and then the reaction was refluxed for 5 hours to give (4,5-dihydro-pyrazol-1-yl)(pyridin-4-yl)methanone **48** (Scheme 20) [93].

4. Biological applications of chalcones

4.1. Chalcones as antimicrobial agents

Nitrofuryl chalcone **49**, 1-(2-fluorophenyl)-3-(5-nitro furan-2-yl)prop-2-en-1-one, was tested for its antibacterial activity and explored that this compound exhibited activity against *Staphylococcus Landon* (Figure 3) [94].

Chalcones which are bearing indole moiety **50** gave antibacterial activity against *Escherichia coli* and *Bacillus cereus*. In addition, chalcones **50** gave antifungal activities against *Fusarium oxysporium* and *Macrophomina phaeolina* (Figure 4) [95].

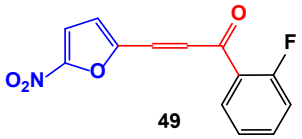


Figure 3. Nitrofuryl chalcone **49** as antibacterial agent.

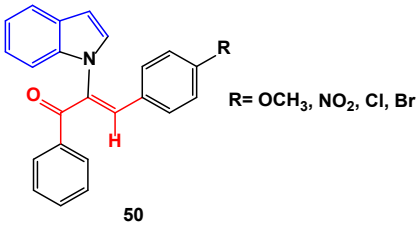


Figure 4. Chalcones containing the indole moiety **50** exhibited antimicrobial activity.

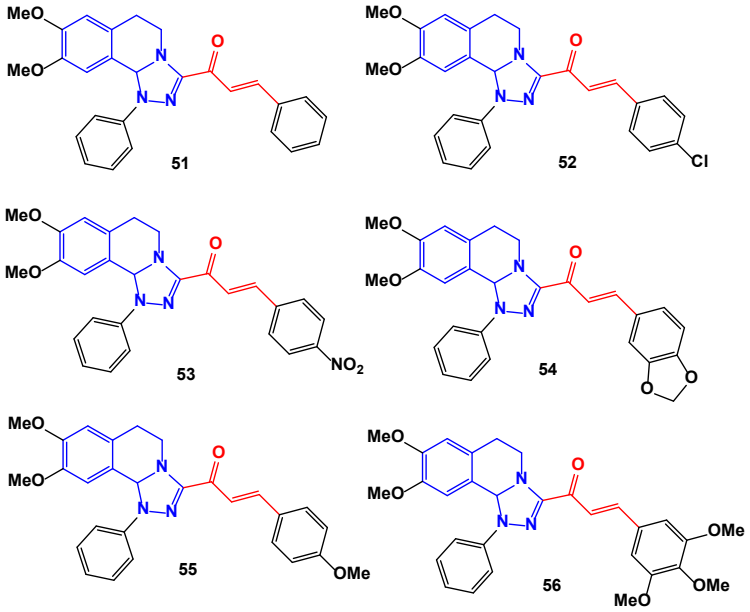
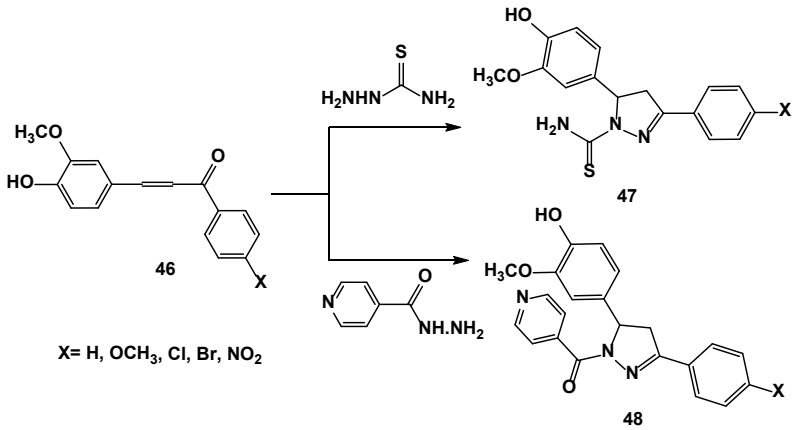


Figure 5. Tetrahydro-[1,2,4]triazolo[3,4-*a*]isoquinoline chalcones **51**-**56** showed anticancer activities.



Scheme 20

4.2. Chalcones as anticancer

The new derivatives of tetrahydro- [1,2,4] triazolo [3,4-a] isoquinoline chalcones **51-56** showed anticancer activities against breast cancer cell lines (MCF-7) especially compounds **53** and **56** that offered the lowest IC_{50} values (50.05, and 27.15 µg/ml) respectively, relative to the positive control 5-fluorouracil (5-FU) (IC_{50} = 178 µg/ml) (Figure 5) [96].

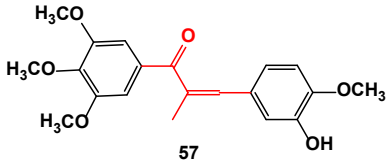


Figure 6. α-Methyl chalcone **57** showed cytotoxic activity against the K562 human leukaemia cell.

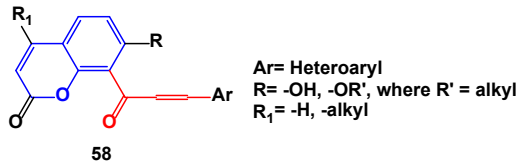


Figure 7. The chalcones-pyran moiety **58** showed biological activities.

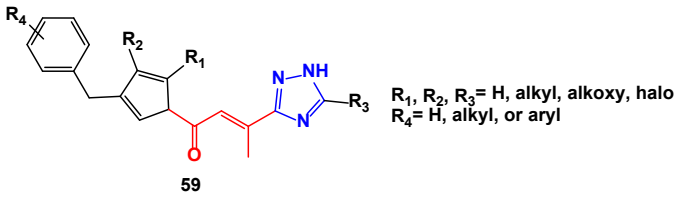


Figure 8. Chalcone **59** showed considerable activities against human immunodeficiency virus (HIV).

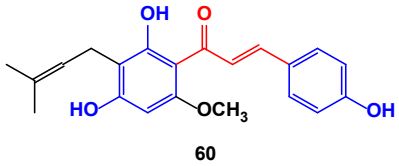


Figure 9. Hydroxy chalcones **60** showed antioxidant properties.

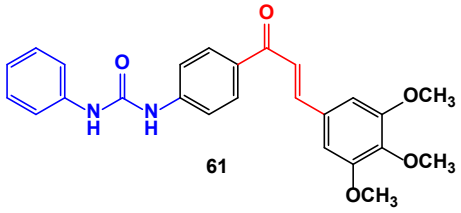


Figure 10. Phenylurenyl chalcone **61** showed antimalarial activity.

A series of substituted chalcones was synthesized and screened for cytotoxic activity against the K562 human leukaemia cell line. α-Methyl chalcone, 3-(3-hydroxy-4-methoxyphenyl)-2-methyl-1-(3, 4, 5-trimethoxy-phenyl)prop-2-en-1-one (**57**), was found to be the most active [IC_{50} (K562) 0.21 nM] (Figure 6) [97].

Chalcones with pyran moiety **58** were reported as anti-breast cancer, osteoporosis, and menopausal disorders (Figure 7) [98].

4.3. Chalcones as antiviral

Chalcones with the substituted triazole moiety and having fluoro substitution **59** showed considerable activity against human immunodeficiency virus (HIV) (Figure 8) [98].

4.4. Chalcones as antioxidants

Hydroxychalcone **60** was examined for its ability to inhibit *in vitro* oxidation of human low-density lipoprotein (LDL). At concentrations of 5 and 25 μM, hydroxy chalcone **60** tested inhibited the oxidation of LDL (50 μg protein/ml) induced by 2 μM copper sulfate. Hydroxy chalcone **60** showed antioxidant properties (Figure 9) [99].

4.5. Chalcones as antimalarial

Phenylurenyl chalcone derivatives have been synthesized and tested as inhibitors of the *in vitro* development of a chloroquine resistant strain of *Plasmodium falciparum*, the activity of the cysteine protease falcipain-2, *in vitro* globin hydrolysis, β-hematin formation, and murine *Plasmodium berghei* malaria. The most active antimalarial compound was 1-phenyl-3-(4-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl)urea (**61**) with an IC_{50} of 1.76 μM for inhibition of *P. falciparum* development (Figure 10) [100].

Chalcone-acridine derivatives **62a-e** have been characterrized and screened for *in vitro* antimalarial activity against *Plasmodium falciparum* NF-54. All chalcones showed complete inhibition at a concentration of 10 μg/mL (Figure 11) [101].

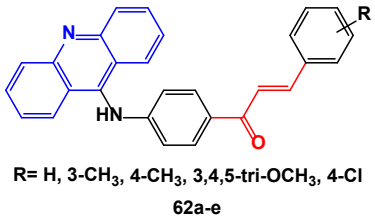


Figure 11. Chalcone-acridine derivatives **62a-e** showed antimalarial activity.

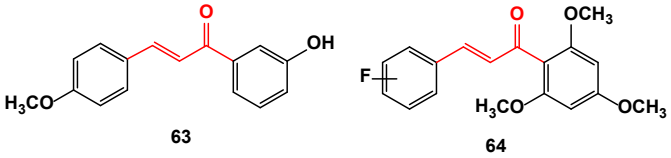


Figure 12. The two chalcones **63** and **64** possess anti-tubercular activity.

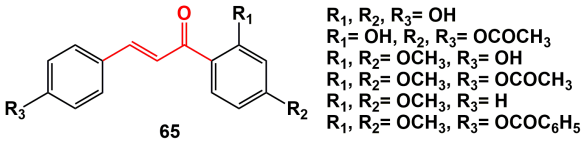


Figure 13. Chalcones **65** possess anti-diabetic activity.

4.6. Chalcones as anti-tubercular

Chalcone **63** having antimycobacterial activity. Furthermore, a new fluorine-substituted chalcone analog 64 was synthesized and its antitubercular efficacy was evaluated against the strain of *Mycobacterium tuberculosis* H37Rv (Figure 12) [102].

4.7. Chalcones as anti-diabetic

Chalcones **65** were synthesized and evaluated for their anti-diabetic activity through an oral glucose tolerance test to gain preliminary information regarding the antihyperglycemic effect in normal Swiss albino male mice. The derivatives showed a significant blood glucose lowering effect. The compounds were selected for *in vivo* antidiabetic activity and found to be potential candidates for the treatment of diabetes (Figure 13) [103].

5. Conclusions

In this Review, a wide range of synthetic strategies of chalcones have been discussed. We started with chemical and other methods for the synthesis of chalcones, followed by their reactions with various reagents under different conditions, and finally, presenting their diverse biological and pharmacological activities such as antimicrobial, anticancer, antiviral, anti-diabetic, and antioxidant. In this report, we explain that chalcones are based on the construction of new heterocyclic compounds that are used in the medical field.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Conceptualization: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Methodology: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Software: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Validation: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Formal Analysis: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Investigation: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Resources: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Data Curation: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Writing - Original Draft: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Writing - Review and Editing: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Visualization: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Funding acquisition: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Supervision: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan; Project Administration: Nesrin Mahmoud Morsy, Ashraf Sayed Hassan.

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