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A Review of Chalcones: Synthesis, Reactions, and Biological Importance

Shorouk S. Mukhtar[a], Nesrin M. Morsy[a,*], Ashraf S. Hassan[a], Taghrid S. Hafez[a], Hamdi M. Hassaneen[b], Fatma M. Saleh[b]

[a]*Organometallic and Organometalloid Chemistry Department, National Research Centre, Cairo, Dokki 12622, Egypt*

[b]*Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt*

Abstract

Chalcones are considered an important scaffold in organic compounds. Many of their derivatives have a lot of applications. Therefore, this review was covered some synthesis methods of chalcones such as Claisen-Schmidt's condensation, coupling reaction, continuous-flow deuteration reaction, and other reactions. Also, some reactions were discussed such as the synthesis of seven, six, and five-membered ring heterocyclic compounds. Moreover, some of their biological applications were mentioned like antimicrobial, anticancer, anti-inflammatory, antioxidants, and others with some details.

Keywords: Chalcones; Synthesis; Reactions; Biological applications

Introduction

Chalcones are presented in some natural compounds that belong to the flavonoids family. It was first served by Stanislaw Kostanecki and Joseph Tambor. Their original work was published in 1899 [1]. Chalcones are active aromatic compounds which is a parent of various bioorganic precursors molecules in medicinal chemistry. Chalcones consist of two aromatic rings that are interconnected by a highly electrophilic three carbons as α, β unsaturated carbonyl system. Chalcones are useful as intermediates in the preparation of different heterocyclic compounds with high biological activities [2] like pyrazoline [3-13] and isoxazole [14-19] (**Figure 1**).

The IUPAC name of the parent chalcone is (*E*)-1, 3-diphenylprop-2-en-1-one, and it has other names such as benzylideneacetophenone, phenyl styryl ketone, benzalacetophenone, α-phenyl-β-benzoylethylene, and others [20].

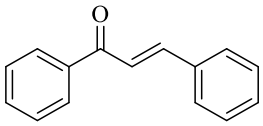

Figure 1

Chalcones skeleton is widely present in many natural products with their valuable bioactivities such as antioxidants for preventing entering the chronic diseases to human bodies which cause damaging of the DNA and proteins as different types of cancer disease, cardiovascular, and neurological diseases [21, 22]. They have great applications as anti-inflammatory [23, 24], xanthine oxidase inhibitors [25], antihistaminic [26, 27], anticancer [28-30], antimalarial [31], antiviral [32], antimicrobial [33-35], antioxidant [36], antidiabetic [37], and etc.

From the above important biological activities facts of chalcones and in continuation of our work [38-86], the goal of this review is to shed a light on the synthesis, reactions, and biological importance of chalcones.

*Corresponding author e-mail: nesrinmorsy@yahoo.com.; (Nesrin M. Morsy).
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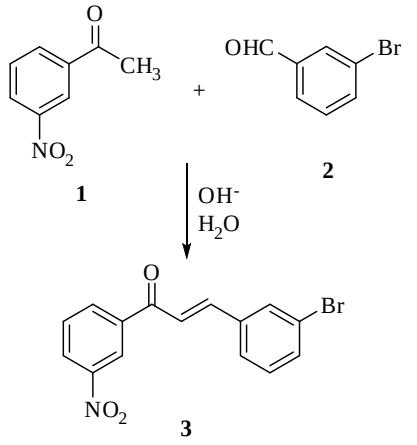
1. Synthesis of chalcones:

1.1. Claisen-Schmidt's condensation:

This method for the preparation of chalcone **3** was performed by the condensation of ketone **1**, 1-(3-nitrophenyl)ethanone, with aldehyde **2,** 3-bromobenzaldehyde, in the presence of aqueous alkaline bases or alcoholic alkali (**Scheme 1**) [3, 87-93].

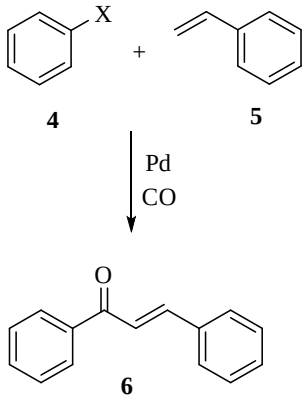


Scheme 1

1.2. Coupling reactions:

1.2.1. Carbonylative Heck's coupling reaction:

Vinylation of phenyl halide **4** with styrene (**5**) under carbon monoxide conditions in the presence of palladium catalyst gives chalcone **6** (**Scheme 2**) [94, 95].



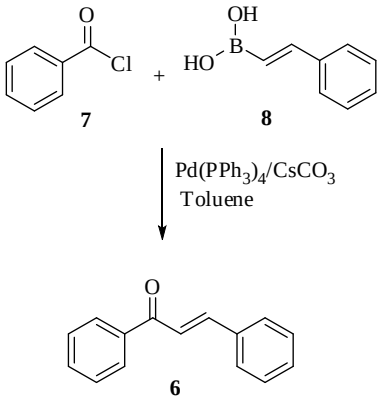
Scheme 2

1.2.2. Suzuki–Miyaura's coupling reaction:

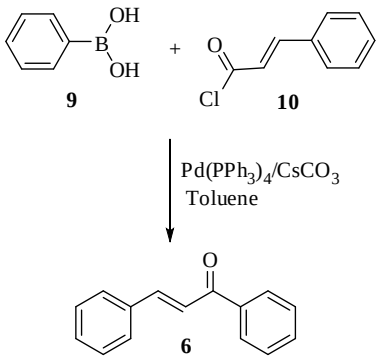
Coupling reaction of benzoyl chloride **(7**) and styryl boronic acid **(8)** using $Pd(PPh_3)_4/CsCO_3$ in toluene yielded chalcone **6** (**Scheme 3**). Also, the chalcone **6** was obtained *via* reaction of phenylboronic acid (**9**) and cinnamoyl chloride (**10)** in the presence of $Pd(PPh_3)_4/CsCO_3$ in toluene (**Scheme 4**) [47].

1.2.3. Sonogashira's isomerization coupling:

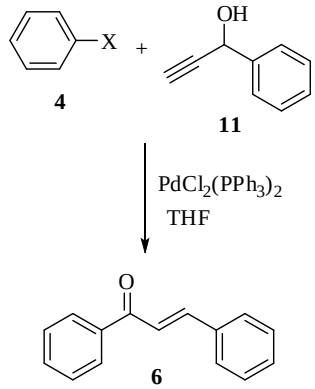
Also, chalcone **6** was prepared by the microwave coupling of the electron-insufficient group, like phenyl halide **4**, and 1-phenylprop-2-yn-1-ol (**11**) in tetrahydrofuran (THF) with the presence of $PdCl_2(PPh_3)_2$ (**Scheme 5**) [97, 98].



Scheme 3



Scheme 4



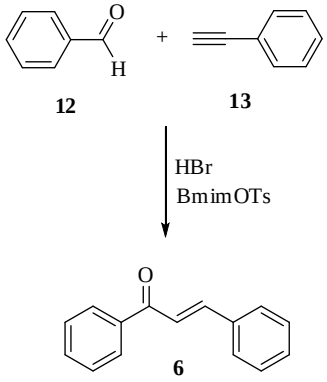
Scheme 5

1.2.4. Miscellaneous reaction:

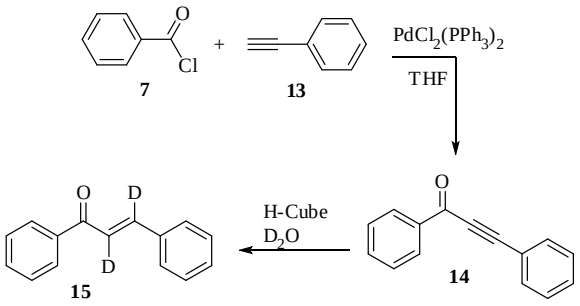
Coupling of benzaldehyde (**12)** with phenylacetylene (**13)** in hydrogen bromide and ionic liquids like 1-butyl-3-methyl-1*H*-imidazolium 4-methylbenzenesulfonate (BmimOTs) for 12 h at 100 °C yielded chalcone **6** (**Scheme 6**) [99].

1.3. Continuous-flow deuteration reaction:

Ynone **(14)**, 1,3-diphenylprop-2-yn-1-one, was synthesized by the reaction of benzoyl chloride (**7**) and phenylacetylene (**13**) under Sonogashira's conditions followed by deuteration, which was carried out in an H-Cube system affording deuterated chalcone **15** (**Scheme 7**) [100, 101].



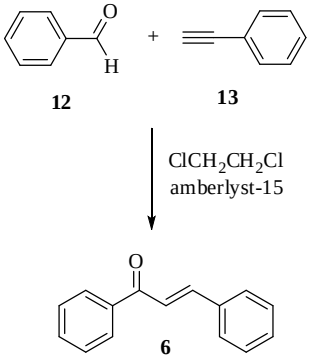
Scheme 6



Scheme 7

1.4. Solid acid catalyst-mediated reaction:

The addition of benzaldehyde **(12)** and phenylacetylene **(13)** in 1,2-dichloroethane under a microwave condition and using ion-exchange resin like amberlyst-15, the solid acid catalyst, gave chalcone **6** (**Scheme 8**) [102].



Scheme 8

1.5. Aldol reaction:

The treatment of ketones **16** with benzaldehyde **(12)** in ethanolic basic medium yields chalcones **17** (**Scheme 9**) [103, 104].

2. Reactions of chalcones:

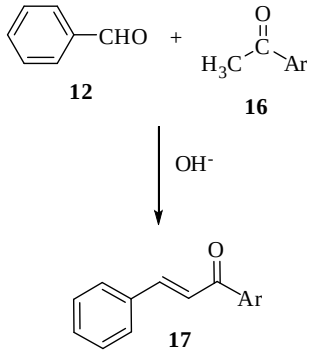
2.1. Synthesis of seven-membered ring heterocyclic compounds:

2.1.1. Reaction with *o*-phenylenediamine:

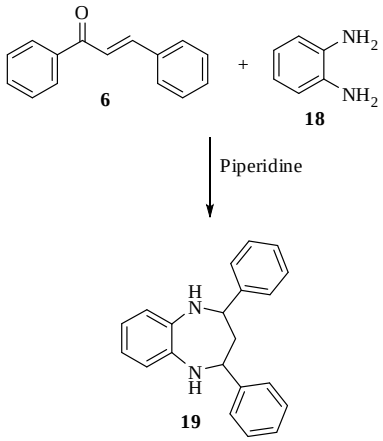
The reaction of chalcone **6**, and *o*-phenylenediamine (**18**) in the presence of piperidine as a catalyst gave 2,4-diphenyl-1,5-benzodiazepine (**19**). This route has been used to synthesize benzodiazepines (**Scheme 10**) [105, 106].

2.1.2. Reaction with 2-aminothiophenol:

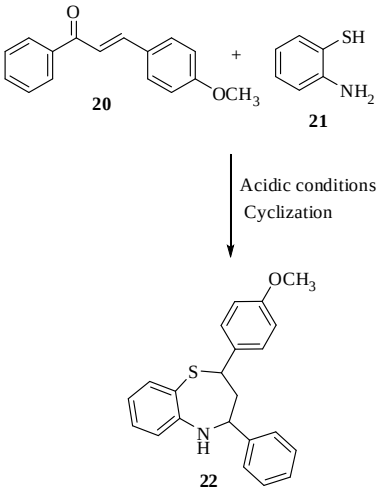
Benzothiazepine derivative **22** was obtained by the reaction of chalcone **20**, (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one, with 2-aminothiophenol **(21)** in acidic conditions (**Scheme 11**) [106].



Scheme 9



Scheme 10

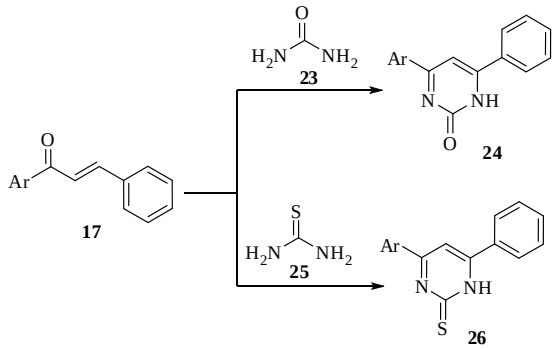


Scheme 11

2.2. Synthesis of six-membered ring heterocyclic compounds:

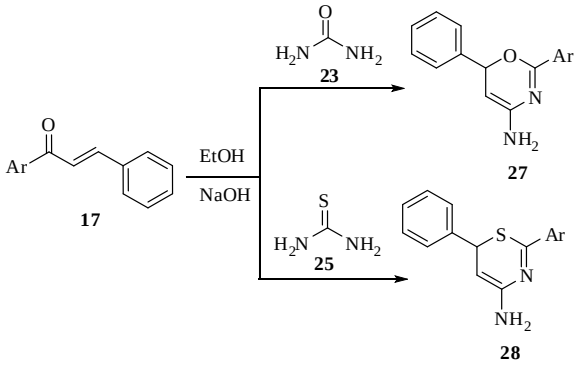
2.2.1. Reaction with urea or thiourea:

Chalcones **17** reacted with urea (**23**), and thiourea (**25**) in acidic medium yielding 6-phenyl-4-aryl-pyrimidin-2(1*H*)-one **24**, and 6-phenyl-4-aryl-pyrimidine-2(1*H*)-thione **26**, respectively (**Scheme 12**) [107-109].



Scheme 12

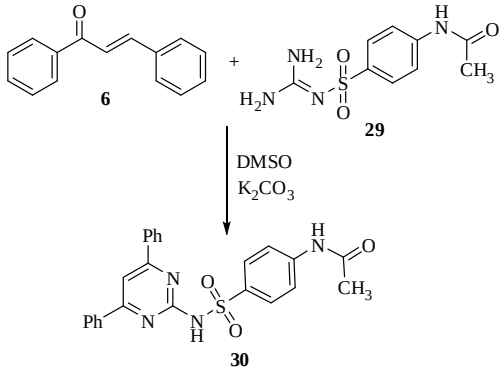
Oxazines **27** and thiazines **28** derivatives were prepared *via* reaction of chalcones **17** with urea (**23**) and thiourea **(25)**, respectively, in ethanol with the presence of sodium hydroxide (**Scheme 13**) [110].



Scheme 13

2.2.2. Reaction with sulphaguanidine acetate:

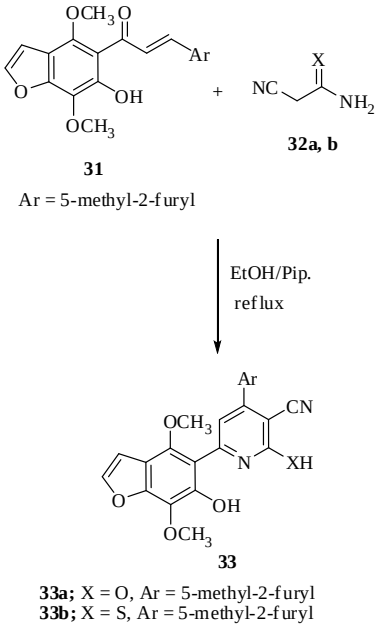
The cyclocondensation of *N*-(4-(*N*-(diaminomethylene)sulfamoyl)phenyl)acetamide (**29)** with chalcone **6** in dimethyl sulphoxide (DMSO) at 110 ºC give 4,6-diphenylsulphapyrimidine acetate **(30)** (**Scheme 14**) [105, 111].



Scheme 14

2.2.3. Reaction of chalcones with 2-cyanoacetamide or 2-cyanothioacetamide:

Refluxing of chalcone **31** and 2-cyanoacetamide **(32a)** or 2-cyanothioacetamide **(32b)** in ethanol with the presence of piperidine gave 6-(6-hydroxy-4,7-dimethoxybenzofuran-5-yl)-4-(5-methylfuran-2-yl)-3-cyanopyridine derivatives **33a, b** (**Scheme 15**) [112].

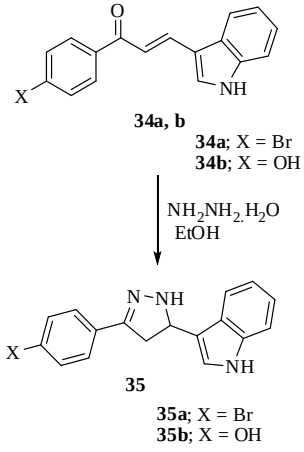


Scheme 15

2.3. Synthesis of five-membered heterocyclic compounds:

2.3.1. Reaction with hydrazine hydrate:

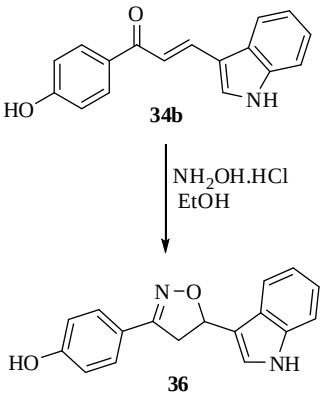
Chalcones **34a, b** were reacted with hydrazine hydrate in ethanol yielded pyrazoline derivatives **35** (**Scheme 16**) [113-116].



Scheme 16

2.3.2. Reaction with hydroxylamine hydrochloride:

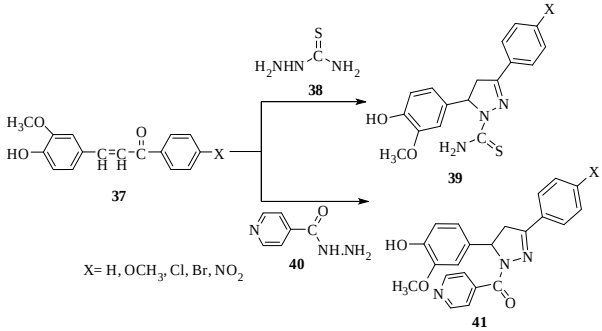
Reaction of chalcone **34b** with hydroxylamine hydrochloride in the presence of sodium acetate in absolute ethanol afforded 4-(5-(1*H*-indol-3-yl)-4,5-dihydroisoxazol-3-yl)phenol (**36)** (**Scheme 17**) [113].



Scheme 17

2.3.3. Reactions of chalcones with thiosemicarbazide and isonicotinic acid:

Treatment of chalcones **37** with thiosemicarbazide **(38)** in absolute ethanol in the presence of sodium hydroxide refluxed for 7 hours to give 4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives **39**. Also, chalcones **37** were reacted with isonicotinohydrazide **(40)** in refluxed ethanol in the presence of glacial acetic acid to give (3-aryl-5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)(pyridin-4-yl)methanone **41** (**Scheme 18**) [117].



Scheme 18

3. Biological applications of chalcones:

3.1. Chalcones as antimicrobial agents:

Some of chalcones **42-44** showed antitubercular activity for *Mycobacterium tuberculosis* H37Rv and antimicrobial activity for fungi and pathogenic bacteria (**Figure 2**) [118].

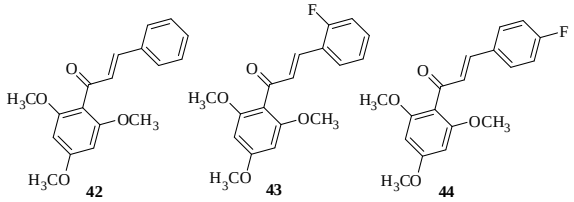


Figure 2

Chalcones **45** showed antimicrobial activities for five pathogenic bacteria and four fungi (**Figure 3**) [119].

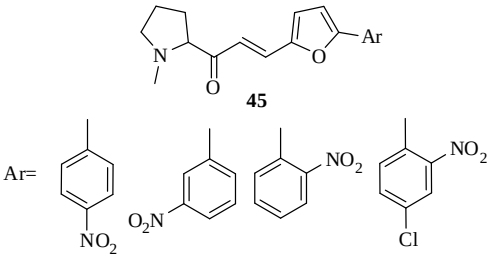


Figure 3

The synthesized chalcone **46** was evaluated for antimicrobial activities against four bacterial and two fungal strains (**Figure 4**) [33].

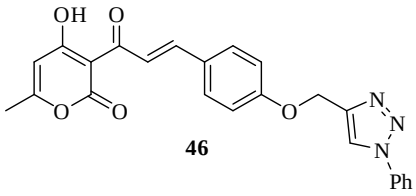


Figure 4

3.2. Chalcones as anticancer:

Isoquinolin-chalcone derivatives **47-52** were found to have anticancer activities against breast cancer (MCF-7) (**Figure 5**) [120].

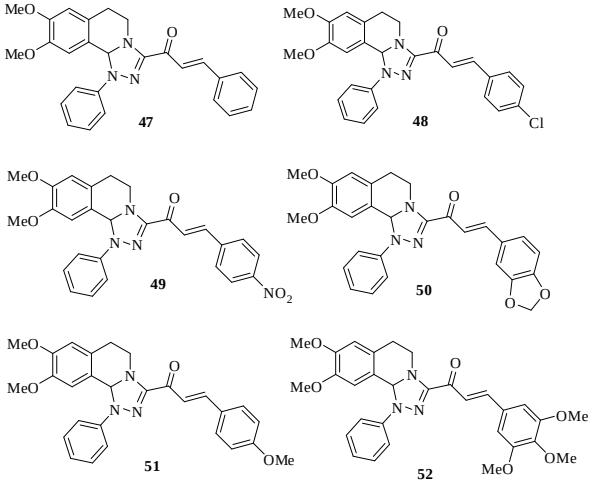
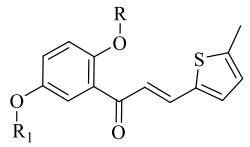


Figure 5

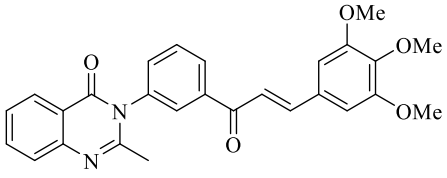
The compounds **53-55** were evaluated to show antitumor and chemopreventive activities (**Figure 6**) [121-123].



	R	R1
53	H	H
54	H	CH_3CH_2
55	CH_3CH_2	CH_3CH_2

Figure 6

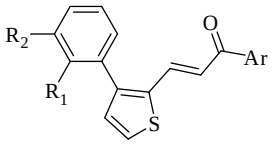
A new quinazolinone–chalcone **56** possessing anticancer activity (**Figure 7**) [124].



56

Figure 7

Chalcones **57-59** showed *in vitro* anticancer property against human colon cancer cell lines (**Figure 8**) [125].



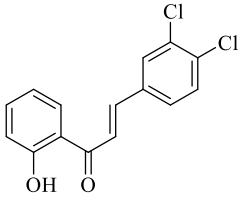
57-59

	Ar	R_1	R_2
57		H	OCH_3
58	OMe	H	OCH_3
59		H	OCH_3

Figure 8

3.3. Chalcones as anti-inflammatory agents:

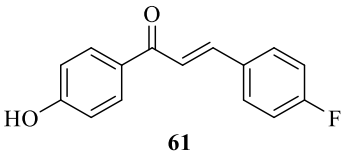
A novel chalcone **60**, (*E*)-3-(3,4-dichlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one, was evaluated for anti-inflammatory activity (**Figure 9**) [3].



60

Figure 9

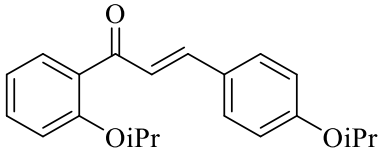
Fluorinated chalcone **61** possesses a powerful anti-inflammatory property (**Figure 10**) [126].



61

Figure 10

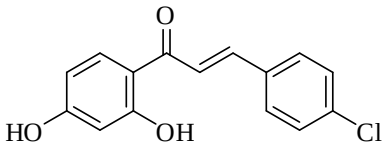
Novel chalcone containing the isopropyl group (iPr) **62** is evaluated as active anti-inflammatory agent (**Figure 11**) [127].



62

Figure 11

A novel chalcone **63**, (*E*)-3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one, was prepared and tested to be a potent anti-inflammatory agent (**Figure 12**) [128. 129].



63

Figure 12

3.4. Chalcones as antioxidants:

Chalcones **64-66** were evaluated as antioxidant agents (**Figure 13**) [130].

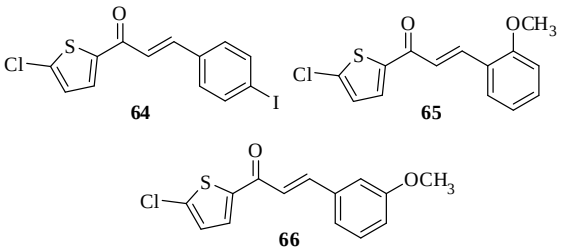


Figure 13

A new series of 2,4-dihydroxy chalcones **67** and **68** were synthesized, followed by their reaction with DMSO in the presence of iodine to give flavonoids **69** and **70** respectively, and then evaluated for antioxidant activity (**Figure 14**) [131].

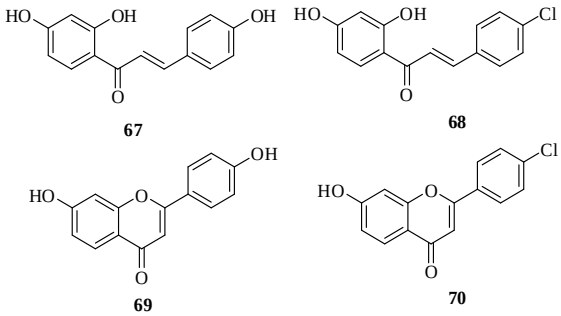


Figure 14

A new series of chalcones **71** and **72** were synthesized and tested for antioxidant activity (**Figure 15**) [132].

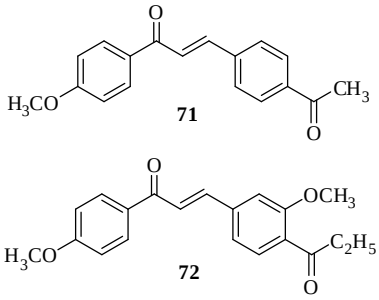


Figure 15

A novel chalcone, i.e., glycyglabrone **73-75** possess antioxidant property (**Figure 16**) [133].

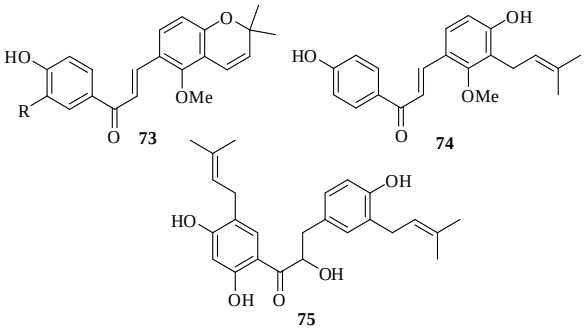
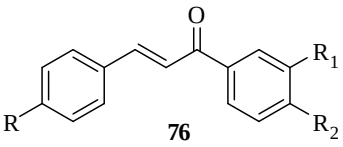


Figure 16

3.5. Chalcones as an antiepileptic:

A new series of chalcones **76** were tested for antiepileptic property (**Figure 17**) [134-136].



76

R=H, R_1=H, R_2= OCH_3
R=H, R_1=Cl, R_2= H
R=OCH_3, R_1=H, R_2= OCH_3
R=CH_3, R_1=Cl, R_2= H
R=Br, R_1=H, R_2= Cl

Figure 17

3.6. Chalcones as antidiabetic agents:

A series of chalcones **77-79** evaluated as powerful antidiabetic and antidyslipidemic agents (**Figure 18**) [137].

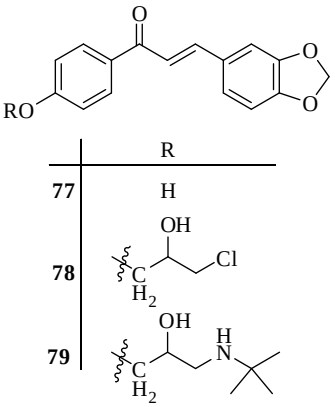
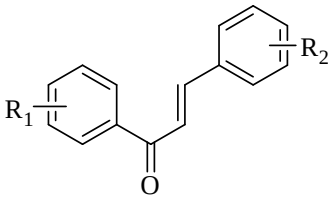


Figure 18

Chalcones **80-85** were found to be active as antidiabetic agents (**Figure 19**) [138].



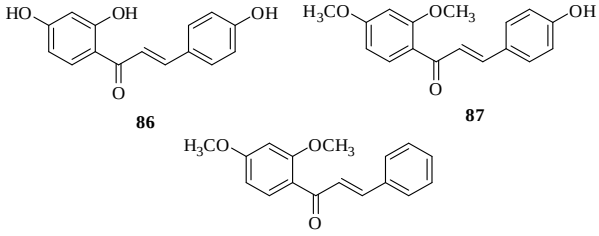
R_1 = OH, F, Cl

R_2 = H, OMe

80-85

Figure 19

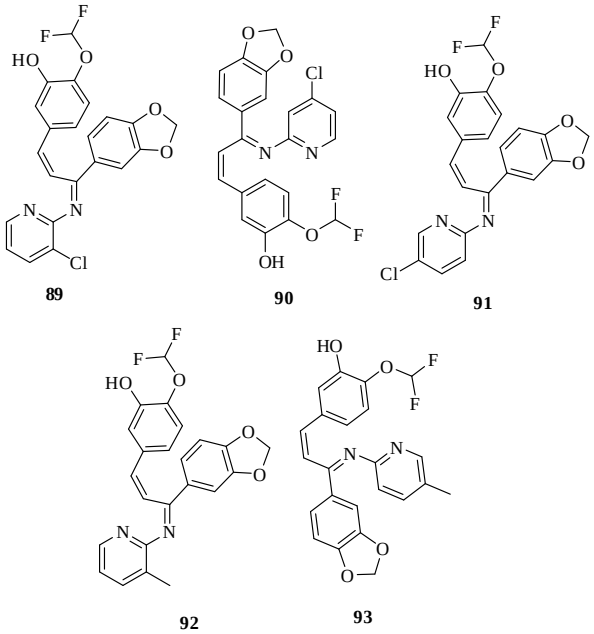
Chalcones **86-88**, which are derived from isoliquiritigenin, and liquiritigenin were evaluated for their antidiabetic activity (**Figure 20**) [139, 140].



86 **87** **88**

Figure 20

A novel series of chalconeimines **89-93** were evaluated for their antidiabetic activity *via* α-amylase inhibition activity (**Figure 21**) [37].



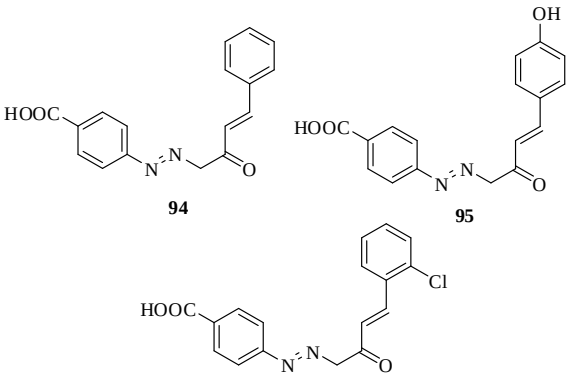
89 **90** **91**

92 **93**

Figure 21

3.7. Chalcones as antihypertensive agents:

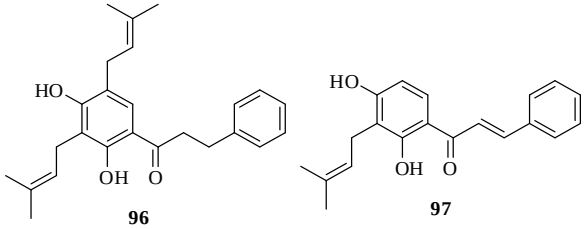
Novel chalcones **94-96** were tested to be potent antihypertensive agents (**Figure 22**) [141].



94 **95** **96**

Figure 22

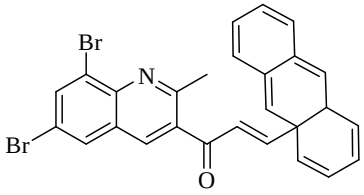
Dihydrospinochalcone **96** and isocordoin **97** were tested to be potent vasorelaxant and antihypertensive properties (**Figure 23**) [142].



96 **97**

Figure 23

Novel chalcone **98** with active quinoline moiety were tested to have powerful antihypertensive activity (**Figure 24**) [143].

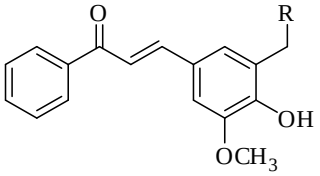


98

Figure 24

3.8. Chalcones as antimalarial agents:

Chalcones **99-101** were evaluated for their antimalarial activity against *Plasmodium falciparum* strain (3D7) and molecular docking was also performed (**Figure 25**) [144].



	R
99	Morpholine
100	Piperidine
101	Diethylamine

99-101

Figure 25

Conclusion:

The review talks about chalcones, their synthesis by different methods. Also, this review covered several reactions of chalcones which lead to the synthesis of new heterocyclic derivatives with vital applications. We covered some of the biological applications of chalcones which were important and versatile.

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Conflict of interest

The authors declare that they have no competing interests.

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