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Systematic Review

Keywords: Chalcones, medicinal chemistry, Claisen–Schmidt condensation, structure–activity relationship, heterocyclic hybrids, pharmacological activities, drug discovery

Posted Date: September 10th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10746277/v1>

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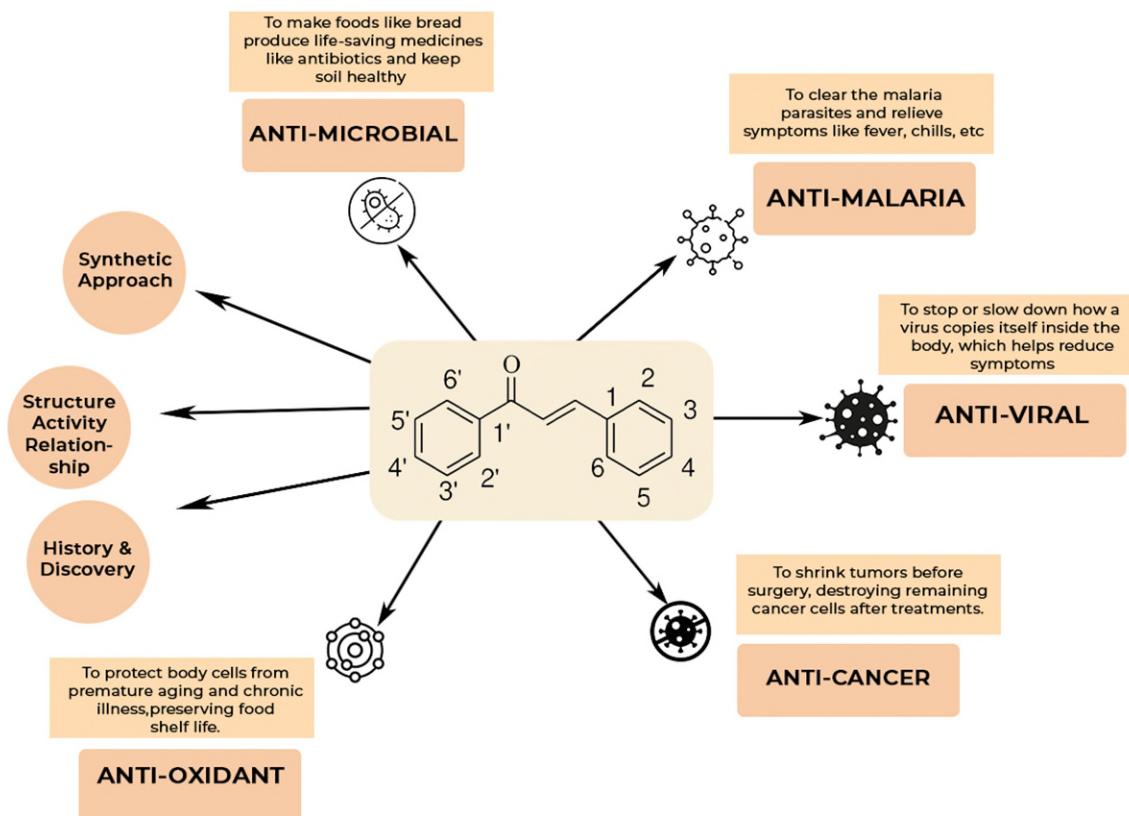
Additional Declarations: No competing interests reported.

CHALCONES IN DRUG DISCOVERY: A COMPREHENSIVE REVIEW OF SYNTHESIS AND BIOLOGICAL ACTIVITIES

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ABSTRACT

Chalcone derivatives represent an important class of bioactive compounds characterized by a versatile α,β -unsaturated carbonyl scaffold and broad pharmacological potential. Their structural simplicity, synthetic accessibility, and amenability to chemical modification have stimulated extensive investigation as promising leads in medicinal chemistry and drug discovery. This review provides a comprehensive overview of recent advances in the synthesis, structural diversification, biological activities, and structure–activity relationships (SAR) of chalcone derivatives. Classical Claisen–Schmidt condensation remains the predominant strategy for constructing the chalcone framework, while complementary approaches involving cross-coupling, nucleophilic substitution, oxidation, and amide bond formation have facilitated the incorporation of diverse pharmacophores. Particular attention is given to chalcones incorporating biologically relevant heterocyclic moieties, including pyridine, piperazine, benzimidazole, quinoline, thiazole, and related scaffolds. The biological potential of chalcone derivatives is discussed across a broad spectrum of activities, including anticancer, antioxidant, antimicrobial, antiviral, antimalarial, anti-inflammatory, and antidiabetic effects. Furthermore, SAR analysis highlights the influence of enone configuration, aromatic substitution, electronic properties, lipophilicity, and heterocyclic hybridization on biological performance. Collectively, the reviewed findings demonstrate that rational structural modification can substantially enhance the potency, selectivity, and pharmacological properties of chalcone-based compounds. Despite considerable preclinical progress, challenges remain regarding pharmacokinetic properties, toxicity, mechanistic validation, and clinical translation. Continued integration of synthetic chemistry, molecular design, biological evaluation, and pharmacological profiling may therefore facilitate the development of chalcone derivatives into clinically relevant therapeutic agents.

KEYWORDS: Chalcones; medicinal chemistry; Claisen–Schmidt condensation; structure–activity relationship; heterocyclic hybrids; pharmacological activities; drug discovery

INTRODUCTION

The identification of small pharmacological molecules is a field that continues to draw extensively upon natural-product chemistry [1]. Natural products provide structurally diverse and evolutionarily optimized molecular frameworks that are difficult to reproduce through combinatorial synthesis [2]. Among the major classes of plant secondary metabolites, flavonoids have received considerable scientific attention due to their diverse pharmacological properties [3]. These properties range from antioxidant to anti-inflammatory, antimicrobial, antineoplastic, and metabolic regulatory activities. A particularly important subclass of flavonoids is the chalcones, chemically defined as 1,3-diaryl-2-propen-1-ones (Fig.1). Chalcones are open-chain precursors in the flavonoid biosynthetic pathway. They function as key intermediates in the formation of several flavonoid classes - flavones, flavanones, isoflavonoids, and aurones [4,5]. The characteristic framework of chalcones consists of two aromatic moieties, referred to as rings A and B, connected by a three-carbon α , β -unsaturated carbonyl linker. This conjugated enone system contains an olefinic bond adjacent to carbonyl functionality. It is this structure that determines the physicochemical and pharmacological properties of the chalcone scaffold. Variation in the substitution pattern of the two aromatic rings also influences these properties and contributes to the broad range of biological activities reported for chalcone derivatives [6,7].

Naturally occurring chalcones are widely distributed in edible plants, fruits, vegetables, and traditional medicinal herbs, where they function as phytoalexins and defensive metabolites against microbial invasion, oxidative stress, and herbivory [8,9]. Examples of naturally occurring chalcones include xanthohumol from *Humulus lupulus*, licochalcone A from *Glycyrrhiza* species, cardamonin from *Alpinia katsumadai*, isoliquiritigenin from *Glycyrrhiza glabra*, phloretin from apples, and butein from *Rhus verniciflua* [10,11]. These natural chalcones have been found to exhibit a variety of pharmacological activities, such as acting as antioxidants, anti-inflammatory agents, anti-cancer agents, and anti-microbial agents [12,13]. Due to these activities, chalcones have become significant areas of study in the fields of natural products and medicinal chemistry. In particular, efforts are being made to modify the structures of these compounds to enhance their biological activity and develop them as pharmaceuticals [14,15].

Chalcones are particularly attractive from a medicinal chemistry perspective because their core framework can be assembled using relatively straightforward synthetic procedures. Among the available methods, the Claisen–Schmidt condensation is the most widely employed route and typically involves base- or acid-mediated condensation of an aromatic aldehyde with an aryl methyl ketone, followed by formation of the conjugated α,β -unsaturated carbonyl system [16,17]. The broad availability of the requisite starting materials, straightforward reaction setup, and tolerance of diverse functional substituents make this transformation especially useful for the systematic preparation of structurally varied chalcone analogues and subsequent structure–activity relationship (SAR) investigations [18].

Recent developments in synthetic methodology have further expanded the efficiency and sustainability of chalcone preparation. In addition to conventional solution-phase reactions, alternative approaches such as mechanochemical solvent-free synthesis, ultrasound-assisted reactions, microwave-mediated condensation, and continuous-flow processing have been investigated to improve reaction rates, reduce solvent consumption, and enhance operational efficiency [19,20]. Structural diversification can also be achieved through transition-metal-mediated cross-coupling reactions, including Suzuki–Miyaura, Heck, and Sonogashira methodologies. These strategies provide additional opportunities for introducing structurally complex substituents, including heteroaryl and fluorinated groups, thereby broadening the chemical space accessible for medicinal chemistry optimization [21,22]. When integrated with computational molecular design, virtual or high-throughput screening, and automated compound evaluation, these advances provide an increasingly efficient framework for the generation and biological assessment of diversified chalcone libraries [23].

The chalcone framework shows strong structural adaptability which makes it an ideal base for organized structure–activity relationship (SAR) optimization. The physicochemical and electronic characteristics of derivatives become highly variable when scientists change the substitution pattern of aromatic rings by adding electron-donating and electron-withdrawing groups together with halogen atoms and nitro groups and heteroaromatic moieties. The structural alterations between chalcone derivatives produce changes in electron distribution and lipophilic characteristics and hydrogen-

bonding potential and molecular shape which determine their binding patterns to biological targets including enzymes and receptors and nucleic acids [24, 25,26]. Different pharmacological uses show clear evidence about how particular substituents affect biological systems. The B-ring hydroxyl substitution generates stronger antibacterial effects against MRSA but researchers have found methoxy groups and prenyl substituents to boost anticancer and anti-inflammatory properties [27,28]. Scientists use two main methods to modify chalcones through nitrogen-containing heterocyclic system fusion and attachment of these systems which include pyrrole and imidazole and thiazole and pyrazole and pyridine and indole and benzimidazole and benzothiazole and quinoline. The process of adding heterocyclic structures to chalcones creates new hybrid compounds which demonstrate better biological effects than their original chalcone framework [29,30].

Chalcone derivatives are known to have a variety of pharmacological properties, but the focus of much research has been on their potential as anticancer agents. Both synthetic and naturally occurring chalcone compounds have been shown in preclinical studies to have cytotoxic and antiproliferative effects on various types of cancer cells. These include breast cancer cells (MCF-7 and MDA-MB-231), cervical cancer cells (HeLa cells), liver cancer cells (HepG2 cells), lung cancer cells (A549 cells), colorectal cancer cells (HT-29 cells), and various types of blood cancer cells [31,32]. The mechanisms by which chalcone derivatives exhibit their anticancer effects appear to be diverse and include the induction of apoptosis through caspase pathways, interrupting the cell cycle, inhibiting tubulin polymerization, inhibiting topoisomerases, inhibiting angiogenesis, and regulating signaling pathways such as NF- κ B and MAPK pathways [33,34].

A variety of naturally occurring chalcone derivatives have also been explored for their chemopreventive properties. These include compounds like xanthohumol, flavokawain A, and isoliquiritigenin, which have demonstrated promising anticancer properties in preclinical studies and are thus worthy of further exploration and potential clinical investigation [35,36]. The antimicrobial properties of chalcone derivatives extend across a wide spectrum of pathogenic microorganisms, encompassing both Gram-positive and Gram-negative bacteria, fungi, mycobacterial species, protozoan parasites, and viruses [37,38]. Their antibacterial effects have been attributed to several mechanisms, including

perturbation of bacterial membrane integrity, inhibition of membrane-associated efflux systems, and interference with enzymes involved in cell-wall biosynthesis. Among the reported molecular targets are β -(1,3)-glucan synthase and chitin synthase, which are essential for the structural integrity and biosynthetic processes of susceptible microorganisms [39,40]. Of particular therapeutic interest is the potential of selected chalcone derivatives to restore or enhance bacterial susceptibility to existing antimicrobial agents. Studies have indicated that some analogues can overcome resistance phenotypes in methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant bacterial strains, either through direct antimicrobial activity or through synergistic interactions when administered in combination with conventional antibiotics [41]. Beyond antibacterial applications, antiviral effects have also been reported. These activities may involve inhibition of critical viral proteins and enzymes, including neuraminidase, HIV-1 protease, and reverse transcriptase, in addition to interference with processes required for efficient viral assembly and maturation [42,43]. Chalcones possess significant anti-inflammatory and antioxidant properties. The anti-inflammatory effects of chalcones are linked to their ability to reduce the synthesis of inflammatory mediators like nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor-alpha (TNF- α), and interleukins. These effects are also linked to the inhibition of enzymes like cyclooxygenases (COX), lipoxygenases (LOX), and inducible nitric oxide synthase (iNOS) [44,45]. Chalcones can inhibit the signaling of nuclear factor kappa B (NF- κ B), which regulates the expression of pro-inflammatory genes within cells. These mechanisms work to reduce inflammation in conditions like arthritis and neurodegenerative disorders [46,47]. In addition to their anti-inflammatory effects, chalcones also exhibit antioxidant activity. The phenolic hydroxyl substituents and conjugated enone moiety in chalcones contribute to their ability to scavenge free radicals. Furthermore, chalcones can interact with transition metals to exhibit antioxidant properties. These effects of chalcones help to reduce the accumulation of reactive oxygen species (ROS) within the body and limit oxidative damage to the cellular components like proteins, lipids, and nucleic acids [48,49].

Beyond their antimicrobial, anti-inflammatory, and anticancer properties, chalcone derivatives have been explored for their potential therapeutic applications in metabolic and neurodegenerative disorders. Various chalcone analogues have been investigated

for their ability to inhibit enzymes involved in carbohydrate metabolism, such as α -amylase and α -glucosidase, in addition to aldose reductase, protein tyrosine phosphatase 1B (PTP1B), and dipeptidyl peptidase-4 (DPP-4), which are implicated in the metabolic syndrome and diabetes mellitus [50,51]. In addition to regulating these metabolic enzymes, chalcones are also thought to have an impact upon glucose transporter activity, as well as the AMP-activated protein kinase (AMPK)-dependent signaling pathways, which may influence conditions such as the metabolic syndrome and diabetes mellitus [50,51]. Chalcones have also been explored for their potential therapeutic applications in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Their potential therapeutic activities include the inhibition of acetylcholinesterase, butyrylcholinesterase, monoamine oxidases, suppression of neuroinflammatory processes, and attenuation of neuronal apoptosis [52]. In addition, some chalcone derivatives have been reported to upregulate the expression of neurotrophic factors, which may play a role in the preservation of neuronal function. Such activities of chalcones illustrate the diverse pharmacological potential of the chalcone scaffold, as well as its potential to regulate the complex molecular pathways involved in multifactorial diseases such as metabolic syndrome, diabetes mellitus, and neurodegenerative diseases.

Although extensive preclinical pharmacology studies have been conducted on chalcone derivatives, their development into clinically useful therapeutics has been limited by several physicochemical and pharmacokinetic challenges. Issues such as poor aqueous solubility, metabolic instability, low oral bioavailability, and potential off-target effects pose significant challenges to achieving optimal therapeutic exposure and safety profiles for these compounds [53,54]. Despite these challenges, a limited number of clinical studies have evaluated the effects of naturally occurring chalcones in humans. Specifically, compounds like xanthohumol and chalcones derived from *Angelica keiskei* (ashitaba) have been investigated in human subjects, with reported effects on inflammatory biomarkers, visceral adiposity, and vascular function [55,56]. While these studies offer some insights into the potential benefits of these chalcones, further research with larger and more controlled clinical trials is necessary to confirm their efficacy and safety in humans. Further research efforts focusing on the structure–activity relationships (SAR)

of chalcone derivatives, coupled with advanced computational methods to predict their ADMET properties, can play a crucial role in overcoming these limitations. By employing such strategies, researchers can identify and optimize chalcone compounds with improved pharmacokinetic profiles, enhanced target specificity, and greater therapeutic potential [57,58]. The chalcone literature is extensive, and there have been many advances in synthetic methods and biological applications of chalcones. Despite the existence of many reviews of chalcones, there remains a gap in the literature for a review that combines both the chemical and biological aspects of chalcone research, especially focusing on heterocyclic chalcone hybrids and their emerging therapeutic applications. The objectives of the review are to examine contemporary synthetic methods for chalcones, especially focusing on various synthetic approaches and green chemistry methods; to analyze the biological and pharmacological activities of chalcones, especially focusing on their mechanisms of action and structure-activity relationships; and to review the drug-likeness and pharmacokinetic properties of chalcone-based lead compounds. This review will provide a useful resource for scientists interested in the development of chalcone-based therapeutic agents.

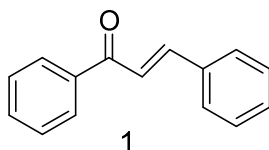


Fig 1: Structure of Chalcone

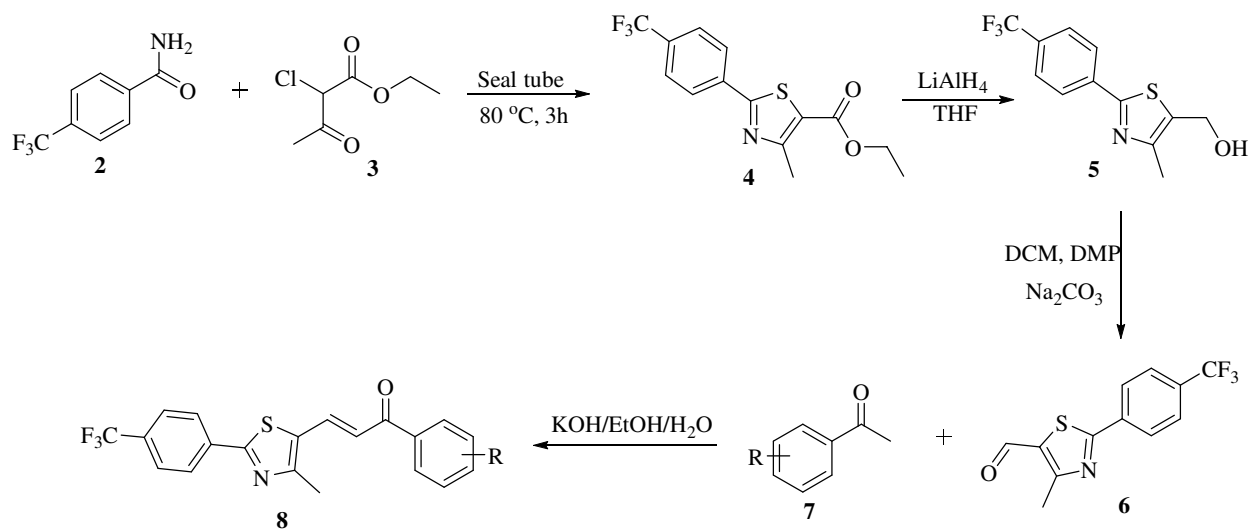
SYNTHESIS OF CHALCONE DERIVATIVES

Heterocycle-containing chalcone derivatives have attracted considerable attention in medicinal chemistry due to their ability to exhibit biological activities that are comparable to, or even surpass, those of conventional chalcone analogues [59]. Owing to its structural versatility and pharmacological relevance, the chalcone core continues to serve as a key framework for the development of novel bioactive compounds across various drug discovery programs [60]. Consequently, significant attention has been directed toward the synthesis and structural modification of chalcone-based molecules through

the incorporation of heterocyclic moieties, with the objective of enhancing their pharmacological properties and expanding their therapeutic potential.

2.1. Chalcones Bearing Thiazole

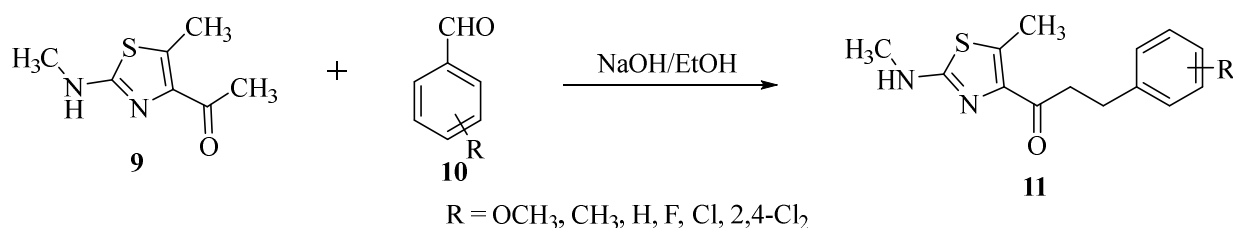
Kasetti and co-workers [61] reported the synthesis of a series of thiazole-containing chalcone derivatives. The synthetic route involved the preparation of the key thiazole-carbaldehyde intermediate **6** through a multistep sequence. Initially, thiazole-carboxylate derivative **4** was obtained via the reaction of benzamide derivative **2** with ethyl 2-chloroacetate **3**. Subsequent reduction of the ester functionality using LiAlH_4 afforded the corresponding alcohol intermediate **5**. Oxidation of compound **5** employing Dess-Martin periodinane then generated the desired aldehyde intermediate **6**. In the final stage, compound **6** underwent Claisen-Schmidt condensation with the appropriate aryl methyl ketone **7** in ethanol under basic conditions. Potassium hydroxide was added gradually with continuous stirring to facilitate the condensation process. Upon completion of the reaction, the resulting precipitate was collected by filtration, thoroughly washed, and dried. The crude product was subsequently purified by recrystallization from ethanol, yielding the target thiazole-based chalcone derivatives **8** as yellow crystalline solids in good yields, as illustrated in Scheme 1.



Scheme 1: Synthesis of thiazole-containing chalcone derivatives.

Farghaly *et al.* [62] reported the synthesis of a series of thiazole-incorporated chalcone derivatives with notable antitumor activity. The target compounds **11** were prepared via a

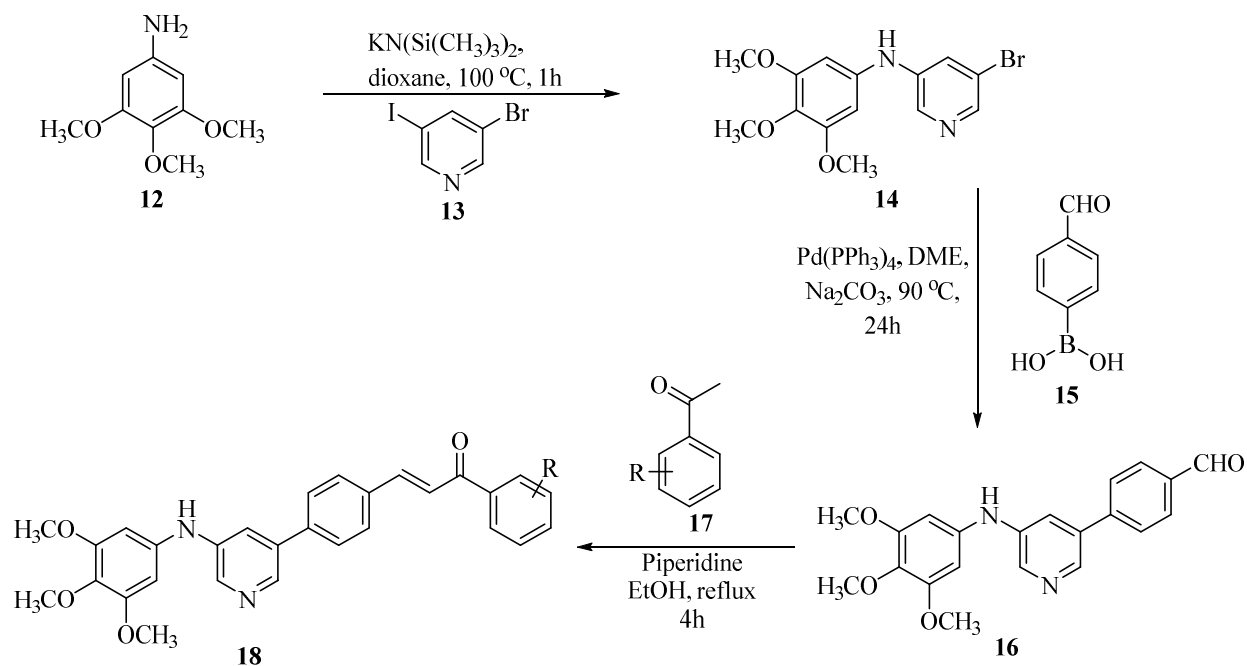
Claisen-Schmidt condensation reaction between 4-acetylthiazole derivative **9** and various aromatic aldehydes **10** in anhydrous ethanol. The reaction was initiated by the gradual addition of an aqueous sodium hydroxide solution, followed by continuous stirring to promote the formation of the desired chalcone framework. Upon completion, the precipitated products were isolated by filtration and subsequently purified through recrystallization from an ethanol-dioxane solvent system, affording the corresponding thiazole-based chalcone derivatives **11**, as depicted in Scheme 2.



Scheme 2: Synthetic route for the preparation of thiazole-based chalcone derivatives.

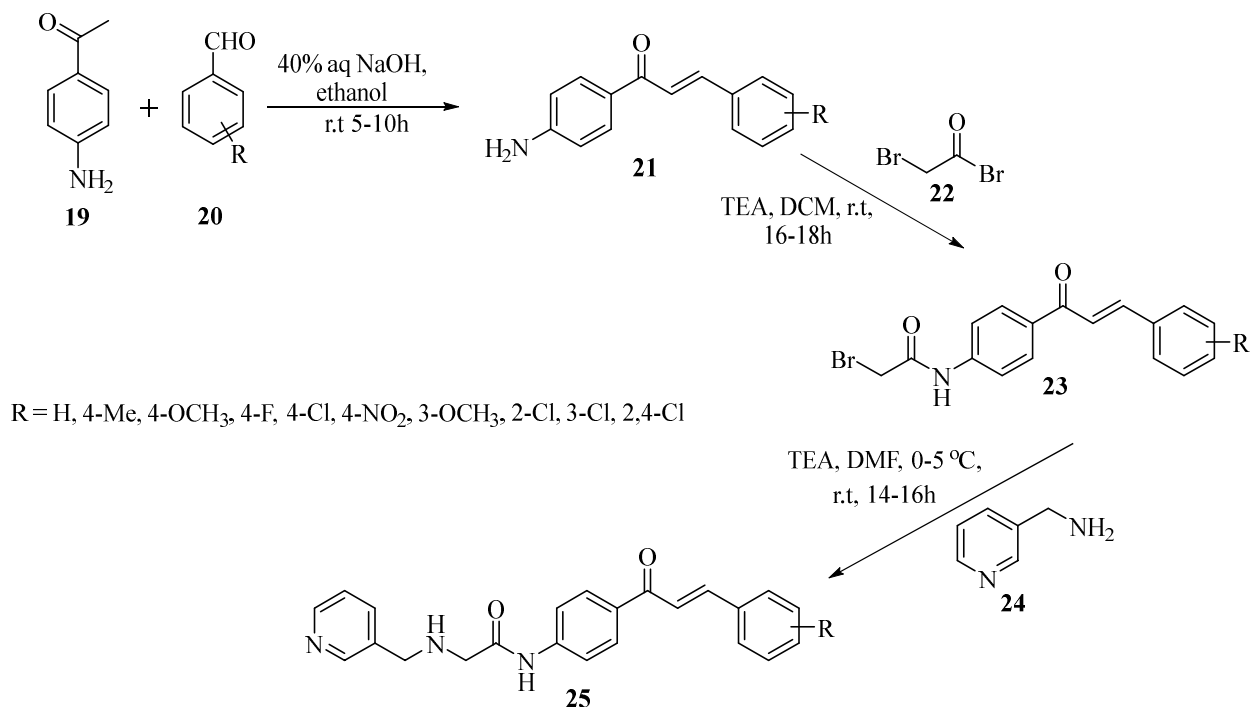
2.2. Chalcones Bearing Pyridine

The incorporation of a pyridine moiety into the chalcone framework has attracted considerable attention as an effective approach for generating structurally diverse chalcone derivatives. In this context, Madhavi and co-workers [63] developed a multistep synthetic route for the preparation of a series of pyridine-based chalcone analogues. The synthetic route commenced with the preparation of pyridin-3-amine intermediate **14** via a Buchwald-Hartwig cross-coupling reaction between iodopyridine **13** and trimethoxyaniline **12** in dioxane under basic conditions, affording the desired product in good yield. Subsequently, intermediate **14** underwent Suzuki-Miyaura cross-coupling with boronic acid derivative **15** in the presence of a palladium catalyst to furnish the key pyridin-3-yl benzaldehyde intermediate **16**. The final chalcone derivatives **18** were obtained through the condensation of compound **16** with various substituted acetophenone derivatives **17** in refluxing ethanol using a catalytic amount of piperidine. This reaction efficiently generated the target pyridine-incorporated chalcone analogues, as shown in Scheme 3.



Scheme 3: Synthetic route for the preparation of pyridine-incorporated chalcone derivatives.

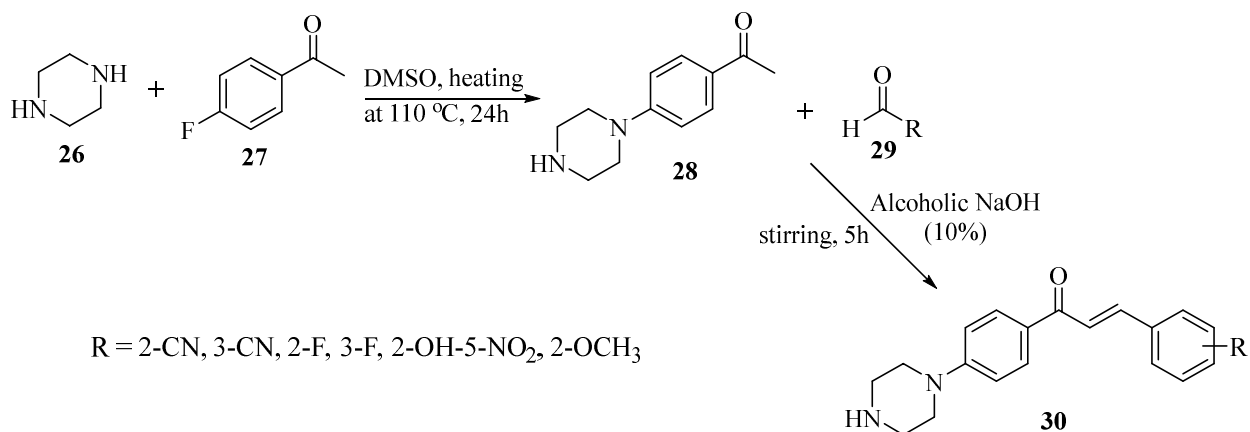
A distinct synthetic strategy for the preparation of pyridine-containing chalcone derivatives was reported by Durgapal and co-workers [64]. The synthetic pathway was initiated by the preparation of 4-amino chalcone intermediates **21** through the base-catalyzed condensation of 4-aminoacetophenone **19** with aldehyde derivative **20**. The resulting chalcones were subsequently treated with bromoacetyl bromide **22** in dichloromethane (DCM) in the presence of triethylamine (TEA), leading to the formation of intermediate **23**. In the subsequent step, intermediate **23** underwent nucleophilic substitution with 3-aminomethylpyridine **24** in DCM using TEA as the base under ambient reaction conditions. This transformation furnished a series of pyridine-based chalcone derivatives **25**, as illustrated in Scheme 4.



Scheme 4: Synthesis of Pyridine-Incorporated Chalcone Derivative

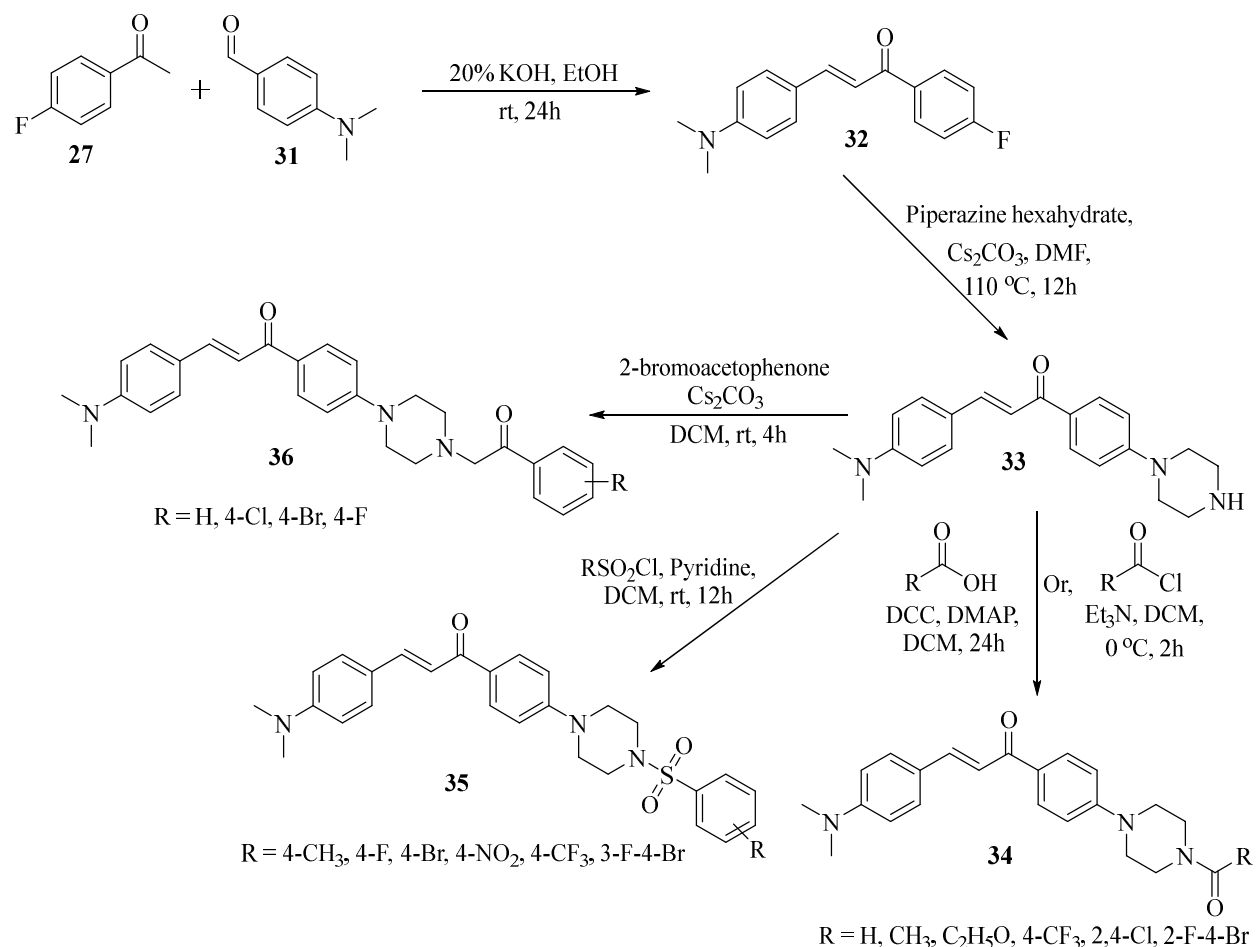
2.3. Chalcones Bearing Piperazine

Ahmed *et al.* [65] reported the synthesis of a series of piperazine-chalcone hybrid derivatives through a straightforward condensation approach. The target compounds **30** were prepared through the condensation of acetophenone derivative **28** with various aromatic aldehydes **29** under alkaline conditions using 10% alcoholic sodium hydroxide as the reaction medium. Following completion of the reaction, the resulting precipitate was isolated by filtration, washed, and dried. Subsequent recrystallization from ethanol afforded the desired piperazine-chalcone hybrids **30** in purified form, as presented in Scheme 5.



Scheme 5: Synthesis of piperazine-based chalcone derivatives.

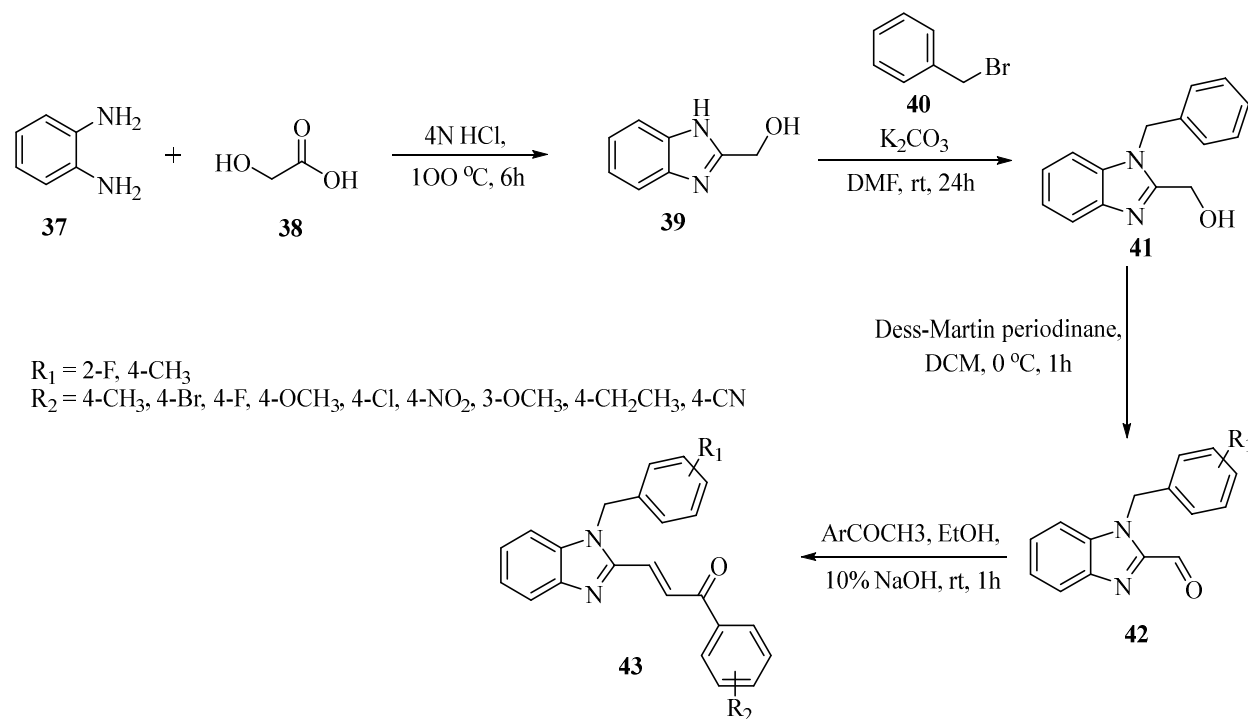
The combination of chalcone and piperazine motifs has provided access to a diverse class of hybrid molecules with intriguing structural features. In this context, a series of novel piperazine-chalcone hybrid derivatives was synthesized through a multistep synthetic sequence [66]. Chalcone intermediate **32** was generated through a potassium hydroxide-mediated Claisen-Schmidt condensation between acetophenone **27** and benzaldehyde **31**. Subsequent nucleophilic displacement of the fluorine substituent in compound **32** by piperazine afforded the key intermediate **33**. Structural modification of intermediate **33** was then accomplished through acylation or sulfonylation of the secondary amino group using the corresponding acylating and sulfonylating reagents, affording derivatives **34** and **35**, respectively, in good yields. In addition, treatment of the piperazine intermediate with 2-bromoacetophenone enabled the synthesis of tertiary amine derivatives **36**, as shown in Scheme 6.



Scheme 6: Synthetic route for the preparation of piperazine-incorporated chalcone derivatives

2.4. Chalcones Bearing Benzimidazole

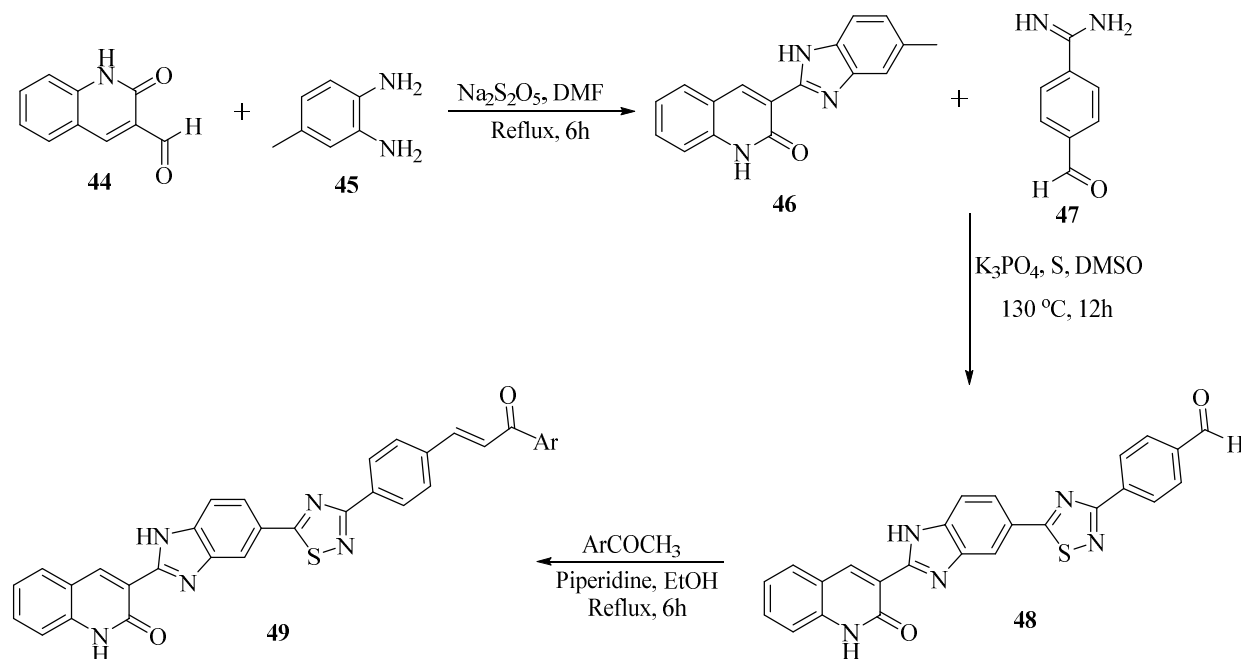
A series of benzimidazole-based chalcone derivatives was synthesized by Kumar and co-workers [67]. The synthesis began with the preparation of benzimidazole intermediate **39** via the cyclocondensation of *o*-phenylenediamine **37** with glycolic acid **38** under reflux in the presence of hydrochloric acid. Alkylation of compound **39** with benzyl bromide derivative **40** in the presence of potassium carbonate afforded the corresponding benzimidazole-2-methanol derivatives **41**. Conversion of intermediates **41** into the corresponding benzimidazole-2-carbaldehydes **42** was accomplished through Dess-Martin oxidation. The target benzimidazole-chalcone derivatives **43** were subsequently generated by condensing compounds **42** with appropriately substituted acetophenone derivatives under Claisen-Schmidt reaction conditions, as illustrated in Scheme 7.



Scheme 7: Synthetic route for the preparation of benzimidazole-based chalcone derivatives.

Similarly, Pragathi *et al.* [68] described the synthesis of a series of benzimidazole-based chalcone derivatives incorporating quinoline, benzimidazole, and thiadiazole heterocyclic motifs. The synthesis started with the formation of intermediate **46** through a double

condensation reaction between 1,2-dihydro-2-oxoquinoline-3-carbaldehyde **44** and benzene-1,2-diamine **45**. Subsequent reaction of compound **46** with 4-formylbenzimidine hydrochloride **47** afforded intermediate **48**, which served as the key precursor for further structural elaboration. The chalcone framework was subsequently introduced via an aldol (Claisen-Schmidt) condensation of intermediate **48** with appropriately substituted acetophenone derivatives. This transformation furnished the target benzimidazole-based chalcone derivatives **49**, as illustrated in Scheme 8.

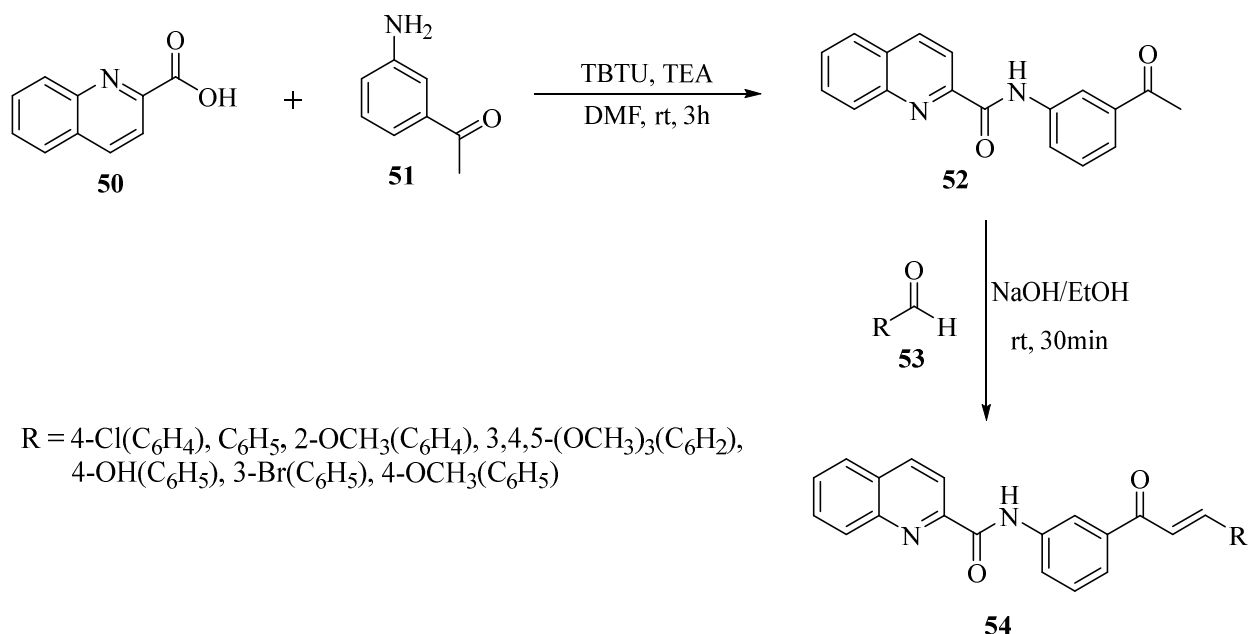


Scheme 8: Synthetic route for the preparation of thiadiazole-benzimidazole-quinolinone-based chalcone derivatives.

2.5. Chalcones Bearing Quinoline

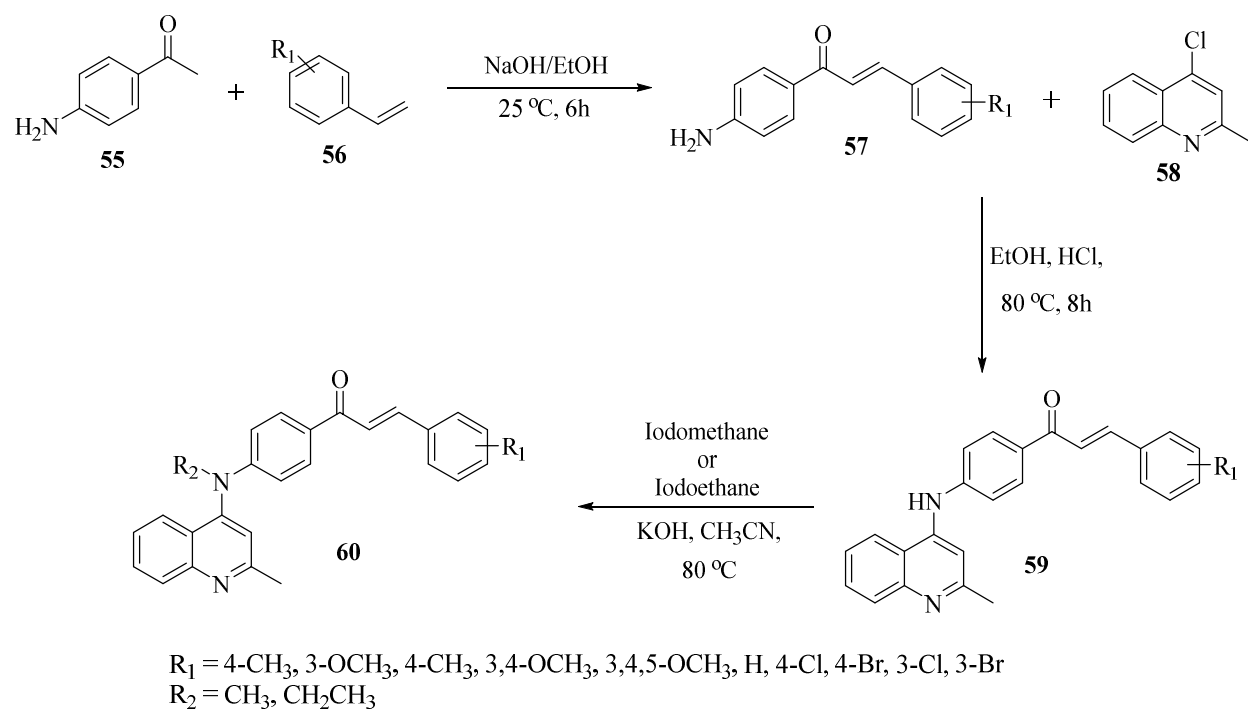
Quinoline-based chalcone derivatives were prepared by Thirumurugan and co-workers [69] through a synthetic strategy involving amide bond formation followed by Claisen-Schmidt condensation. Initially, quinoline-2-carboxylic acid **50** was coupled with ethanone derivative **51** in the presence of triethylamine (TEA) and TBTU to afford the corresponding N-quinoline-2-carboxamide intermediates **52**. Following the formation of the amide-linked scaffold, compounds **52** were reacted with various benzaldehyde derivatives **53** under

basic conditions using NaOH in ethanol at room temperature. This aldol (Claisen-Schmidt) condensation facilitated the construction of the α,β -unsaturated carbonyl framework, yielding the desired quinoline-2-carboxamide chalcone derivatives **54**, as depicted in Scheme 9.



Scheme 9: Synthetic route for the preparation of quinoline-based chalcone derivatives.

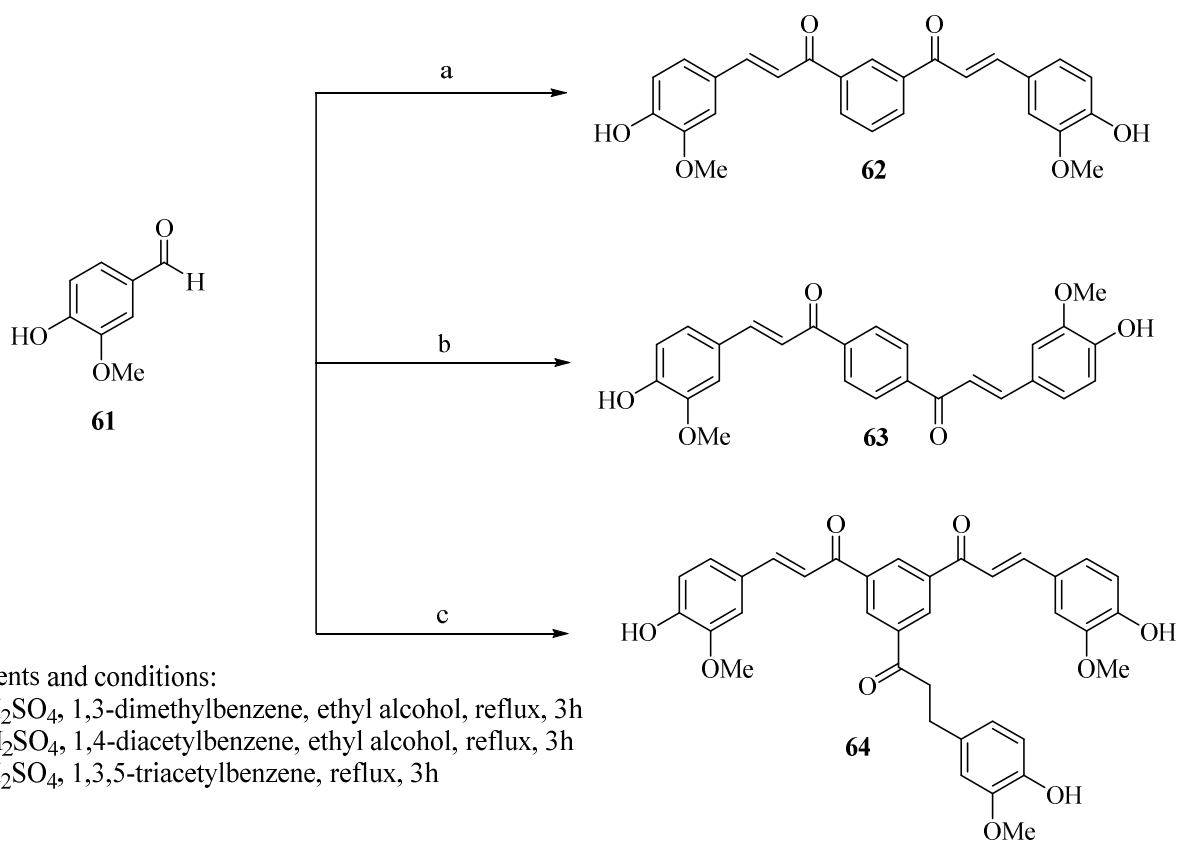
Quinoline-containing chalcone frameworks have been widely employed as versatile building blocks in the development of structurally diverse chalcone derivatives. In this regard, Guan and co-workers [70] reported the synthesis of a series of quinoline-based chalcone analogues through a multistep synthetic sequence. Initially, 4-aminoacetophenone **55** underwent Claisen-Schmidt condensation with various aromatic aldehydes **56** to furnish intermediates **57**. Subsequent reaction of these chalcone intermediates with 4-chloro-2-methylquinoline **58** afforded compounds **59** through nucleophilic substitution. Further functionalization of intermediates **59** was achieved by alkylation with iodomethane or iodoethane in the presence of potassium hydroxide in acetonitrile, yielding the corresponding derivatives **60**, as illustrated in Scheme 10.



Scheme 10: *Synthesis of quinoline-based chalcone derivatives.*

2.6. Synthesis of Chalcone Derivatives from 1,3-Diacetylbenzene and 1,4-Diacetylbenzene

The synthesis of chalcone derivatives **62-64** was accomplished through a one-step acid-catalyzed condensation reaction involving 1,3- and/or 1,4-diacetylbenzene as well as 1,3,5-triacetylbenzene and 4-hydroxy-3-methoxybenzaldehyde **61** [71]. Various acidic catalysts, including acetic acid, concentrated hydrochloric acid, phosphoric acid, and concentrated sulfuric acid, were evaluated for their effectiveness in promoting the condensation process. Among the reaction conditions investigated, concentrated sulfuric acid in ethanol proved to be the most efficient catalytic system, affording the desired chalcone derivatives in superior yields. The synthetic route is illustrated in Scheme 11.

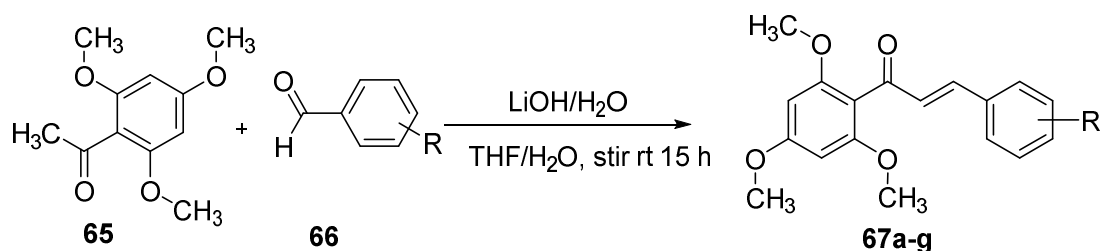


Scheme 11: Synthetic route for the preparation of chalcone derivatives from 1,3-diacetylbenzene and 1,4-diacetylbenzene.

BIOLOGICAL ACTIVITIES OF CHALCONE DERIVATIVES

ANTIMICROBIAL ACTIVITY

Çöl and Tunç (2024) reported the synthesis of seven new chalcone derivatives (67a-g), which were subsequently evaluated for their antimicrobial activities. The new chalcone derivatives (67a-g) were synthesized through a one-pot Claisen–Schmidt condensation of 2,4,6-trimethoxyacetophenone (65) with fluoro- and trifluoromethyl-substituted benzaldehydes (66a-g) in the presence of LiOH and THF/H₂O under stirring at room temperature for 15 hours. The compounds (67a-g) were evaluated for their antibacterial activity against four bacterial and two fungal strains. The results showed MIC values ranging from 7.81–250 µg/mL. Compounds (67e) and (67f) demonstrated broad antibacterial activity, with compound (67f) showing particularly strong activity against *S. aureus*, while compound (67e) exhibited the highest antifungal activity (Scheme 12) [72].

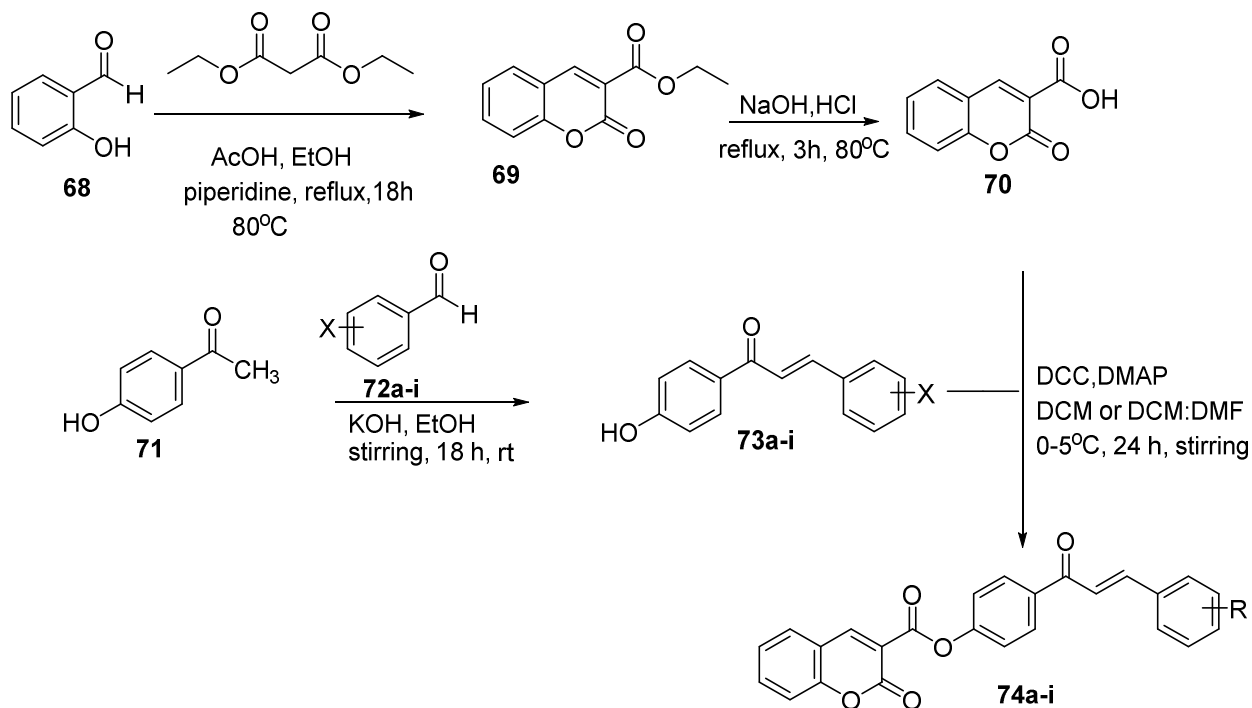


67a; R = H, 67b; R = 2-F, 67c; R = 3-F,
67d; R = 4-F, 67e; R = 2-CF₃, 67f; R = 3-CF₃,
67g; R = 4-CF₃,

Scheme 12: Syntheses of novel Chalcone derivatives with antimicrobial activities

Ngaini *et al.*, 2026 reported the synthesis and antimicrobial activities of coumarin-chalcone hybrid derivatives. In this synthesis, 2-hydroxybenzaldehyde (68) was treated with diethyl malonate in the presence of acetic acid, ethanol, and piperidine via Knoevenagel condensation. The reaction mixture was refluxed at 80 °C for 18 h, affording ethyl 2-oxo-2H-chromene-3-carboxylate (69). The intermediate (69) was further esterified with NaOH and HCl under reflux at 80 °C for 3 h to give 2-oxo-2H-chromene-3-carboxylic acid (70). In another reaction, 1-(4-hydroxyphenyl)ethan-1-one (71) was treated with various halogenated benzaldehydes (72a-i) in the presence of potassium hydroxide and ethanol, and the reaction mixture was stirred at room temperature for 18 hours to give

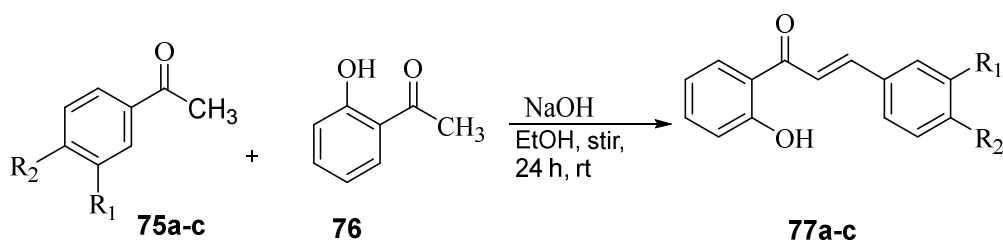
(E)-1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one (73a-i). Finally, the halogenated chalcones (73a-i) were coupled with the carboxyl coumarin (70) in the presence of DCC, DMAP, and DCM via a facile Steglich esterification reaction, and the mixture was stirred at 0- 5 °C for 24 hours to give their target derivatives(74a-i). The compounds (73a-i and 74a-i) were evaluated for their antimicrobial activities using a disc diffusion method against *P. aeruginosa* and *E. Coli* using DMSO as a negative control and ampicillin as a reference standard drug. Compound (74a-i) displays effective inhibition against *P. aeruginosa* (7-13 mm) and *E. Coli* (8- 12 mm). However, compound 74b and 74g were shown to have the highest inhibition zone against *P. aeruginosa* (13 mm) and *E. Coli* (12mm). (Scheme 13) [73].



Scheme 14: Synthesis of new coumarin-chalcones analogs

ANTIOXIDANT ACTIVITY

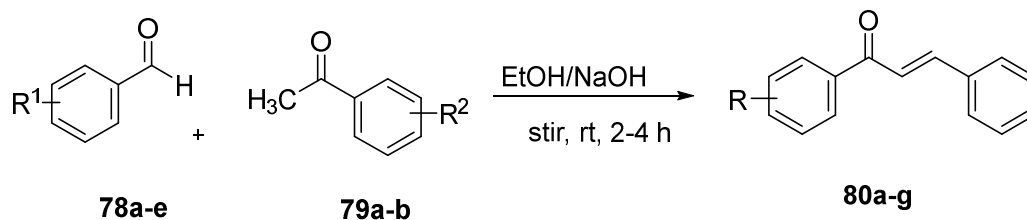
Mulula *et al.*, (2022) reported a one-pot synthesis of new chalcone derivatives (77a-c). They reacted 2-hydroxyacetophenone (76) with various acetophenones (75a-c) in the presence of ethanol and sodium hydroxide. The reaction mixture was stirred at room temperature for 24 hours to achieve the target products. The antioxidant activity of the compounds (77a-c) was evaluated against DPPH, using ascorbic acid as a reference standard drug. All three chalcones showed strong DPPH antioxidant activity, with IC_{50} values of 8.22, 6.89, and 3.39 $\mu\text{g/mL}$ for chalcones (77a-c), versus 2.17 $\mu\text{g/mL}$ for ascorbic acid, the reference standard drug. Compound (77c) was the most potent at 10 $\mu\text{g/mL}$; it reached 87.71% inhibition, closely matching ascorbic acid. All three chalcones are notable antioxidants, with (77c) as the standout performer, approaching ascorbic acid's potency (Scheme 15) [74].



77 a: $R_1 = \text{H}$, $R_2 = \text{OH}$
 77b: $R_1 = \text{H}$, $R_2 = \text{OCH}_3$
 77c: $R_1 = R_2 = \text{OCH}_3$

Scheme 15: Synthesis of new Chalcone derivatives with antioxidant activity.

Öztürk and coworkers in (2026) reported a one-pot synthesis of new chalcone derivatives with antioxidant activities. They achieved this by reacting various acetophenone derivatives (78a-e) and benzaldehydes (79a-b) via a base-catalyzed condensation reaction in the presence of ethanol under stirring at room temperature to obtain their target derivatives (80a-g). The compounds (80a-g) were screened for their antioxidant activity using BHA, BHT, and α -tocopherol as reference standard drugs, and compound 80e displayed very high activity, surpassing the reference standard drugs, BHA, BHT, and α -tocopherol, in both DPPH (RSE%: 87.43; IC_{50} : 14.57 μM) and ABTS (RSE%: 93.93; IC_{50} : 4.34 μM) assays. (Scheme 16) [75].



80a: R¹ = C₆H₅; R² = H

80b: R¹ = H; R² = H

80c: R¹ = ; R² = CH₃

80d: R¹ = 4-CH₃; R² = H

80e: R¹ = 4-CH₃; R² = 4-CH₃

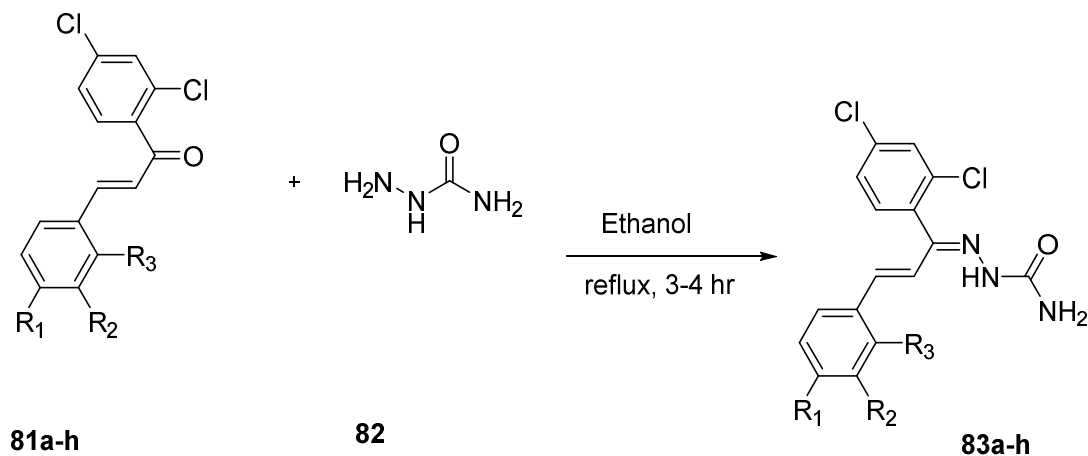
80e: R¹ = 4-CH₃; R² = 4-CH₃

80f: R¹ = 2-OCH₃, 4-OCH₃; R² = H

80g: R¹ = 2-OCH₃, 3-OCH₃; R² = H

Scheme 16: Synthesis of novel chalcone scaffolds with antioxidant activity

Punkhia *et al*; (2026) reported a one-pot synthesis of novel chalcone derivatives with antioxidant activity. They reacted different chalcones derivatives (81a-h) with semicarbazone (82) in ethanol. The reaction mixture was refluxed for 3-4 hours to obtain their target derivatives (83a-h). The compounds were screened for their antioxidant activity using the DPPH scavenging assay and compared with ascorbic acid, a reference standard drug. Compound 83a showed the best activity among all the compounds. (Scheme 17) [76].



83a : R₁ = OH; R₂ = H; R₃ = H

83b : R₁ = N(CH₃)₂; R₂ = H; R₃ = H

83c : R₁ = Cl; R₂ = H; R₃ = Cl

83d : R₁ = Cl; R₂ = H; R₃ = H

83e : R₁ = H; R₂ = OH; R₃ = H

83f : R₁ = H; R₂ = NO₂; R₃ = H

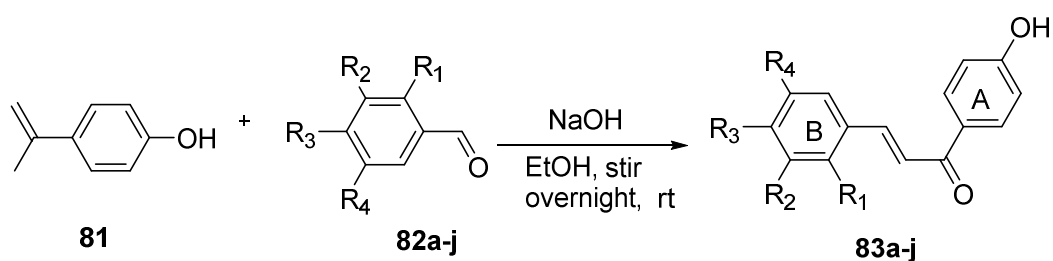
83g : R₁ = Br; R₂ = H; R₃ = H

83h : R₁ = OCH₃; R₂ = OCH₃; R₃ = H

Scheme 17: Synthesis of Chalcone-Semicarbazide hybriide

ANTICANCER ACTIVITY

Sirka *et al.*, (2022) reported a one-pot synthesis of novel chalcone derivatives with anticancer activities. They achieved this by reacting 4-hydroxyacetophenone (81) with various benzaldehydes (82a-j) in the presence of absolute ethanol and sodium hydroxide. The reaction mixture was stirred at room temperature overnight to achieve their target compounds (83a-j) (Scheme 19). The Compounds (83a-j) were screened for cytotoxic activity against four human cancer cell lines representing three tissue origins: A2780 (ovarian), LNCaP and PC-3 (prostate), and MCF-7 (breast). Compounds (83a-e) exhibited greater activity against A2780 and LNCaP cells than against PC-3 and MCF-7 cells, with compound 83b emerging as the most potent analogue, particularly against A2780 and LNCaP cells, although compounds (83g-j) displayed the broadest cytotoxic profile (Scheme 17) [77].

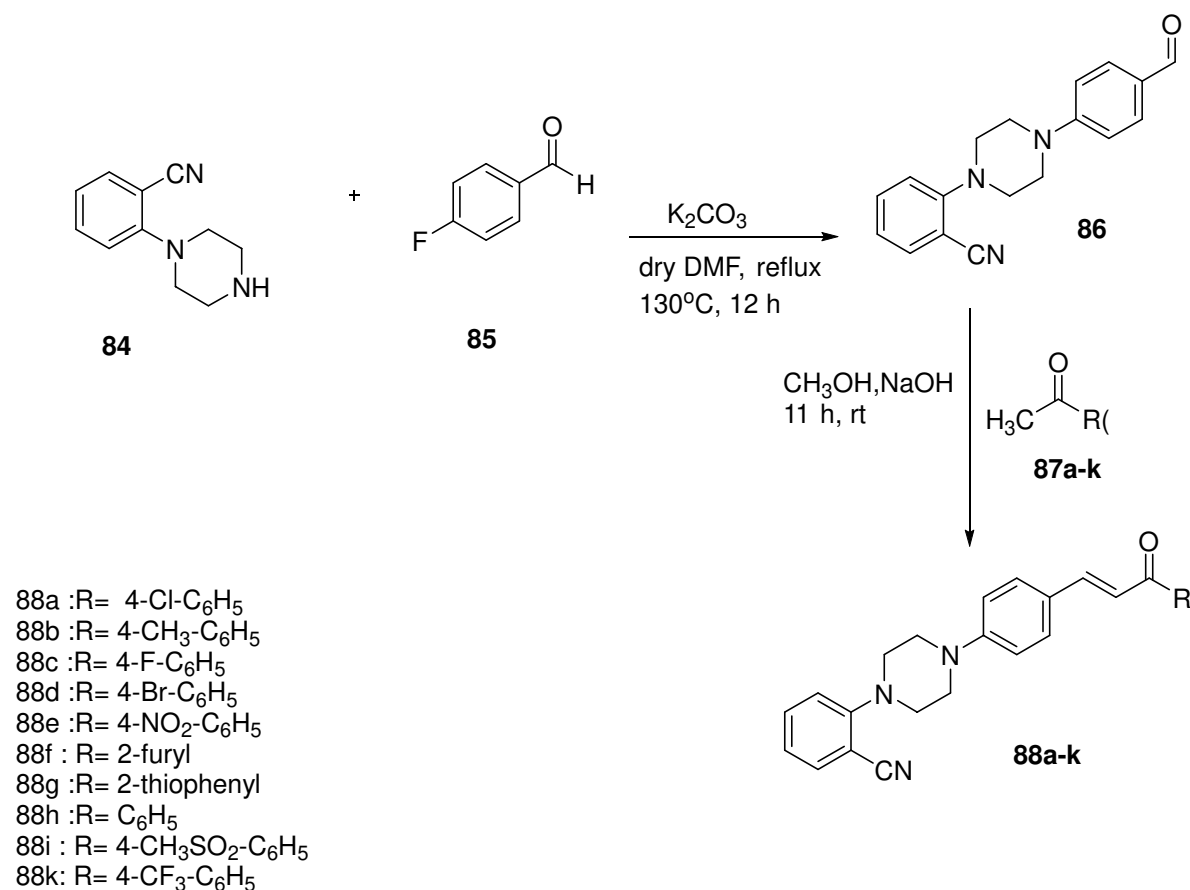


- 83a; R₁=H, R₂=OCH₃, R₃=H, R₄=H
83b; R₁=OCH₃, R₂=H, R₃=OCH₃, R₄=H
83c; R₁=H, R₂=OCH₃, R₃=OCH₃, R₄=H
83d; R₁=OCH₃, R₂=OCH₃, R₃=OCH₃, R₄=H
83e; R₁=OCH₃, R₂=H, R₃=OCH₃, R₄=OCH₃
83f; R₁=H, R₂=H, R₃=ph, R₄=H
83g; R₁=H, R₂=F, R₃=H, R₄=F
83h; R₁=F, R₂=H, R₃=Cl, R₄=H
83i; R₁=H, R₂=CF₃, R₃=H, R₄=H
83j; R₁=H, R₂=CF₃, R₃=Cl, R₄=H

Scheme 17: Synthesis of Novel Chalcone analogs with antioxidant activity.

Baltaci *et al.*, (2026) reported the synthesis and anticancer activity of new chalcone derivatives. In this synthesis, 1-(2-cyanophenyl)piperazine (84) was reacted with para-florobenzaldehyde (85) in the presence of DMF and potassium carbonate as a base. The reaction mixture was refluxed at 130°C for 12 hours to obtain 2-[4-(4-

formylphenyl}piperazin-1-yl)benzonitrile (86). The intermediate (86) was further reacted with different aromatic ketones (87a-k) in MeOH and sodium hydroxide via a Claisen-Schmidt's condensation to give the target derivatives(88a-k). The compounds(88a-k) were evaluated for their anticancer activities against three human cancer cell line: human colon cancer (HT29), lung (A549) and breast (MCF-7) carcinoma cells. Compounds 88f, 88j, and 88k exhibited the highest anticancer activity with IC_{50} values of 0.118 ± 0.019 , 0.071 ± 0.009 , and 0.0235 ± 0.069 μ M. (Scheme 18) [78].

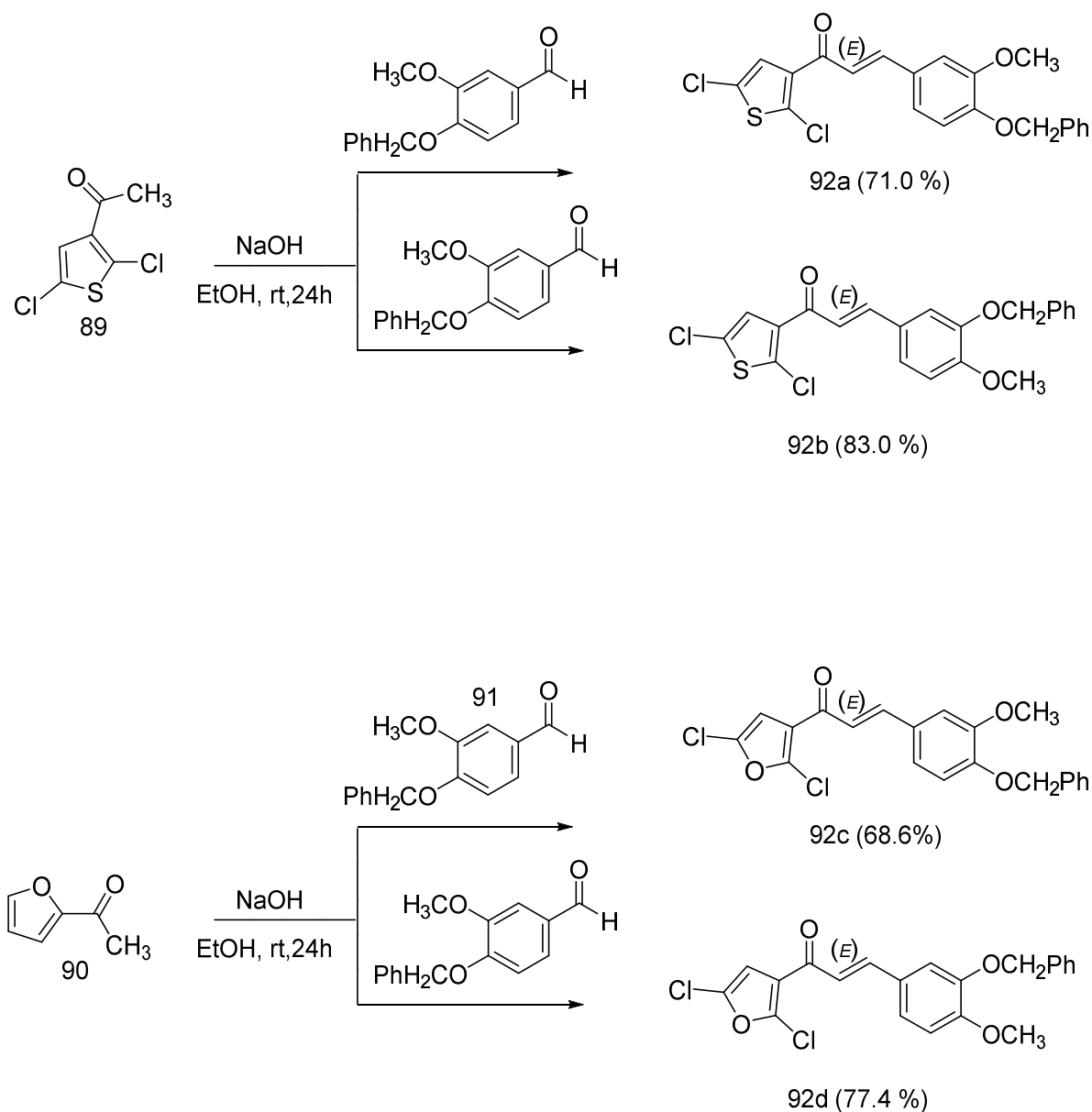


Scheme 18: Synthesis of New chalcone analogs with anticancer activities

ANTIMALARIAL ACTIVITY

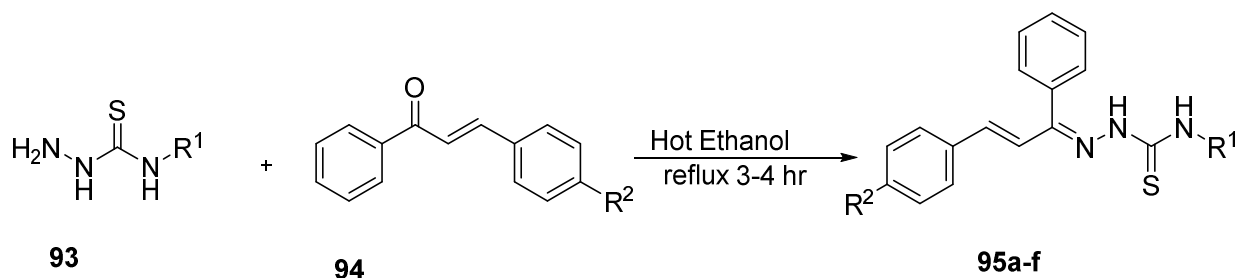
Alidmat et al. (2021) reported the synthesis and antimalarial activity of chalcone derivatives. The reaction involved a Claisen-Schmidt condensation of 3-acetyl-2,5-dichlorothiophene (89) or 2-acetylfuran (90) and 4-benzyloxy-3-methoxybenzaldehyde (91) or 3-benzyloxy-4-methoxybenzaldehyde in 25ml of ethanol in the presence of NaOH

acting as a catalyst. After stirring the mixture at room temperature for 6-24hrs, the progress of the reaction was monitored by TLC after which the precipitate formed was filtered, washed with cold water and dried to give a yellow solid which was recrystallized from methanol to give a yellow powder (92a-d) (Scheme 24). Biologically, compound 92a showed measurable antimalarial activity against *Plasmodium falciparum*. Against the chloroquine-sensitive 3D7 strain, it exhibited an IC₅₀ of 8.4µg/mL and an IC₈₀ of 19µg/mL [79].



Scheme 24: One pot synthesis of new Chalcones analogs

Zhou et al. (2026) reported the synthesis, in vitro antimalarial activity, cytotoxicity, and pharmacokinetic evaluation of chalcone-derived thiosemicarbazones. The chalcone derived thiosemicarbazones were prepared by condensation of N-substituted thiosemicarbazide derivatives (93) with 4-substituted chalcone derivatives (94). A hot ethanolic solution of 4-methy-3-thiosemicarbazole (10 mmol) was added into a hot ethanolic solution of trans-chalcone and the mixture was added with a few drops of conc. HCl and refluxed for 3-4hrs upon stirring, then monitored with TLC, after which the precipitate was filtered, washed with cold ethanol, and dried. The in-vitro evaluation revealed potent antimalarial activity ($IC_{50} = 6.0-205.1\mu M$), with 95d exhibiting the highest potency giving value $IC_{50} = 6.0\mu M$) (Scheme 25) [80].

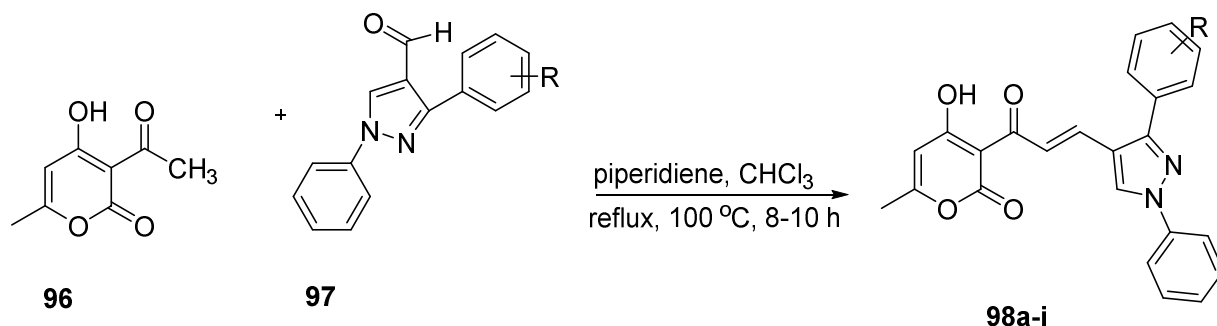


- 95a : $R^1 = CH_3$, $R^2 = H$
 95b : $R^1 = C_6H_5$, $R^2 = H$
 95c : $R^1 = CH_3$, $R^2 = Cl$
 95d : $R^1 = C_6H_5$, $R^2 = Cl$
 95e : $R^1 = CH_3$, $R^2 = OCH_3$
 95f : $R^1 = C_6H_5$, $R^2 = OCH_3$

Scheme 25: Synthesis of Chalcone derivatives of thiosemicarbazones

Rani et al. (2026) reported the synthesis and antimalarial activity of chalcone derivatives. The derivatives were synthesized via a single-step process, wherein the Claisen-Schmidt condensation between dehydroacetic acid (96) and formyl pyrazoles (97) proceeded at reflux temperature in chloroform using catalytic amounts of piperidine as the base. The reaction process was monitored using TLC and the products were purified by recrystallization from ethanol, affording the chalcone derivatives (98a-i) in consistent yields (68% - 92%). The methoxy derivative 98c exhibited the highest potency, with an

IC₅₀ value of $0.95 \pm 0.06 \mu\text{M}$ which was attributed to the presence of the electron-donating group (Scheme 26) [81].



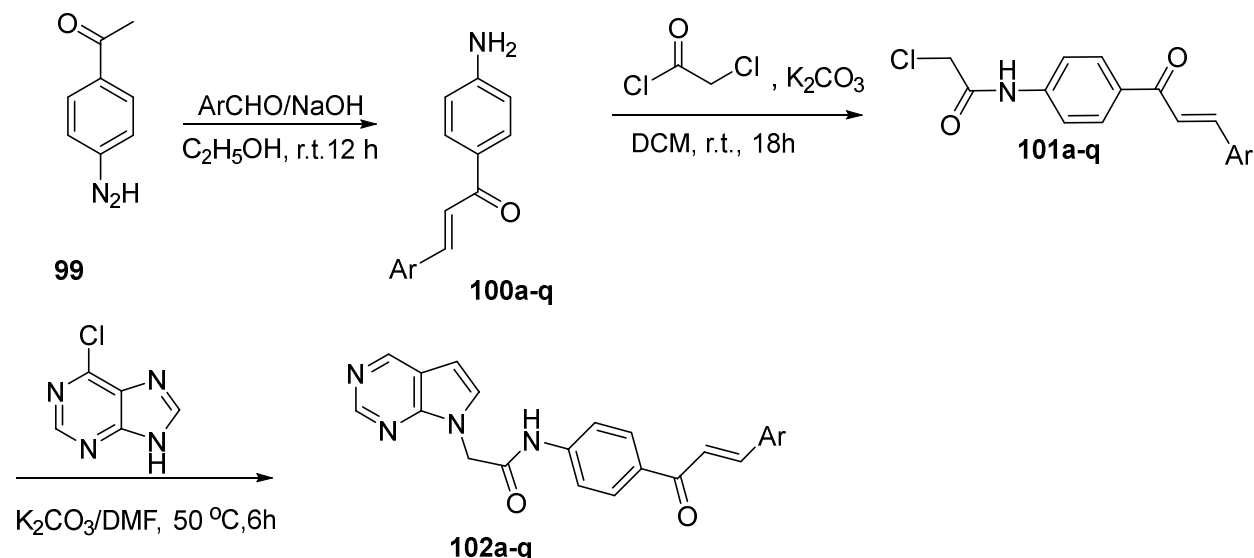
- | | |
|-----------------------------|----------------------------|
| 98a: R = H | 98f: R = 3-NO ₂ |
| 98b: R = 3-Br | 98g: R = 4-Cl |
| 98c: R = 4-OCH ₃ | 98h: R = 4-NO ₂ |
| 98d: R = 3-CH ₃ | 98i: R = 4-F |
| 98e: R = 4-Br | |

Scheme 26: Synthesis of New Chalcone analogs

ANTIVIRAL ACTIVITY

Xiuhai *et al.* (2017) reported the synthesis, characterization, and antiviral activity of novel chalcone derivatives containing a purine moiety. They reacted 1-(4-diazenylphenyl)ethan-1-one (**99**) with various aromatic aldehydes in ethanol and sodium hydroxide. The reaction mixture was stirred at room temperature for 12 hours to yield intermediate (**100a-q**). Subsequently, the corresponding intermediates (**100a-3q**) were treated with 2-chloroacetyl chloride in the presence of potassium carbonate and DCM, and the mixture was stirred at room temperature for 18 hours to give (*E*)-N-(4-(but-2-enoyl)phenyl)-2-chloroacetamide derivatives (**101a-q**). Finally, compounds (**101a-q**) were reacted with 6-chloro-9H-purine in anhydrous potassium hydroxide in DMF and the mixture was reflux at $50\text{ }^{\circ}\text{C}$ yield the target compounds **102a-4q**. (Scheme 1). They evaluated the compounds for their antiviral activities and compounds 102n and 102p displayed an excellent curative, protective and inactivation activities against TMV, with the EC₅₀ values of 452.4, 416.2, 241.2 and 438.7, 418.6, 261.7 $\mu\text{g}\cdot\text{mL}^{-1}$ respectively,

which were better than those of ribavirin (585.8, 436.0 and 268.7 $\mu\text{g}\cdot\text{mL}^{-1}$. (Scheme 27) [82]



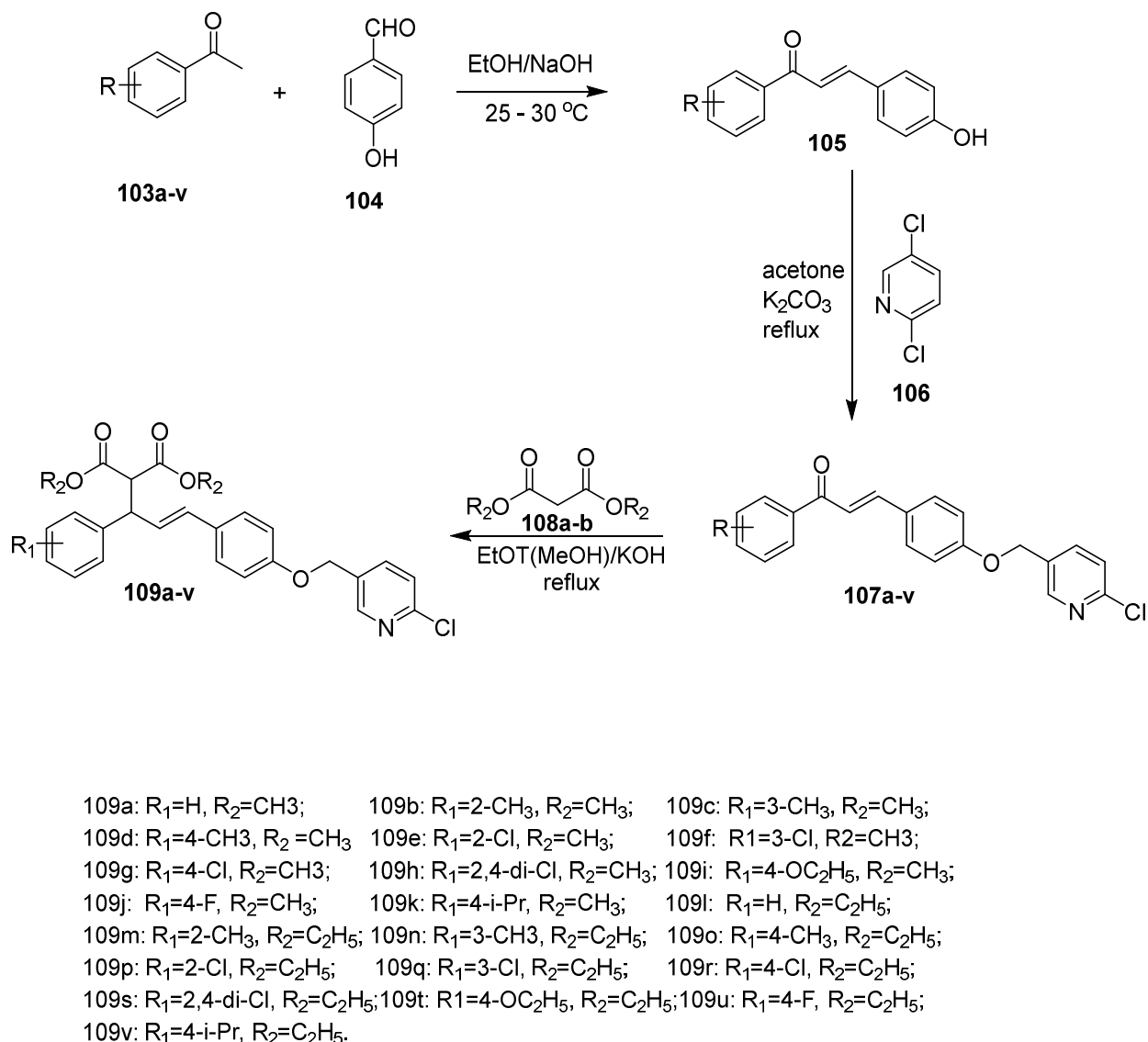
Ar =

- | | |
|--|--|
| 102a: 4- CH_3 - C_6H_4 ; | 102b: 4- OCH_3 - C_6H_4 ; |
| 102c: 2,4-(OCH_3) $_2$ - C_6H_3 ; | 102d: 3,4,5-(OCH_3) $_3$ - C_6H_2 ; |
| 102e: 3-F- C_6H_4 ; | 102f: C_6H_5 ; |
| 102g: 4-Cl- C_6H_4 ; | 102h: 2-F- C_6H_4 ; |
| 102i: 2,3- Cl_2 - C_6H_3 ; | 102j: 2-Br- C_6H_4 ; |
| 102k: 4-Br- C_6H_4 ; | 102l: 2,4- Cl_2 - C_6H_3 ; |
| 102m: 2-Cl- C_6H_4 ; | 102n: 2,4-F $_2$ - C_6H_3 ; |
| 102o: 2,6-F $_2$ - C_6H_3 ; | 102p: 4- NO_2 - C_6H_4 ; |
| 102q: 4-F- C_6H_4 | |

Scheme 27. Synthesis of Novel Chalcones derivatives with antiviral activities.

Chen *et al.* (2019) also reported the synthesis and antiviral activity of novel compounds **109a-v**. They reacted substituted acetophenone (**103a-v**) with 4-hydroxybenzaldehyde (**104**) to yield intermediate (**105**). Upon further reaction with dichloropyridine (**106**), it afforded **compound** (**107a-v**). On addition of dimethyl malonate or diethyl malonate(**108a-b**), the target compounds (**109a-v**) were yielded. (Scheme 2). The antiviral properties of the synthesized compounds (**109a-v**) were evaluated against CMV, with ningnanmycin as the control. It was found that they exhibited moderate to good

antiviral activity against CMV *in vivo*, with significant inhibition rates of 65.0%- 69.8%. (Scheme 28) [83]



Scheme 28. Synthesis of New chalcone analogs with antiviral activity

STRUCTURE-ACTIVITY RELATIONSHIP OF CHALCONE DERIVATIVES

The structure-activity relationship (SAR) of chalcone derivatives is strongly influenced by the nature, position, and electronic properties of substituents on the two aromatic rings, as well as the integrity and configuration of the α,β -unsaturated carbonyl linker. The basic chalcone framework, consisting of two aromatic rings connected through an α,β -

unsaturated ketone, provides a versatile pharmacophore whose biological properties can be modulated through systematic structural modification. In particular, the enone moiety acts as an electrophilic Michael acceptor and is considered an important determinant of the biological activity of many chalcone derivatives [84,85].

The geometry of the enone linker is also an important structural feature. The trans (E) configuration is generally associated with greater biological activity because it maintains the extended and relatively planar conformation required for optimal conjugation and interaction with biological targets. Conversely, conversion of the enone double bond to the saturated dihydrochalcone framework frequently results in reduced activity, particularly in biological systems in which electrophilic interactions with target proteins are important [86]. Modulation of the electronic character of the enone through aromatic-ring substitution can consequently alter its electrophilicity and influence the potency and selectivity of the resulting derivatives.

Substitution on the aromatic rings represents one of the major strategies for optimizing chalcone activity. Hydroxyl groups, particularly at the 2'- and 4-positions, have been associated with enhanced antioxidant, anti-inflammatory, and antidiabetic activities through hydrogen bonding, radical stabilization, and metal-chelating interactions. The 2'-hydroxyl group may additionally facilitate intramolecular hydrogen bonding with carbonyl oxygen, thereby maintaining a favorable molecular conformation. However, the effect of hydroxyl substitution is activity dependent. Although phenolic hydroxyl groups can enhance antioxidant activity, excessive electron donation may reduce the electrophilicity of the enone and consequently diminish certain anticancer effects [87-89].

Methoxy substitution provides another important means of modifying chalcone activity. Methoxy groups can increase lipophilicity and influence interactions with hydrophobic regions of biological targets. Specific methoxy substitution patterns have been associated with improved anti-inflammatory and anticancer activities, particularly when combined with appropriate hydroxyl or other substituents. Thus, the biological effect of methoxylation depends not only on the number of methoxy groups but also on their position and their relationship with other substituents on the chalcone scaffold [90, 91].

Electron-withdrawing substituents, particularly halogens such as chlorine, bromine, and fluorine, have also demonstrated considerable importance in chalcone SAR.

Halogenation can increase lipophilicity and enhance the electrophilic character of the enone system, thereby improving interactions with biological targets and, in some cases, facilitating membrane penetration. Halogen-substituted chalcones have consequently demonstrated improved anticancer and antimicrobial activities in several reported series [92]. Nevertheless, the biological outcome remains dependent on the position of substitution and the nature of the remaining functional groups.

The introduction of lipophilic groups such as prenyl substituents represents another strategy for modulating chalcone activity. Prenylation can enhance membrane association and tissue distribution, which may contribute to improved antioxidant and antiparasitic effects. Natural prenylated chalcones such as xanthohumol and licochalcone A illustrate how hydrophobic substituents can complement phenolic functionalities and generate compounds with significant biological activity [93]. These findings indicate that an appropriate balance between hydrophilic and lipophilic structural features is essential for optimizing chalcone pharmacological properties.

Structural hybridization with heterocyclic pharmacophores has further expanded the SAR landscape of chalcones. Incorporation of indole, triazole, pyrazole, thiazole, quinoline, and related heterocyclic systems can introduce additional hydrogen-bonding and hydrophobic interactions while potentially improving potency, selectivity, and metabolic stability. For example, indole–chalcone and triazole–chalcone hybrids have demonstrated enhanced anticancer properties, whereas thiazole- and quinoline-containing derivatives have shown promising antimicrobial and antiparasitic activities [94, 95]. These observations demonstrate that hybridization can provide a useful approach for overcoming some of the limitations associated with the parent chalcone scaffold.

Overall, the SAR of chalcone derivatives demonstrates that biological activity is governed by a delicate interplay between enone electrophilicity, aromatic substitution, hydrogen-bonding capacity, lipophilicity, molecular conformation, and target-specific interactions. Hydroxyl groups generally favor antioxidants, anti-inflammatory, and antidiabetic effects, whereas selected electron-withdrawing and lipophilic substituents may improve anticancer and antimicrobial activities. Preservation of the E-configured α,β -unsaturated carbonyl system and strategic incorporation of heterocyclic pharmacophores provide opportunities for optimizing potency and selectivity. Therefore, rational modification of the

chalcone scaffold, rather than indiscriminate substitution, remains essential for achieving desirable pharmacological profiles.

CONCLUSION

Chalcone derivatives continue to occupy a prominent position in medicinal chemistry owing to the unique combination of synthetic accessibility, structural adaptability, and diverse pharmacological properties. The studies reviewed demonstrate that substantial progress has been made in developing structurally diverse chalcone analogues through both classical and contemporary synthetic methodologies. Although the Claisen-Schmidt condensation remains the cornerstone for constructing the α,β -unsaturated ketone framework, the integration of multistep synthetic strategies, including cross-coupling reactions, nucleophilic substitution, oxidation, and amide bond-forming reactions, has considerably broadened the chemical space of chalcone derivatives. These approaches have also enabled the successful incorporation of biologically important heterocyclic pharmacophores such as thiazole, pyridine, piperazine, benzimidazole, and quinoline, providing access to compounds with enhanced structural diversity and improved therapeutic potential. The biological investigations discussed in this review further establish the chalcone scaffold as a privileged framework for drug discovery. Structural modification of the parent chalcone nucleus has generated analogues with promising antimicrobial, antioxidant, anti-inflammatory, antiviral, antimalarial, anticancer, antidiabetic, and other pharmacologically relevant activities. Collectively, these findings emphasize that judicious molecular design, particularly through heterocyclic hybridization and appropriate substitution of the aromatic rings, plays a crucial role in optimizing biological performance and expanding the therapeutic applicability of chalcone-based compounds. Despite these encouraging advances, relatively few chalcone derivatives have progressed beyond preclinical evaluation. Consequently, future investigations should extend beyond synthetic development and preliminary biological screening to include comprehensive structure-activity relationship studies, mechanistic investigations, pharmacokinetic and toxicological profiling, as well as rigorous **in vivo** and clinical validation. Such integrated efforts will facilitate the translation of promising chalcone

analogues into clinically relevant therapeutic agents. Overall, the continued convergence of innovative synthetic chemistry with rational medicinal chemistry strategies is expected to further establish chalcone derivatives as valuable lead compounds for the development of next-generation pharmaceuticals.

Funding

This work did not receive any form of funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Ethics, Consent to Participate, and Consent to Publish declarations

Not Applicable

Clinical Trial Number

Not Applicable

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