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Review

Synthesis and Pharmacological Activities of Chalcone and Its Derivatives Bearing *N*-Heterocyclic Scaffolds: A Review

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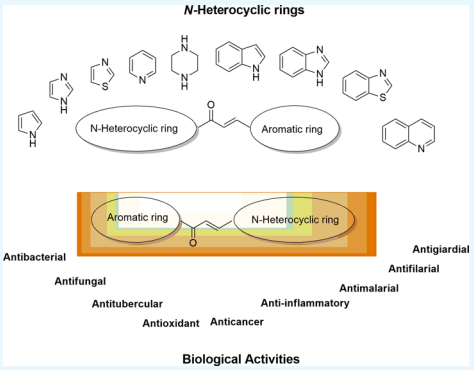
ABSTRACT: The incorporation of heterocyclic moieties into the standard chemical structure with a biologically active scaffold has become of crucial practice for the construction of pharmacologically potent candidates in the drug arena. Currently, numerous kinds of chalcones and their derivatives have been synthesized using the incorporation of heterocyclic scaffolds, especially chalcones bearing heterocyclic moieties that display improved efficiency and potential for drug production in pharmaceutical sectors. The current Review focuses on recent advances in the synthetic approaches and pharmacological activities such as antibacterial, antifungal, antitubercular, antioxidant, antimalarial, anticancer, anti-inflammatory, antigiardial, and antifilarial activities of chalcone derivatives incorporating *N*-heterocyclic moieties at either the A-ring or B-ring.



INTRODUCTION

Chalcone scaffolds are privileged chemical structures in the medicinal chemistry sector.[1] They are secondary metabolites of plants and found in α,β-unsaturated forms, which have a more thermodynamically stable *trans*-conformation between two aryl groups.[2] Chalcone and its derivatives are the cores of various biologically interesting compounds, and frequently they have been isolated from different medicinal plants such as *Dracaena cinnabari*, *Medicago sativa*, and *Angelica keiskei* (Figure 1).[3−6]

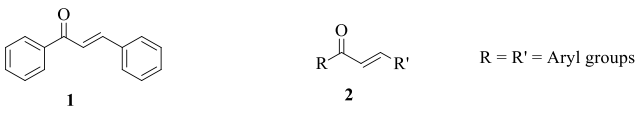


Figure 1. General chemical structures of chalcone **1** and its derivative **2**.

Chemically chalcones are easily prepared using various reaction procedures and strategies. For instance, the named reaction Claisen-Schmidt condensation is one common methodology to prepare the title compound through carbonyl derivative condensation in the presence of base. Additionally, the carbonylative Heck coupling reaction, the Sonogashira isomerization coupling reaction, the continuous flow deuteration reaction, the Suzuki−Miyaura coupling reaction, and solid acid catalyst-mediated reactions are known.[7] The precursors of the flavonoids and isoflavones, chalcones serve as promising template scaffolds for synthesizing and developing pharmacologically active compounds in conjugation with other heterocyclic moieties[8,9] which have a large role in the sector of medicine to prepare potential drug discovery and improve pharmaceuticals (Figure 2).[10]

Chalcone derivatives incorporating heterocyclic scaffolds are become promising candidates as future drug sources owing to their similar or superior activities compared to those of the standard derivatives.[11] To date, the basic chemical structure of chalcone serves as potential source of much research for planning to design and develop various drugs. On top of this, many researchers are exhaustively devoted to synthesizing a chalcone derivative incorporating a heterocyclic scaffold. Chalcones incorporating heterocyclic scaffolds have been reported with various biological and pharmacological activities, such as antioxidant activity,[12] antibacterial activity,[12] antifungal activity,[13] antileishmanial activity,[14] anti-inflamatory activity,[15] anticancer activity,[16] antitubercular activity,[17] antiproliferative agents,[17] antimalarial activity,[18] antiplatelet activity,[19] carbonic anhydrase inhibitors,[20] an inhibitor of microsomalenzyme glutathione-*S*-transferases,[21] and CYP1 enzyme inhibitors.[22]

Chalcones with an *N*-heterocyclic moiety such as pyrrole, imidazole, thiazole, pyrazole, oxazole, isooxazole, pyridine, pyrazoline, indole, benzothiazole, benzimidazole, and quinoline scaffolds play a significant role in the area of medicine.[11] Compounds **10**, imidazole-based chalcone derivatives, displayed

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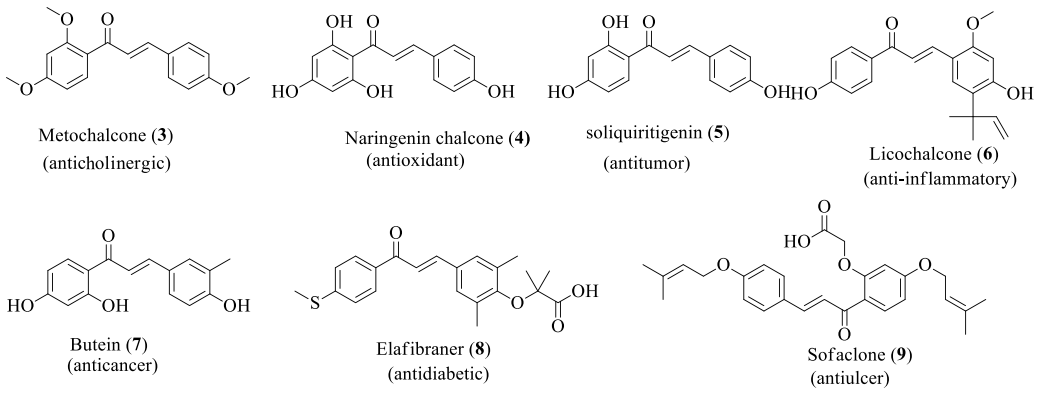


Figure 2. Chemical structures of chalcone scaffold-based drugs.

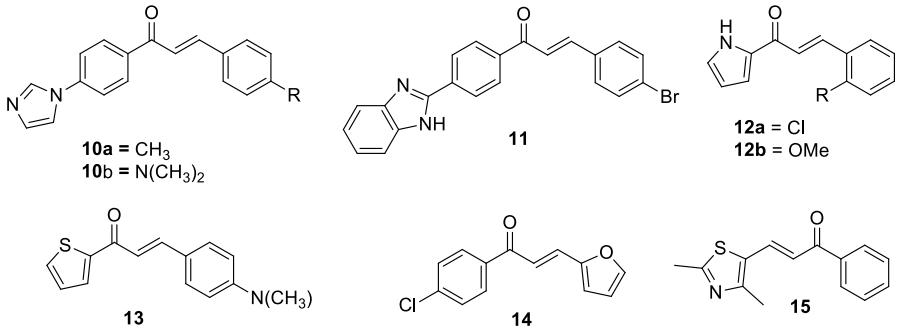
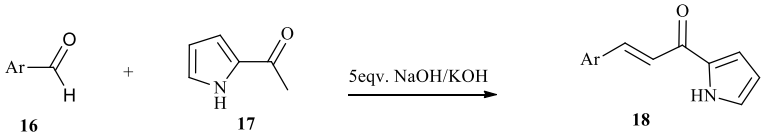


Figure 3. Chemical structures of heterocycle-based chalcone derivatives.

Scheme 1. General Synthetic Route toward Chalcone Derivatives Incorporating Pyrrole



Ar = Ph (3-OMe), Ph (2,6-di-OMe), Ph (2-Cl,5-NO_2), Ph (2,3-di-OMe), Ph (3,4-Methylene-dioxy) Ph (2,4-di-OMe), Cinnamyl, Ph (3,5-di-OMe), Ph (2-F), Ph (2-OMe), Cinnamyl (4-OMe), Ph (4-$N(CH_3)_2$), Ph (4-OMe), Ph (2-Cl), Ph (3-Br), Ph (3-Br, 4-OMe), Furan-2-yl (5-Et) Ph (3,4.5-tri-MeO), Ph (4-OCF_3), Ph (4-COOH), Anthracen-9-yl, Ph (3-Cl), Ph (4-Br)

inhibition activity on MAO-A better than the standard drug.[23] 2-Benzimidazole chalcone (**11**) with a *p*-bromo group substituted to the phenyl ring acted as an insect antifeedant agent.[24] Williams and co-workers reported a series of pyrrole-based chalcone derivatives and evaluated the biological activity of the CPY1 enzyme inhibition potential. The derivative **12a** displayed the most selective inhibition of CYP1B1, and **12b** was shown to inhibit both CYP1A1 and CYP1B1 isoforms with minimum IC_{50} values.[25] Among the heterocyclic derivatives, thiophene-based chalcone derivative **13** displayed a calculated inhibitory constant value of approximately 0.64 μM toward the active site of MAO-B.[26] Most of the time, furan-containing chalcone derivatives were found to be more active than the others. Derivative **14** displayed high activity against *Streptococcus mutans* and was the most potent derivative.[27] The chalcone derivative **15** containing a difluorophenyl scaffold displayed 2.6× more activity than the standard drug. This suggests that the degree of electronegativity played a key role in modulating the physicochemical properties of the derivative (Figure 3).[17]

Thus, the current Review presents the various synthetic protocols used to prepare chalcones incorporated with *N*-heterocyclic moieties and their wide spectrum of biological activities.

2. SYNTHESIS OF CHALCONE BEARING AN *N*-HETEROCYCLIC SCAFFOLD

2.1. Chalcone Bearing Pyrrole. Series of pyrrole-based chalcone derivatives were reported through the classical Claisen−Schimdt condensation reaction protocol.[28] The synthesized compounds displayed potential activity on the inhibition of CYP1 isoforms. As depicted in Scheme 1, the reaction afford products of various derivatives **18** starting from aromatic aldehyde derivatives **16** and pyrrole-based acetophenone **17** in basic media. The 2-pyrrole chalcone derivatives **18** were possible to synthesize using either a liquid phase or solid through a grinding method with moderate to good yields.

Özdemir and co-workers synthesized and reported new potent antimicrobial and anticancer active pyrrole-based chalcone derivatives using the Claisen−Schmidt condensation

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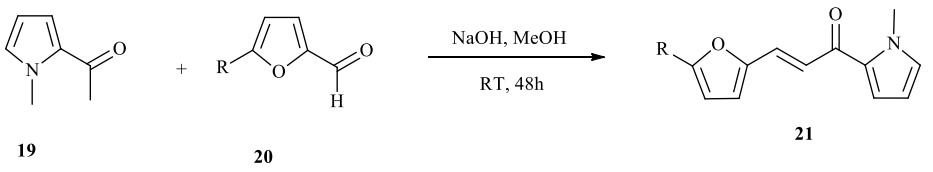
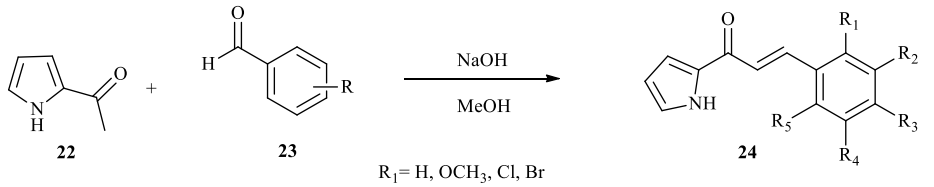
ACS Omega 2023, 8, 19194−19211

Scheme 2. General Synthetic Route toward Pyrrole-Based Chalcone Derivatives



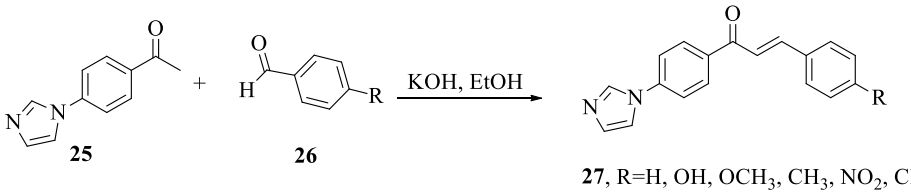
R=1-Methyl-4-nitro-benzene, 1-Methyl-2-nitro-benzene, 4-Chloro-1-methyl-2-nitro-benzene, 1-Chloro-2-methyl-benzene, 1-Methyl-3-nitro-benzene, 2,4-Dichloro-1-methyl-benzene, 1-Chloro-3-methyl-benzene, 1,4-Dichloro-2-methyl-benzene, 1-Chloro-4-methyl-benzene, 1,2-Dichloro-4-methyl-benzene

Scheme 3. General Synthetic Route toward Chalcone Derivatives Incorporating a Pyrrole Scaffold



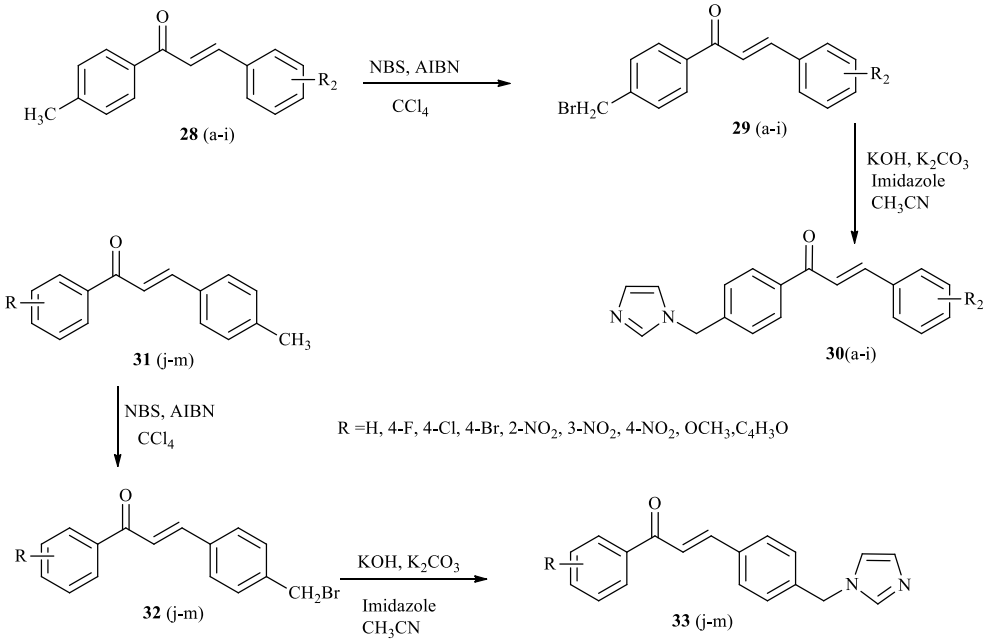
R_1= H, OCH_3, Cl, Br
R_2= H, OCH_3, Cl, NO_2
R_3= H, OCH_3, Cl, Br, NO_2, F, $N(CH_3)_2$
R_4= H, NO_2
R_5= H, OCH_3, Cl

Scheme 4. General Synthetic Route toward Imidazole-Based Chalcone Derivatives



27, R=H, OH, OCH_3, CH_3, NO_2, Cl, $N(CH_3)_2$, C_2H_5, Br,F, CF_3

Scheme 5. Synthetic Route toward Chalcone Derivatives Incorporating an Imidazole Moiety



R =H, 4-F, 4-Cl, 4-Br, 2-NO_2, 3-NO_2, 4-NO_2, OCH_3,C_4H_3O

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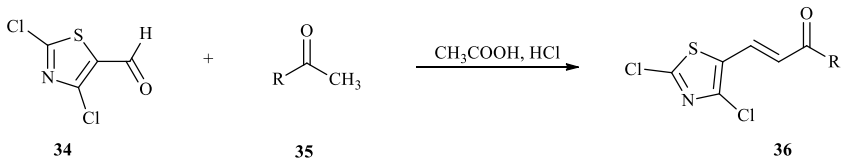
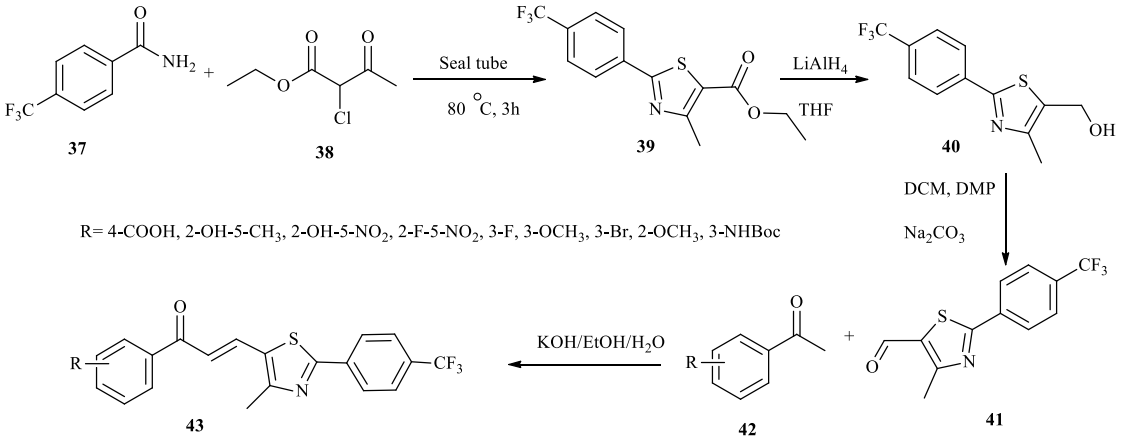
ACS Omega 2023, 8, 19194−19211

Scheme 6. General Synthesis of Thiazole-Based Chalcone Derivatives



a = 2-chlorophenyl f = 2,5-dichlorophenyl k = 4-fluorophenyl p = 3,5-difluorophenyl
b = 3-chlorophenyl g = 2,4-dichlorophenyl l = 2,4-difluorophenyl q = 2-pyridinyl
c = 4-chlorophenyl h = 3,4-dichlorophenyl m = 2,5-difluorophenyl r = 3-pyridinyl
d = 2,3-dichlorophenyl i = 2-fluorophenyl n = 2,6-difluorophenyl s = 4-pyridinyl
e = 2,6-dichlorophenyl j = 3-fluorophenyl o = 3,4-difluorophenyl u = 2-thiazoyl

Scheme 7. General Synthesis of Thiazole-Based Chalcone Derivatives 43



reaction.[28] Using the reaction procedure of the reference, 2-acetyl-1-methylpyrrole **19** and aryl-furfural **20** were subjected to sodium hydroxide in methanol and further stirred at room temperature for about two days. At the completion of the reaction, the final chalcone derivatives **21** were recrystallized from ethano, and the precipitated reaction mixture was filtered, washed, and dried to afford a good yield (Scheme 2).

Similarly, Sharma and co-workers' pyrrole-based chalcone derivatives **24** were synthesized and reported from 2-acetylpyrrole with substituted benzaldehyde derivatives using a condensation reaction under basic conditions.[29] During the reaction, substituted benzaldehyde derivative **23** was added to 2-acetylpyrrole **22** that was dissolved in methanol and a 10% aqueous NaOH solution was added, and the reaction mixture was kept in stirred conditions until the completion of the reaction. After the completion of the reaction, the mixture was diluted with distilled water, and precipitated solid was filtered and recrystallized from the EtOH/EtOAc solvent mixture to afford chalcone derivatives **24** (Scheme 3).

2.2. Chalcones Bearing Imidazole. Sasidharan and co-workers reported a series of 11 imidazole-based chalcone-substituted derivatives using the Claisen−Schmidt condensation reaction between ethanone **25** and various *para*-substituted aromatic aldehyde derivative **26**.[30] A mixture of ethanone **25** and *para*-substituted benzaldehyde **26** in ethanol and aqueous potassium hydroxide was added and stirred at room temperature. The resulting product was kept overnight in a refrigerator, and the solid was filtered off, washed with water, and recrystallized from ethanol and methanol to afford pure imidazole chalcone derivatives **27**, as depicted in Scheme 4.

An antimicrobial active novel series of chalcone-imidazole derivatives **36**(a−m) were synthesized and reported through the common Claisen−Schmidt condensation reaction procedure.[30] Here, the synthesized derivatives of chalcone further functionalized using the known reaction procedure to afford imidazole-based chalcone derivatives. The synthesized substituted chalcones **28** were mixed with NBS and CCl_4 in a round flask in the presence of AIBN. The mixture was refluxed and then filtered and distilled with CCl_4 in vacuum to get compounds **29**(a−i). Compounds **29** were subsequently further subjected to imidazole to afford compounds **30**(j−m) through S_N2 nuclephilic substitution reaction. Compounds **32**(a−m) were subjected to K_2CO_3 and KOH with stirring, followed by the addition of imidazole in anhydrous CH_3CN at ambient temperature under a nitrogen atmosphere. Finally, the chalcone−imidazole derivatives **33**(a−m) were obtained after removal of the solvent following purification using column chromatography (Scheme 5).

2.3. Chalcones Bearing Thiazole. Kasetti and co-workers reported antioxidant active thiazole-based chalcone derivatives through the common Claisen−Schmidt condensation reaction.[31] Here, thiazole-carbaldehyde **34** was dissolved in glacial acetic acid and hydrochloric acid. To this mixture was added aryl or heteroaryl ketone moiety **35**, which was previously dissolved in ethanol, and the mixture was refluxed. Once the reaction completed, the precipitate was filtered, washed, and dried, followed by procedural purification by column chromatography

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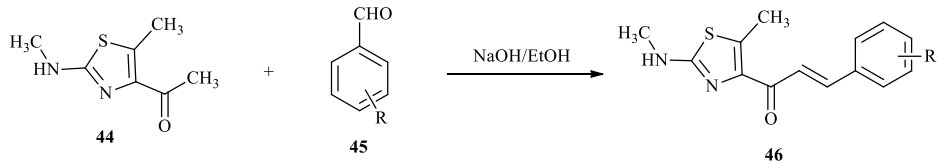
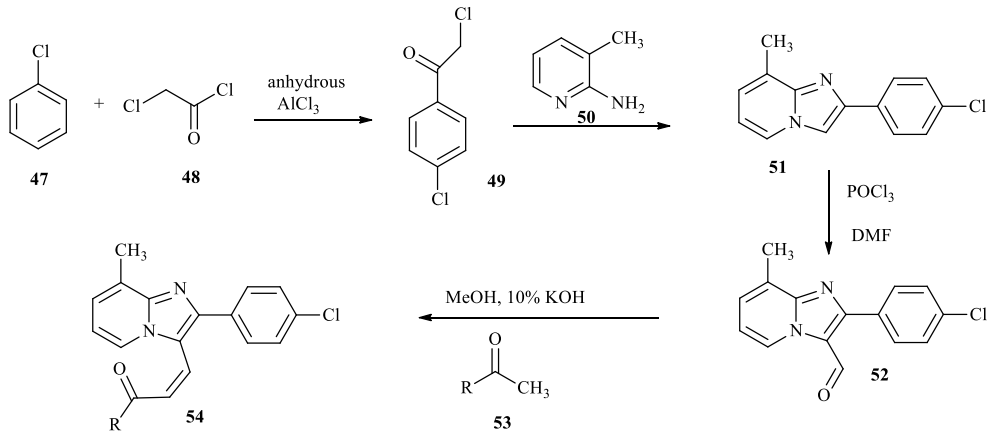
ACS Omega 2023, 8, 19194−19211

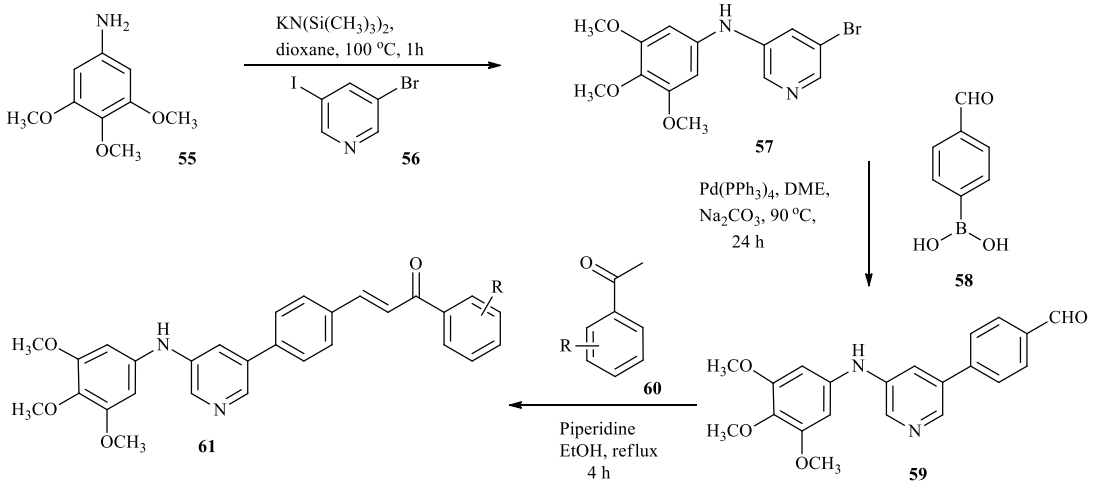
Scheme 8. General Synthesis of Thiazole-Based Chalcone Derivatives 46



Scheme 9. General Synthesis of Pyridine-Based Chalcone Derivatives



Scheme 10. General Synthesis Routes toward Pyridine-Incorporated Chalcone Derivatives 61



a; R= H
b; R = 3-chloro
c; R= 4-chloro
d; R = 4-bromo
e; R = 3-bromo
f; R = 2-fluoro-4-trifluoromethyl
g; R = 4-trifluoromethyl
h; R = 3-fluoro
i; R = 3,4-dimethoxy
j; R= 4-methoxy

to isolate pure thiazole-based chalcone derivatives **36**(a−u), as depicted in Scheme 6.

A series of anticancer active thiazole-based chalcone derivatives **43** were reported by Kasetti and co-workers.[31] Here, thiazole-carbaldehyde **41** was synthesized in three steps. First, thiazole-carboxylate **39** was formed through subjecting benzamide **37** to 2-chloroacetate **38**. The ester moiety of compound **39** was reduced using $LiAlH_4$ to alcohol compound **40**, followed by a Dess−Martin oxidation reaction to afford the key target intermediate **41**. The synthesized aldehyde was reacted with aryl methyl ketone in ethanol, and KOH was added dropwise to the mixture with continuous stirring. Finally, the mixture was filtered, washed, and dried to get a yellow solid compound, which was further purified using recrystallization with ethanol to get pure yellow solid thiazole-based chalcone derivatives **43** with a good yield, as described in Scheme 7.

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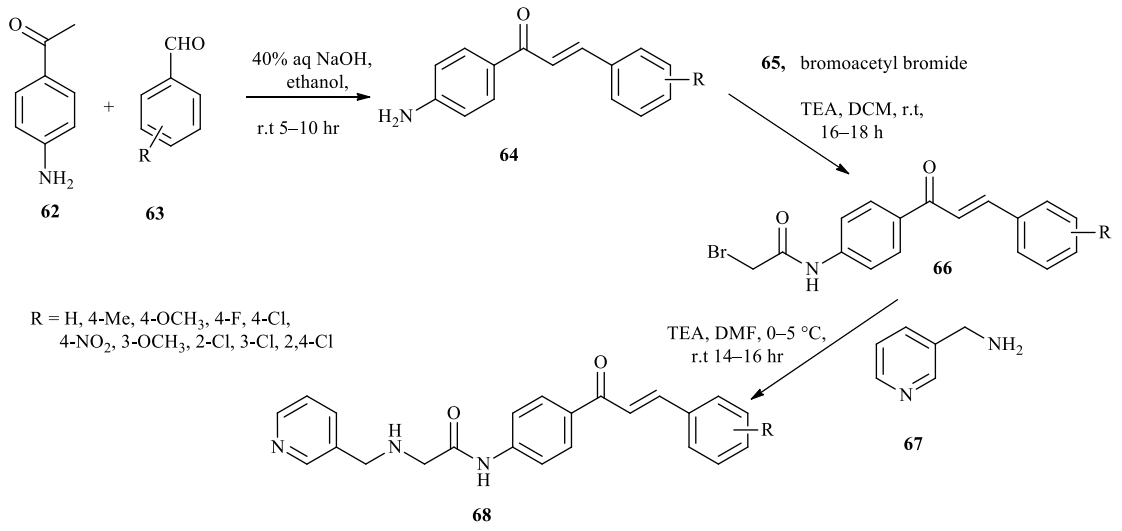
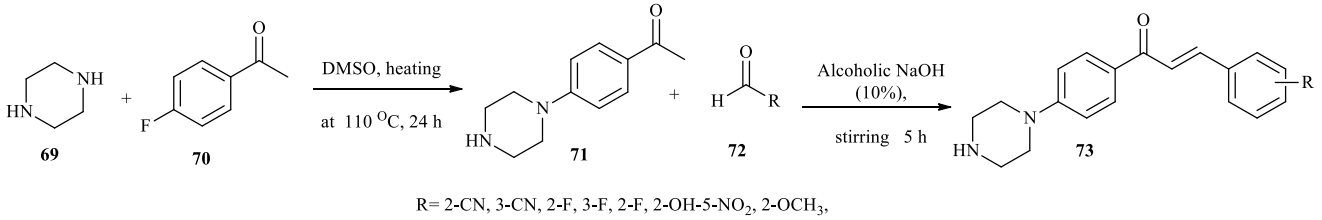
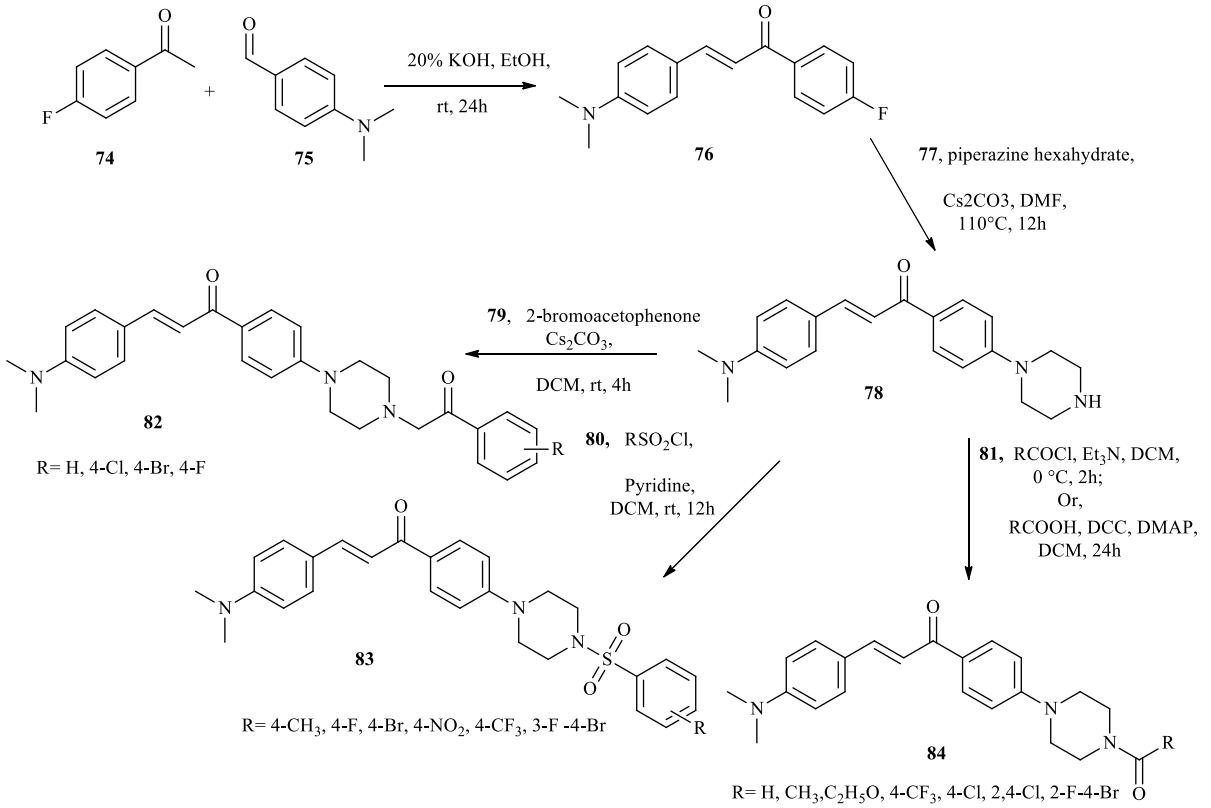
Scheme 11. General Synthesis Routes toward Chalcone Incorporating a Pyridine Moiety



Scheme 12. General Synthesis Routes toward Chalcone Derivatives Incorporating Piperazine



Scheme 13. General Synthesis Routes Towards a Chalcone−Piperazine Hybrid



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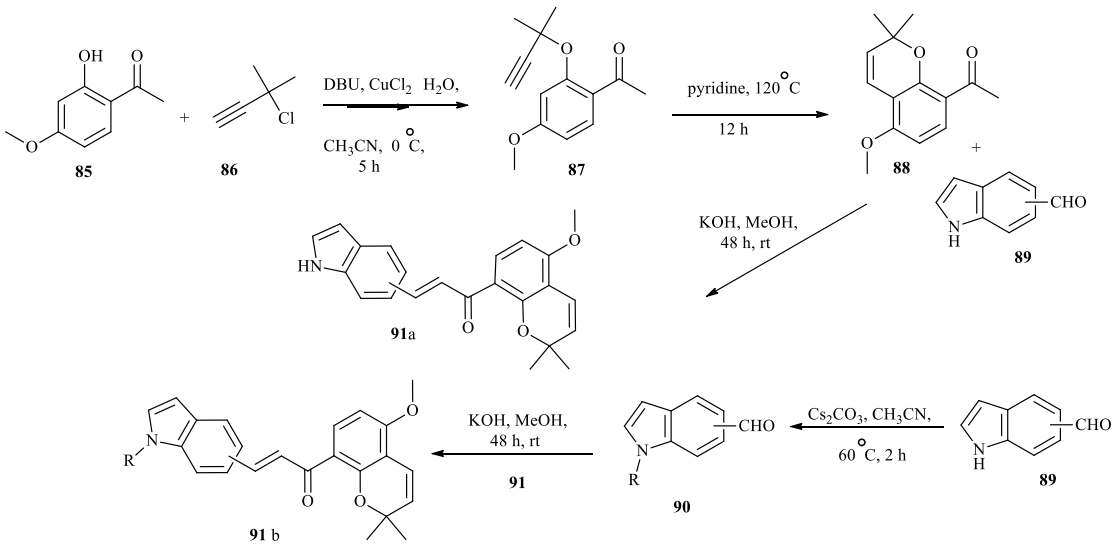
Scheme 14. General Synthesis Routes toward Chalcone Containing an Indole Scaffold



R= H, Methoxymethyl, Methyl, Ethyl, Isobutyl, Prenyl, 2-Morpholinoethyl, Benzyl, 2-Fluorobenzyl, 3-Fluorobenzyl, 4-Fluorobenzyl, 2-Chlorobenzyl, 3-Chlorobenzyl, 4-Chlorobenzyl, 2-Bromobenzyl, 3-Bromobenzyl, 4-Bromobenzyl, 2-Trifluoromethylbenzyl, 3-Trifluoromethylbenzyl, Methyl, Ethyl, 4-Trifluoromethylbenzyl, 3-Fluorobenzyl, 3-Chlorobenzyl, 3-Bromobenzyl, Methyl, 2-(Piperidin-1-yl)ethyl, Methyl, 3-Fluorobenzyl, 3-Chlorobenzyl, 3- Bromobenzyl, Methyl, 3-Fluorobenzyl, 3-Chlorobenzyl, 3-Bromobenzyl

Antitumor active thiazole-incorporated chalcone derivatives were reported by Farghaly and co-workers.[32] A mixture of 4-acetylthiazole **44** derivative was subjected to the aromatic aldehyde derivatives **45** in anhydrous ethanol. An aqueous solution of NaOH was added dropwise, and the reaction mixture was stirred. The solid formed was collected using filtration and recrystallized from a mixture of ethanol/dioxane solvents to afford the thiazole-based chalcone derivatives **46** (Scheme 8).

2.4. Chalcones Bearing Pyridine. Rupala and co-workers reported a series of imidazo-pyridine derivatives through the condensation of aryl methyl ketone and aryl aldehyde in the presence of alcoholic alkali media.[32] The synthesis mixture of pyridine-3-carbaldehyde **52** and ethanone **53** was refluxed in methanol, followed by the addition of NaOH as a catalyst. The crude was poured on to crushed ice, and the resulting product was further recrystallized from dichloromethane to give compound **54**, as provide in Scheme 9.

The synthesis of novel anticancer active chalcone incorporating a pyridine scaffold was reported by Madhavi and co-workers.[33,34] The iodopyridine **56** was subjected to a Buchwald coupling reaction with trimethoxyaniline **55** in the presence of dioxane as the solvent and mild base to afford pyridin-3-amine compound **57** in a good yield. The intermediate **57** undergoes Suzuki coupling with a boronic acid **58** using a palladium salt to afford the key skeleton pyridin-3-yl benzaldehyde **59**. Finally, the intermediate aldehyde **59** was refluxed with substituted acetophenone derivatives **60**(a−j) in ethanol as the solvent and a catalytic amount of piperidine base to afford compounds **61**(a−j), as shown in Scheme 10.

Similarly, the synthesis of a series of anticancer active pyridine-based chalcone derivatives was reported by Durgapal and co-workers from 3-aminomethylpyridine and 4-amino chalcone.[35] Procedurally, 4-aminoacetophenone **62** was subjected to aldehyde **63** under basic reaction conditions to afford 4-amino chalcone derivatives **64**. Further, 4-amino chalcones **64** react with bromoacetyl bromide in the presence of DCM and TEA with stirring to afford **66**. Compounds **66** were further allowed to react with 3-aminomethylpyridine **67** in DCM with TEA base at room temperature to afford various pyridine-based chalcone derivatives **68**, as described in Scheme 11.

2.5. Chalcones Bearing Piperazine. Ahmed and co-workers reported the synthesis of piperazine-chalcone hybrid derivatives as potential vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors.[36] A mixture of a derivative of acetophenone **71** and corresponding aldehyde derivatives **72** was dissolved in 10% alcoholic sodium hydroxide and stirred at room temperature. After the reaction completed, the precipitate was filtered, washed, dried, and recrystallized from ethanol to afford the target compounds **73** (Scheme 12).

A series of novel chalcone hybrids with piperazine derivatives were synthesized and reported as potent antitumor agents.[37] During the preparation of the target compounds, acetophenone **74** reacted with benzaldehyde **75** in the presence of KOH via aldol condensation to give chalcone **76**. Subsequently, the key intermediate **78** was prepared through the substitution of the fluorine atom of **76** with piperazine **77**. Finally, acylation and sulfonylation of the −NH group with acyl chloride or carboxylic acid and sulfonyl chloride afforded hybrid compounds **84** and **82** in good yields, respectively. Further tertiary amines **83** were synthesized by treatment with 2-bromoacetophenone (Scheme 13).

2.6. Chalcones Bearing Indole. Antiproliferative active compounds based on pyrano-chalcone derivatives containing an indole moiety as a major scaffold were reported by Wang and coworkrs.[38] Here, ethanone derivative **85** in acetonitrile was subjected to 3-chloro-3-methyl-1-butyne **86** in the presence of DBU and catalytic copper salt to afford 1,1-dimethylpropargyl ether **87** in a good yield. Further, compound **87** underwent a Claisen rearrangement reaction in the presence of pyridine, leading to key intermediate compound **88**. Finally, condensation of compound **88** with N−H indole-aldehyde derivatives **89** or *N*-alkyl indole aldehyde derivatives **90** under Claisen−Schmidt

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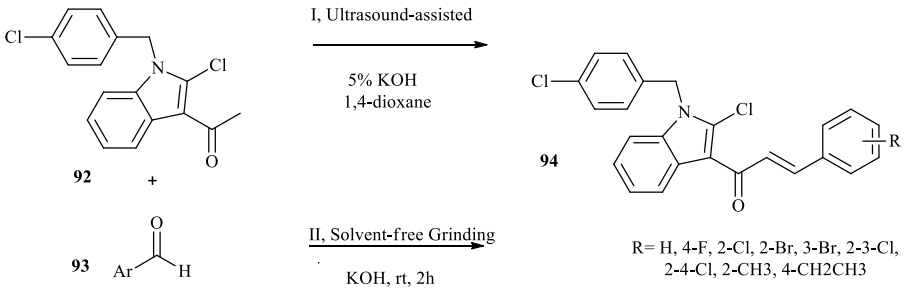
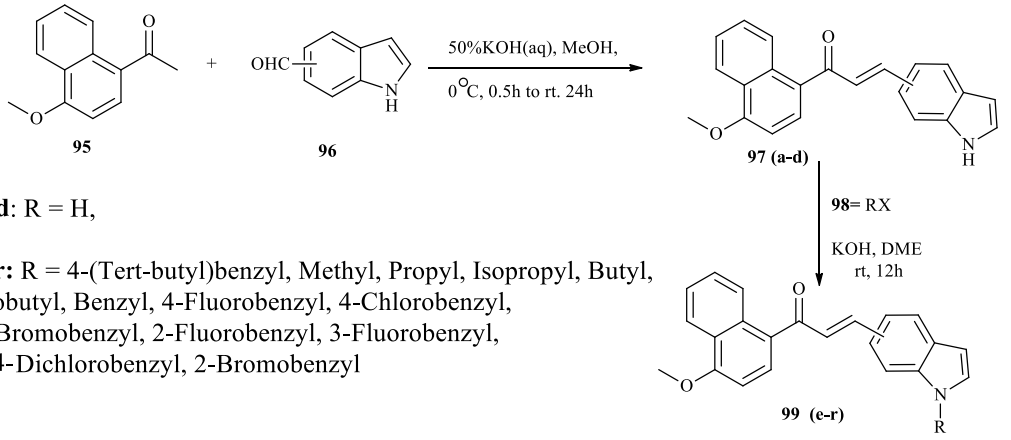
ACS Omega 2023, 8, 19194−19211

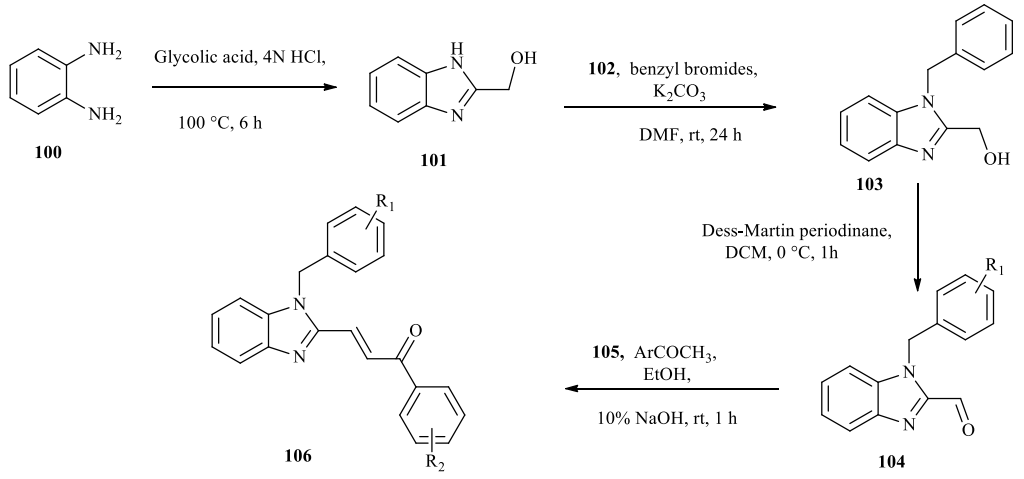
Scheme 15. Ultrasound-Assisted (I) and Solvent-Free (II) Synthesis Protocols for the Preparation of Indole-Based Chalcone Derivatives



Scheme 16. General Synthesis Routes toward Indole-Based Chalcone Derivatives



Scheme 17. General Synthesis Routes toward Benzimidazole-Based Chalcone Derivatives



R_1 = 2-F, 4-CH_3, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 2-F, 4-CH_3, 2-F

R_2= 4-CH_3, 4-CH_3, 4-Br, 4-Br, 4-F, 4-F, 4-OCH_3, 4-OCH_3, 4-Cl, 4-Cl, 4-NO_2, 3-OCH_3 -4-OCH_3, 3-OCH_3 4-OCH_3, 3-OCH_3 -4-OCH_3 -5-OCH_3, 3-OCH_3 -4-OCH_3 -5-OCH_3, 4-CH_2CH_3, 4-CH_2CH_3, 4-$CH(CH_3)_2$, 4-$CH(CH_3)_2$, 4-CN, 4-CN

reaction conditions using the standard reaction procedure provided the desired compounds **91**(a and b) (Scheme 14).

Previously, the syntheses of novel indole-based chalcone derivatives were reported by Gao and co-workers using two powerful methods, the ultrasound-assisted and solvent-free Claisen Schmidt condensation reactions.[39] On one hand, using the ultrasound-assisted method, indole **92** was subjected to aromatic aldehyde **93** in dioxane under basic reaction condition to furnish indole-based chalcone derivatives **94**. On the other hand, using the solvent-free grinding method, similarly indole **92** and aromatic aldehydes **93** under basic reaction condition were intimately ground using pestle and mortar at room temperature, and the resulting product was treated with HCl, filtered, and recrystallized from ethanol to provide indole-based derivatives

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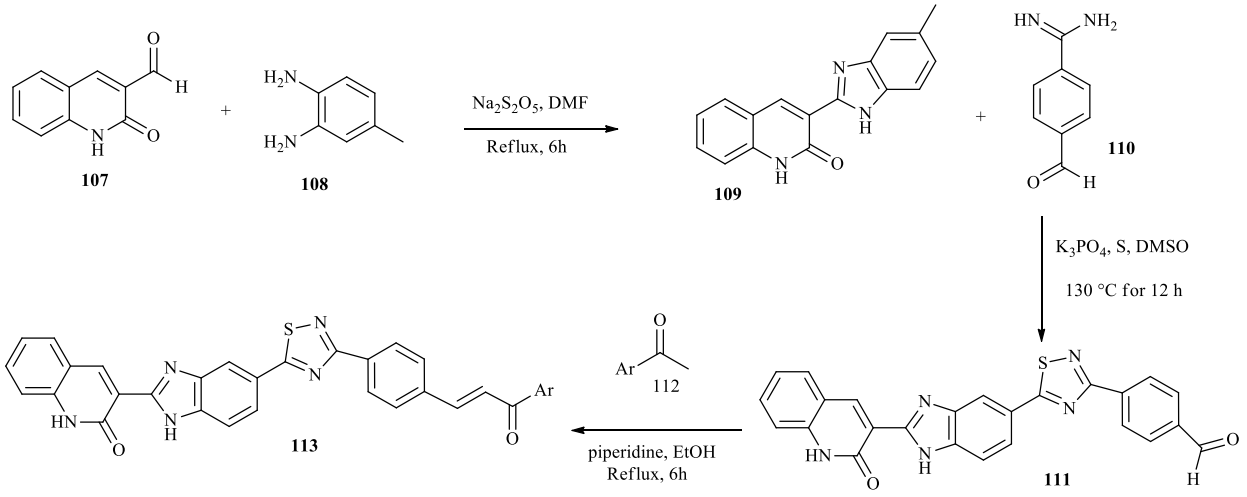
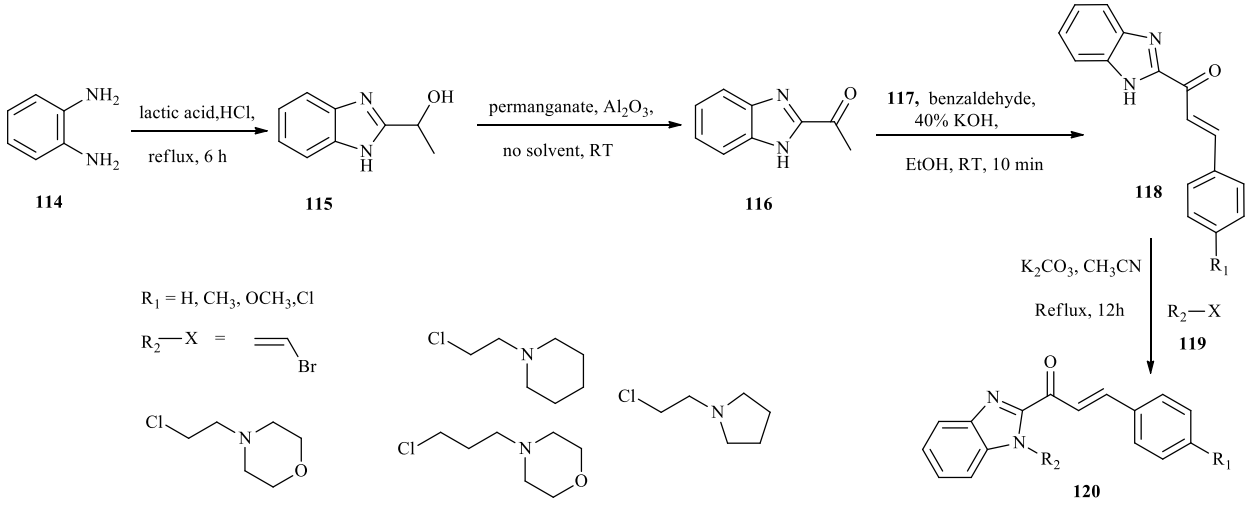
ACS Omega 2023, 8, 19194−19211

Scheme 18. General Synthesis Routes toward Chalcones 113 Incorporating Thiadiazol−Benzimidazol−Quinolinone Heterocyclic Scaffolds



Scheme 19. General Synthesis Routes toward Benzimidazole−Aryl-Based Chalcone Derivatives



94. Finally, the ultrasonication procedure proved that efficient promotion and push using the Claisen−Schmidt reaction condensation move the reaction forward in a short reaction time with better yields, as depicted in Scheme 15.

In recent report, various class of chalcone derivatives containing indole and naphthalene moieties were reported as potent anticancer agents.[40] Through the Claisen−Schmidt condensation reaction, an aromatic ketone derivative **95** and commercial available indole aldehyde derivatives **96** afford indole-based chalcone derivatives **97**(a−d) in moderate to good yields. Indole-based chalcone derivatives **97**(a−d) further reacted with alkyl halides **98** under basic conditions to furnish *N*-alkylated indole-based chalcone derivatives **99**(e−r), as depicted in Scheme 16.

2.7. Chalcones Bearing Benzimidazole. A series of benzimidazole-based chalcone derivatives were synthesized and reported using the Claisen−Schmidt reaction as potential Topo II-targeting anticancer agents.[41] Benzimidazole derivative **101** was obtained through refluxing *o*-phenylenediamine (**100**) with glycolic acid in the presence of HCl. The substituted benzimidazole-2-methanol (**103**) was synthesized through the alkylation of compound **101** using a benzyl bromide in the presence of K_2CO_3. Subsequently, substituted benzimidazole-2-carbaldehyde derivatives **104** were obtained from **103** through oxidation using a Dess−Martin protocol. Compounds **103** were finally prepared from **104** through a Claisen−Schmidt reaction in the presence of appropriate acetophenone derivatives, as depicted in Scheme 17.

Similarly, Pragathi and co-workers reported a series of anticancer active benzimidazole-based chalcones incorporating quinoline−benzimidazole−thiadiazole heterocyclic scaffolds through the aldol condensation reaction.[42] Compound **109** was prepared from 1,2-dihydro-2-oxoquinoline-3-carbaldehyde **107** and benzene-1,2-diamine **108** through a double condensation reaction. Subsequently, the intermediate **109** was reacted with 4-formylbenzamidine hydrochloride **110** to afford derivative **111**. Compound **111** further subjected to the aldol condensation reaction with acetophenone derivatives **112**(a−j)

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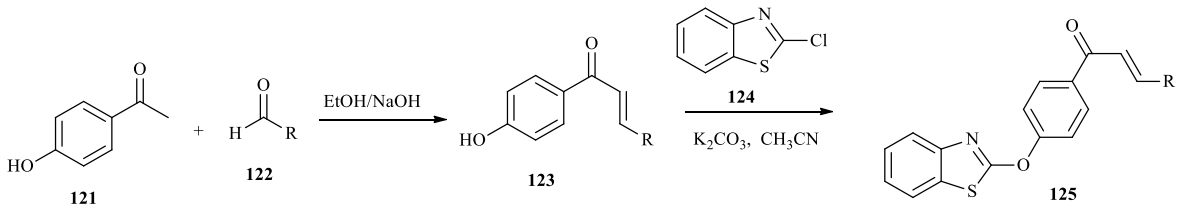
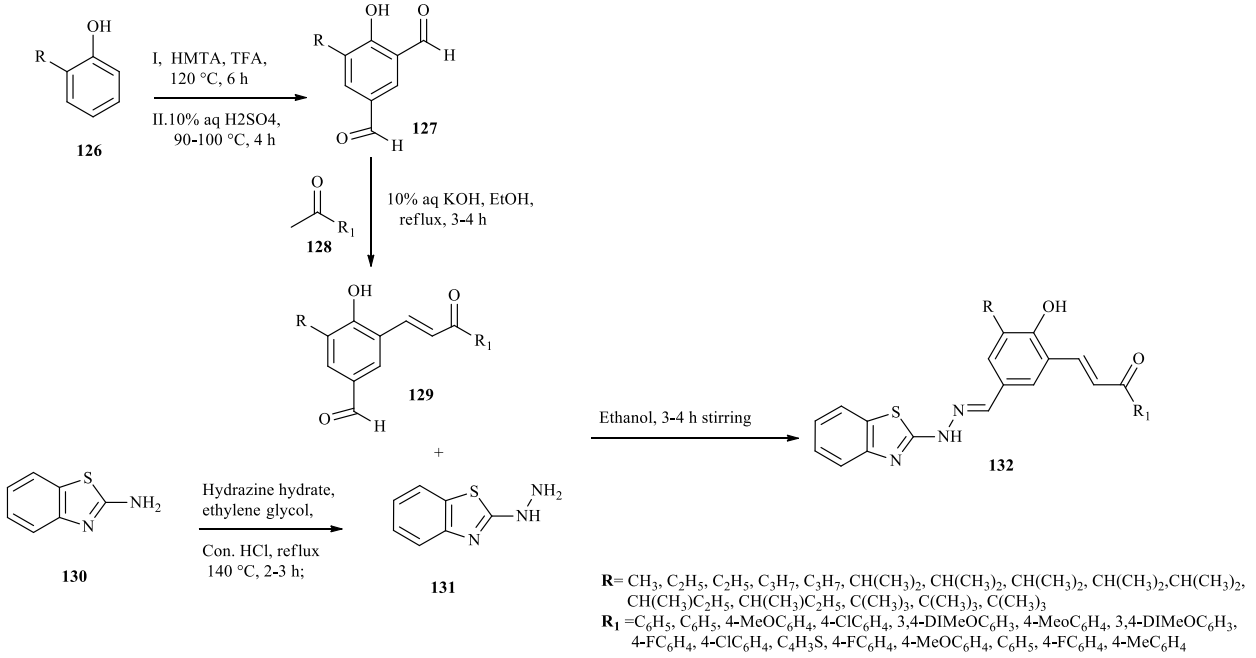
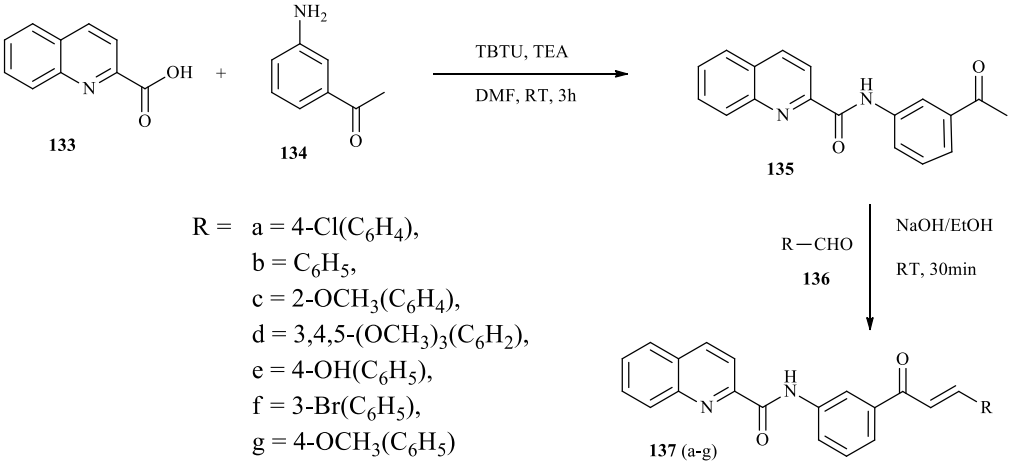
Scheme 20. General Synthesis Routes toward Benzothiazole-Based Chalcone Derivatives



Scheme 21. General Synthesis Routes toward Benzothiazole-Based Chalcone Derivatives



Scheme 22. General Synthesis Routes toward Chalcones Incorporating a Quinoline Moiety



to furnish benzimidazole-based chalcone derivatives **113**(a−j), as depicted in Scheme 18.

A new series of *N*-substituted benzimidazole-based chalcone derivatives were reported by Hsieh and co-workers through the conjugation of benzimidazole and aromatic aldehyde derivatives under basic conditions as anticancer agents.[43] The reaction of *o*-phenylenediamine (**114**) with lactic acid in HCl under reflux reaction conditions prepared benzimidazole derivatives **115**, followed by an oxidation reaction in the presence of potassium permanganate as a strong oxidizing agent and solid aluminum oxide to afford compound **116**. Benzimidazolyl-aryl chalcone derivatives **118**(a−d) were obtained through the aldol

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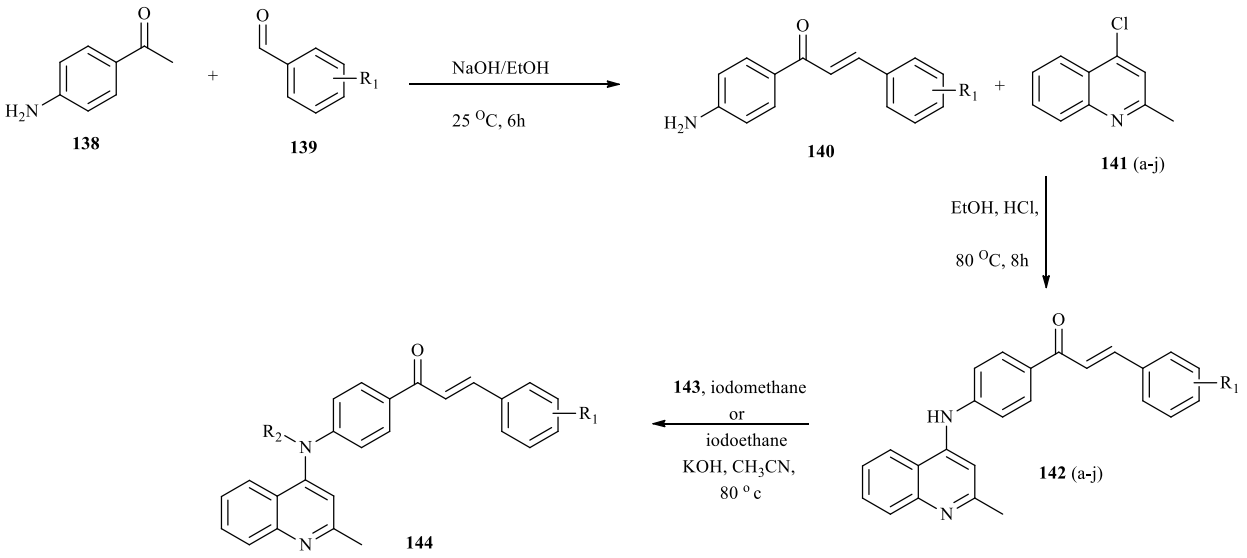
ACS Omega 2023, 8, 19194−19211

Scheme 23. General Synthesis Routes toward Quinoline-Based Chalcone Derivatives



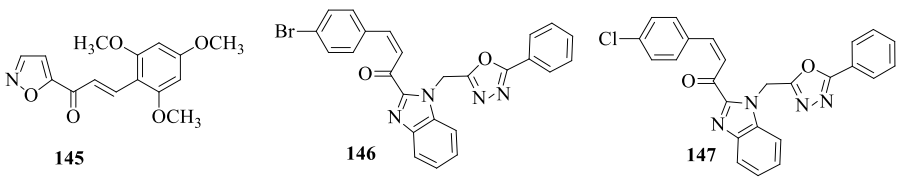


Figure 4. Chemical structures of antibacterial active chalcone derivatives.

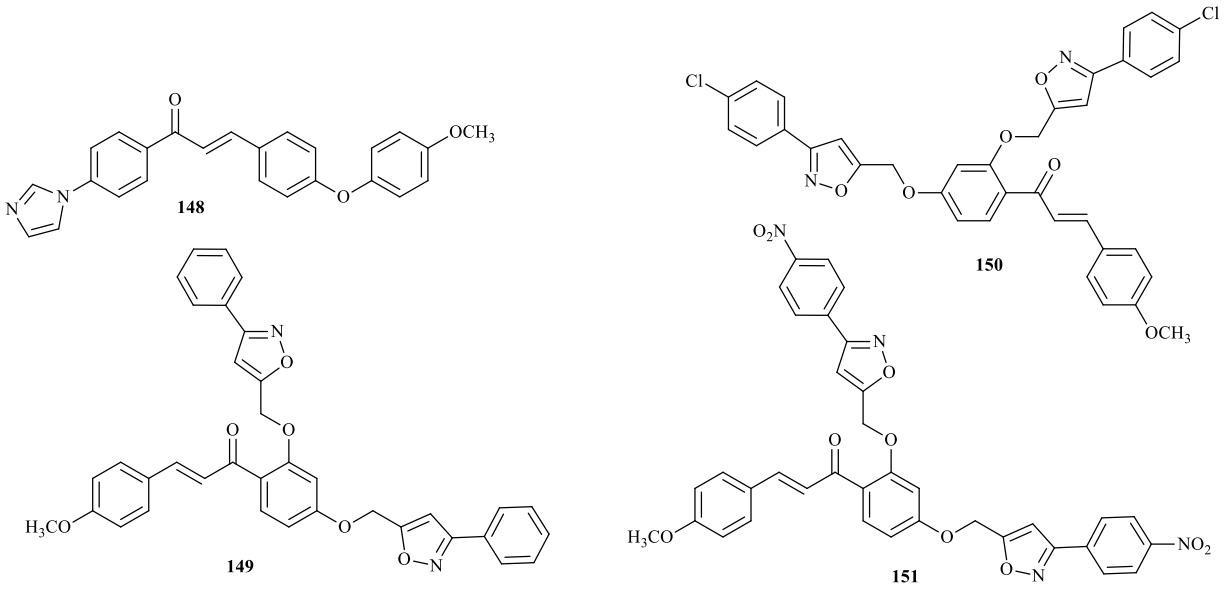


Figure 5. Chemical structures of antifungal active chalcone derivatives.

condensation reaction of compound **116** with substituted aromatic aldehyde derivatives under basic conditions. Further, benzimidazole−aryl chalcone derivatives **118** subjected to a methylation reaction with the corresponding agent to furnished compound **120**, as described in Scheme 19.

2.8. Chalcones Bearing Benzothiazole. Wang and co-workers reported a series of novel benzothiazole-based chalcone derivatives as potential antibacterial agents.[44] Following the standard reaction reported procedure to prepare 4-hydroxy-acetophenone **121**, aldosterone condensations were performed

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ACS Omega 2023, 8, 19194−19211

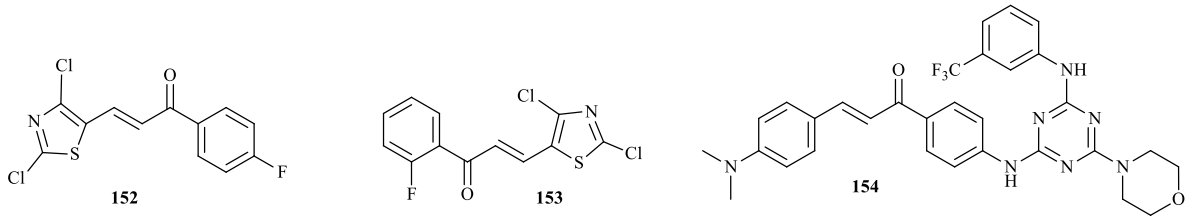

Figure 6. Chemical structures of antitubercular active chalcone derivatives.

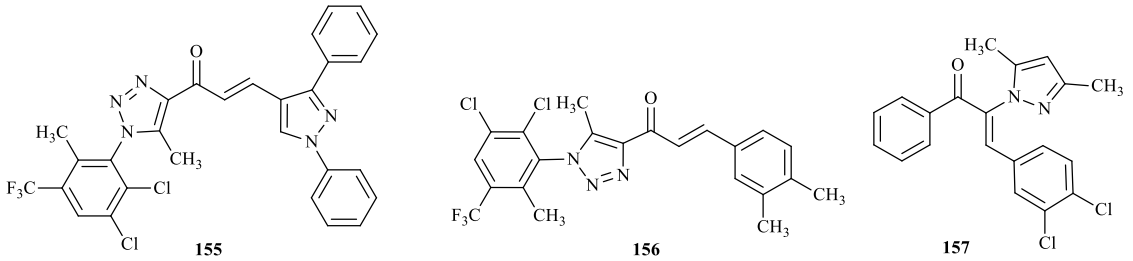

Figure 7. Chemical structures of antioxidant active chalcone derivatives.

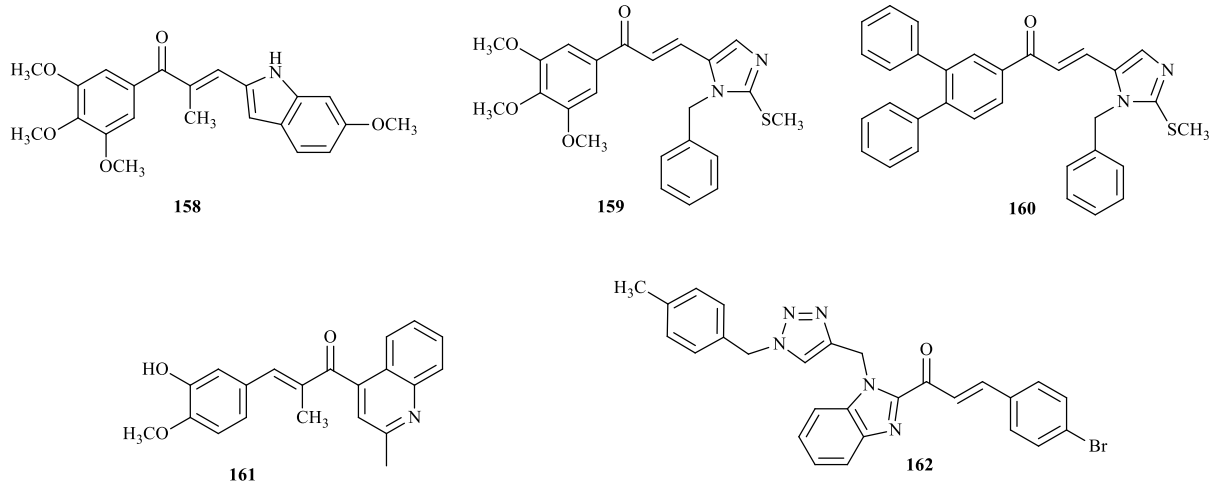

Figure 8. Chemical structures of anticancer active chalcone derivatives.

under alkali conditions to prepare chalcone derivatives **123** with various aldehyde substitutions.[45] Compound **125** was prepared when compound **123** underwent an etherification reaction with 2-chlorobenzothiazole **124** in the presence of acetonitrile as a solvent, potassium carbonate as a catalyst, and reflux, as depicted in Scheme 20.

Similarly, in recent studies a series of benzothiazole-based chalcones were reported to have potential thymidylate kinase (BmTMK) enzyme inhibition activity.[46] Different derivatives of phenol and hexamethylenetetramine were dissolved in TFA at 120 °C with continuous stirring to afford compound **127** in good yields. A dicarbaldehyde compound **127** and different substituted ketone derivatives **128** were dissolved in 10% aq KOH and ethanol, and the resulting solution was refluxed to afford compound **129**. A mixture of *ortho*-substituted chalcone derivatives **129** and 2-hydrazinyl benzothiazole **131** was dissolved in ethanol and stirred at room temperature for 3−4 h to furnish the final benzothiazole-based chalcone derivative **132**, as depicted in Scheme 21.

2.9. Chalcones Bearing Quinoline. A series of quinoline-based chalcone derivatives were synthesized and reported by Thirumurugan and co-workers through the common aldol condensation reaction.[47] Quinoline-based chalcones *N*-quinoline-2-carboxamides **138** were synthesized using quinoline-2-carboxylic acid **136** subjected to ethanone **137** in TEA using TBTU as the base with reflux for 3 h at room temperature (Scheme 22). Compounds **138** undergo the aldol condensation reaction with benzaldehyde derivatives **139** using NaOH/EtOH at room temperature for 30 min to give quinoline-2-carboxamide derivatives **140**(a−g), as shown in Scheme 23.

Commonly, quinoline-based chalcone scaffolds are frequently utilized to design novel anticancer agents. A series of quinoline-based chalcone derivatives were synthesized and reported by Guan and co-workers as described.[48] Here, 4-aminoacetophenone **138** reacted with aromatic aldehyde derivatives **139**(a−j) to afford derivatives **140**(a−j). Compounds **140**(a−j) were subjected to 4-chloro-2-methylquinoline (**141**) to afford derivatives **142**(a−j). Further, compounds **142** (a, b, e, and f) reacted with iodomethane or iodoethane in the presence of KOH in acetonitrile to afford **144**(a, b, e, and f), as depicted in Scheme 23.

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ACS Omega 2023, 8, 19194−19211

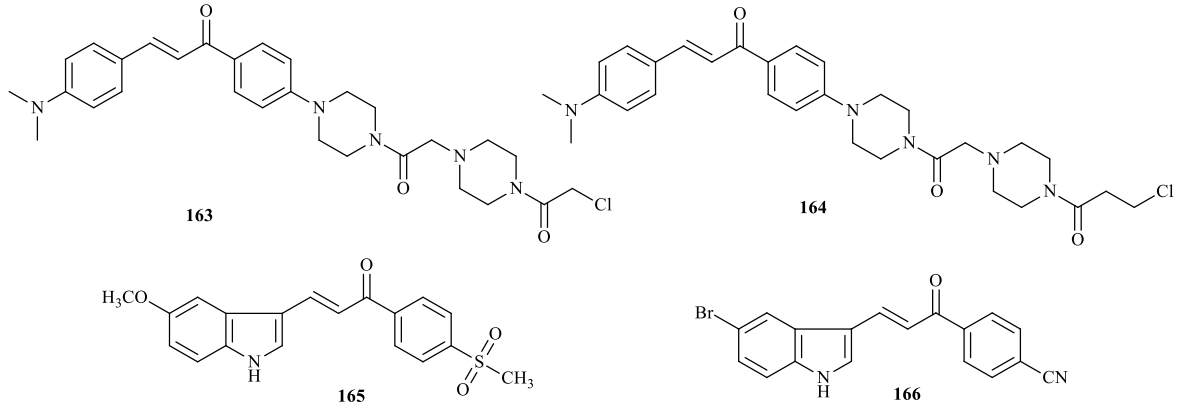

Figure 9. Chemical structures of anti-inflammatory active chalcone derivatives.

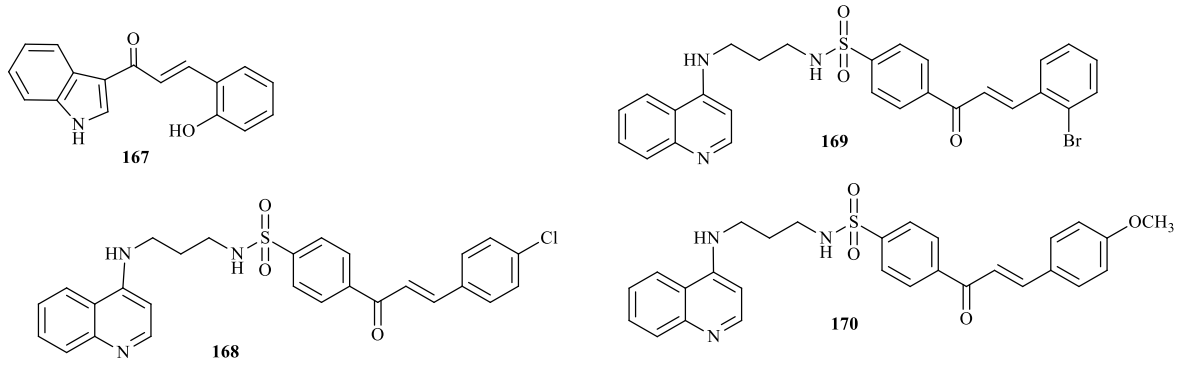

Figure 10. Chemical structures of antimalarial active chalcone derivatives.

3. BIOLOGICAL ACTIVITIES OF CHALCONES BEARING AN *N*-HETEROCYCLIC SCAFFOLD

In the synthesis section, chalcone derivatives incorporating heterocyclic scaffolds such as pyrrole, imidazole, thiazole, pyridine, piperazine, indole, benzimidazole, benzothiazole, and quinoline were briefly discussed and their broad spectrum bioactivities were highlighted. In this section, the scope and biological activities of chalcone derivatives incorporating *N*-heterocyclic scaffolds in the medicinal chemistry arena and therapeutic issues will discussed in detail. The title compound derivatives become impressive, and literature reports stress the significance of the α,β-unsaturated carbonyl moiety to drug target interactions and biological activities.[49] Both natural products and synthetic compounds incorporating *N*-heterocyclic scaffolds displayed a broad band spectrum of pharmaceutical activities such as antibacterial, antifungal, antioxidant, anti-inflammatory, antitubercular, anticancer, antimalarial, and antileishmanial activities.[50]

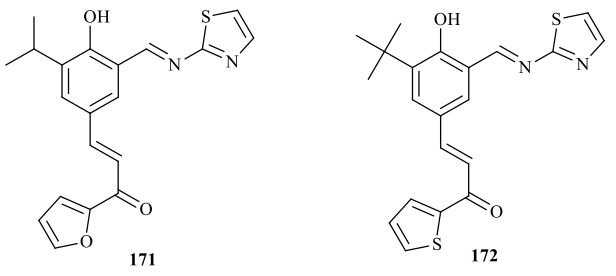

Figure 11. Chemical structures of antifilarial active chalcone derivatives.

3.1. Antibacterial Activity. Chalcone derivatives incorporating heterocyclic scaffolds are basis for the development of antibacterial agents.[51] Shaik and co-workers reported the synthesis of novel bioactive isoxazole-based chalcones and their dihydropyrazole derivatives.[52] All synthesized derivatives were tested for their antibacterial activities through the serial dilution method against two types of bacterial strain, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. All the synthesized compounds exhibited antibacterial activity; in particular, compound **145** containing a 2,4,6-trimethoxyphenyl ring was

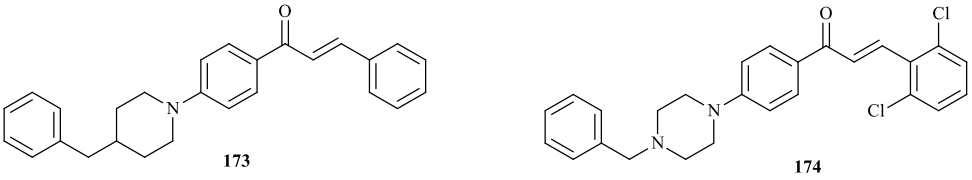

Figure 12. Chemical structures of antigiardial active chalcone derivaties.

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ACS Omega 2023, 8, 19194−19211

the most potent agent among the chalcone series, and its antibacterial activity was found to be greater than that of the reference drug ciprofloxacin (Figure 4). Further, the synthesized compounds exhibited antifungal, antioxidant, and anticancer activities.[53]

Similarly, series of benzimidazole-based chalcone derivatives containing an oxadiazole moiety were reported by Meshram and co-workers through a Claisen−Schimdt condensation reaction.[54] The synthesized compounds were evaluated for their efficiency as antibacterial agents against two Gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) strains of bacteria using the broth microdilution method. Although all tested compounds exhibited potent antibacterial activity, compounds **146** and **147** displayed the most potent activities (Figure 4). Chalcone derivatives possessing an oxadiazole ring with a benzimidazole scaffold have displayed enhanced antimicrobial activity due to incorporation of the heterocyclic moieties compared to the parent compounds.

3.2. Antifungal Activity. Osmaniye and co-workers reported the synthesis of imidazole-based chalcones that incorporate pharmacophores through a Claisen−Schmidt condensation reaction from imidazole-acetophenone with the corresponding 4-substituted benzaldehyde derivatives.[55] The antifungal activity of the synthesized compounds was evaluated for anticandidal activity against *Candida albicans* (ATCC 24433), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019), and *Candida glabrata* (ATCC 90030) in the presence of reference agents ketoconazole and fluconazole. Compound **148** exhibited similar antifungal activity with the reference drug ketoconazole against all *Candida* species and was evaluated as the most active derivative in the series. In a similar fashion, Sunitha and co-workers reported the synthesis of series of bisisoxazole derivatives blended with chalcone derivatives.[56] Antifungal activities of all synthesized derivatives were tested against *Microsporum canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* in 75 and 100 μg/mL concentrations with the reference drug nystatin. Compound **149**, **150**, and **151** display the highest antifungal activity and also show potent antibacterial activity (Figure 5).

3.3. Antitubercular Activity. Tuberculosis (TB) is a chronic infectious disease caused predominantly by *Mycobacterium tuberculosis*. The World Health Organization (WHO) reported that about a third of the world's population is infected with *M. tuberculosis*.[57] Kasetti and co-workers reported bioactive compounds containing thiazole and chalcone pharmacophores.[31] All synthesized compounds were evaluated for their antitubercular activities by MTT assays. Among the tested compounds, the monofluorinated compounds **152** and **153** bearing fluorine atoms at *ortho*- and *para*-positions showed activity at MIC 20.68 μM that was 0.81× greater than the pyrazinamide derivative (Figure 6). Solankee and Tailor reported a new series of chalcones bearing a 1,3,5-triazine group that were synthesized by the classical Claisen−Schmidt condensation of a substituted ketone with the corresponding substituted aldehydes.[58] The *in vitro* antitubercular activities of all the newly synthesized compounds were determined using a Lowenstein−Jensen medium against *Mycobacterial tuberculosis* H37Rv strain relative to the reference drugs isoniazid and rifampicin. Among the compounds, a compound **154** was found to possess the greatest potency against *Mycobacterium tuberculosis* with 92% inhibition.

3.4. Antioxidant Activity. Recently, Bhat and co-workers reported a novel series of bioactive 1,2,3-triazolyl chalcone derivatives that were synthesized via the Claisen−Schimidt reaction.[59] The antioxidant activities of the compounds were further evaluated using the ABTS (2,2′-azino-bis(3-ethyl benzothiazoline-6-sulfonic acid)) antioxidant assay technique. Evaluation of the antioxidant activity revealed that most of the tested compounds exhibited moderate to excellent DPPH and ABTS radical scavenging potential compared to the positive control ascorbic acid. Among the synthesized compounds, **155** and **156** bearing 3,4-dimethyl phenyl and 1,3-(biphenyl)-1*H*-pyrazole at the third position of chalcone moiety, respectively, were found to be more effective and potent. They further displayed DPPH radical scavenging ability with IC_{50} values 15.33 and 14.48 μM compared with ascorbic acid with an IC_{50} value of 12.27 μM at a 31.5 μg/mL concentration by the DPPH radical scavenging activity method. The antioxidant activity of the derivatives **155** and **156** was further illustrated by ABTS assay method with 80.4% and 81.8% inhibition compared to the positive control ascorbic acid with 88.5% inhibition. Similarly, arylic substitutions with pyrazolic chalcones were reported as potent antimicrobial and antioxidant agents by Kumari and co-workers through Claisen−Schmidt condensation.[60] The *in vitro* antioxidant potential of the synthesized compounds was evaluated using the DPPH method, with ascorbic acid as a standard reference. Among the synthesized compounds assayed for antioxidant activity in the DPPH method, compound **157** exhibited good radical scavenging activity an IC_{50} value of 88.04 μg/mL, and the value of standard drug ascorbic acid was found to be 48 μg/mL (Figure 7).

3.5. Anticancer Activity. Cancer is one of the most serious of a devastating diseases and a multifactorial disease. In 2020, 19.3 million patients were diagnosed and approximately 10 million deaths were related to cancer.[61] These data indicate that the improvement of effective anticancer drugs with minimized side effects is needed. Novel bioactive indole-based chalcone derivatives were reported by Yan and co-workers.[62] Antiproliferative activities of all synthesized compounds were evaluated against various human cancer cell lines by MTT assay. Among the tested compounds, compound **158** exhibited the most potent activity, with IC_{50} values of 3−9 nM against six cancer cells. Similarly, a new series of imidazole-based chalcone derivatives were reported as tubulin inhibitors and anticancer agents.[63] The cytotoxic activity of the synthesized compounds was evaluated against four cancer cell lines including MCF7, A549, HepG2, and MCF7/MX by MTT assay. Compounds **159** and **160** exhibited strong cytotoxic activity with IC_{50} values ranging from 7.05 to 63.43 μM against all four human cancer cells. In previous work, a series of novel chalcones containing quinoline were reported as antiproliferative agents.[63] The *in vitro* antiproliferative efficacy of the prepared compounds was assessed by MTT assays using human chronic myelogenous leukemia cell K562 and compared to that of the reference compound CA-4. Among them, compound **161** exhibited the most potent activity with IC_{50} values ranging from 0.009 to 0.016 μM in a panel of cancer cell lines. Furthermore, a series of triazole−benzimidazole−chalcone derivatives were reported from the combination of different azide derivatives and substituted benzimidazole terminal alkynes bearing a chalcone moiety.[64] The antiproliferative activities of synthesized compounds were examined against two human breast cancer cell lines (T47-D and MDA-MB-231) and one prostate cancer cell line (PC3) using a resazurin-based method. Among the

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ACS Omega 2023, 8, 19194−19211

evaluated compounds, **162** exerted highest cytotoxic effects on all the selected PC-3, MDA-MB-231, and T47-D cell lines, with IC_{50} values of 10.7, 5.89, and 6.23 μM compared to the reference drug doxorubicin (0.13, 1.51, and 0.73 μM), respectively (Figure 8).

3.6. Anti-Inflammatory Activity. In previous work, a series of chalcone derivatives bearing a bispiperazine linker were reported by Tang and co-workers via a condensation reaction.[65] The synthesized compounds were evaluated for their *in vitro* anti-inflammatory activity in LPS-induced RAW 264.7, and piperazinochalcone significantly inhibited the production of TNF-α. Most bispiperazine chalcone derivatives exhibited excellent anti-inflammatory activities. Specially, the IC_{50} values of **163** and **164** were 0.42 and 0.82 μM, respectively, compared to that of the positive control dexamethasone (IC_{50} < 20 μM). Recently, Özdemir and co-workers were synthesized and reported new indole-based chalcone derivatives through the Claisen−Schmidt condensation reaction.[66] Colorimetric COX (ovine) inhibitor screening assay was carried out to evaluate the ability of the compounds to inhibit COX-1 and COX-2 *in vitro*. Compound **165** (IC_{50} = 8.6 ± 0.1 μg/mL) and compound **166** (IC_{50} = 8.1 ± 0.2 μg/mL) were found as the most potent COX-1 inhibitors when compared with indometacin (IC_{50} = 0.7 ± 0.2 μg/mL). Furthermore, compound **166** exerted a COX-2 inhibitory effect with an IC_{50} value of 9.5 ± 0.8 μg/mL when compared with indometacin (IC_{50}= 10.0 ± 4.2 μg/mL). Moreover, according to the CCK-8 assay, the cytotoxic doses of compounds **165** (IC_{50}= 32.3 ± 6.7 μg/mL) and **166** (IC_{50}= 51.6 ± 15.3 μg/mL) for NIH/3T3 cells were higher than their effective doses (Figure 9).

3.7. Antimalarial Activity. Earlier malarial reports indicate that it is one of the most prevalent and lethal parasitic diseases in the world, affecting more than 300 million people every year.[67] As there is high level of resistance to all the classes of antimalarial compounds, including artemisinin derivatives, it has increased the global malaria burden and is a major threat to malaria control.[68] There is an urgent need for the design and development of novel and potent antimalarial drugs, particularly against the *Plasmodium falciparum*, which causes severe malaria. Accordingly, Jyoti and co-workers reported indolyl−chalcone derivatives.[69] All the indolyl−chalcones were evaluated for their *in vitro* antimalarial activity against *P. falciparum*, NF54 strain. Antiplasmodial IC_{50} activity against malaria parasites *in vitro* provides good screening for identifying the antimalarial potential of the synthesized compounds. Among them, compound **167** was the most active compound against plasmodia with an IC_{50} value of 2.1 mM/L. In previous work it was reported that novel molecular hybrids were synthesized when the quinoline moiety was coupled with various chalcone derivatives using the appropriate linker.[70] The antiplasmodial activities of all synthesized molecular hybrids were evaluated against the drug-sensitive strain (NF54) of *P. falciparum* using chloroquine as reference drug. Compounds **168**, **169**, and **170** (Figure 10) with IC_{50} values of 0.10, 0.10, and 0.11 μM, respectively, were the most active against the plasmodia. These compounds were further tested against the multidrug-resistant K1 strain of *P. falciparum*. Compound **170** exert about a twofold enhancement in rthe esistivity index (RI = 5.36, PfK1 IC_{50} = 0.59 μM) relative to Chloroquine, whereas compounds **168** and **169** were less active against the K1 strain with IC_{50} values of 2.97 and 6 μM, respectively (Figure 10).

3.8. Antifilarial Activity. Lymphatic filariasis is a parasitic infection that causes acute and chronic inflammation.[71] It is caused by thread like nematodes *Wucheria bancrofti*, *Brugia malayi*, and *Brugia timori* and spread via mosquitos infected with worm larvae.[72] Different research has been carried to get an effective drug for this disease. Sashidhara and co-workers reported a series of chalcone−thiazole derivatives.[72] All the synthesized compounds were evaluated for their *in vitro* activity using motility and MTT 17 reduction assays against microfilaria and female adult worms of *B. malayi*. Compounds **171** and **172** were found to be effective in 19 killing microfilaria (LC_{100} = 5 and 10 μM; IC_{50}= 1.8 and 3.5 μM) and adult worms (LC_{100} = 2.5 and 10 20 μM; IC_{50} = 0.9 and 3.2 μM); both the compounds also inhibited the MTT reduction potential of 21 adult parasites to 49 and 63%, respectively. The *in vivo* activity of the tested active compound **172** further exhibits a 100% embryostatic effect (Figure 11).

3.9. Antigiardial Activity. Giardia is a leading cause of infectious gastroenteritis worldwide and is treatable. It is a waterborn parasitic disease caused by the *Giardia lamblia*.[73,74] Different researchers were conducting their research to develop a novel drug for overcoming Giardia-born disease. In previous work, novel chalcone derivatives were reported by Bahadur and co-workers that were synthesized via microwave-assisted Claisen−Schmidt condensation.[75] The newly synthesized compounds were first tested for their antigiardial activity under anaerobic conditions. Among the tested compounds, only three of them display significant antigiardial activity. These active compounds were tested for their toxicity against Giardia trophozoites under microaerobic conditions and exhibited good activity. Finally, to assess the selectivity of compounds against Giardia, their toxicity toward a mammalian cell line, Caco-2 cells, was tested after 48 h of incubation. According to the IC_{50} measured on Giardia cells under microaerobic conditions, compounds **173** and **174** show preferential toxicity against parasitic cells (Figure 12).

4. CONCLUSION

Chalcone derivatives incorporating heterocyclic scaffolds such as pyrrole, imidazole, thiazole, pyridine, piperazine, indole, benzimidazole, benzothiazole, and quinoline are briefly highlighted to give a basic information to the researchers who work with these scaffolds. The above heterocycle-based chalcone derivatives almost all displayed a broad spectrum with a variety of pharmacological activities. Especially, chalcones containing *N*-heterocyclic scaffolds have become potential candidates for the development of effective medicines and pharmaceutical drugs. Chalcone derivatives incorporating nitrogen heterocyclic biological activities greatly attract the attention of researchers, and currently a lot of papers have been reported to find effective and potent drugs to overcome the influence of different diseases. Conventionally, these chalcones are synthesized through Claisen−Schmidt condensation reactions under basic or acidic media. Currently, findings proved that chalcones containing *N*-heterocyclic moieties display various pharmacological activities. The most known are antibacterial, antifungal, antitubercular, antioxidant, anti-inflammatory, anticancer, antimarial, antigiardial, and antifilarial activities. This implies that further investigations are needed to design and develop potent, novel, and effective chalcone derivatives with *N*-heterocyclic scaffold-based drugs.

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Notes

The authors declare no competing financial interest.

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